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Review

Microbial Biopesticides: Diversity, Scope, and Mechanisms Involved in Plant Disease Control

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Abstract: Food losses, defined as a reduction in the quantity and quality of food during production and storage, impact food safety and security. Losses caused by plant pathogens are among the most significant. Chemical pesticides have been extensively used to prevent microbial diseases. Their toxicity and reduced efficacy, however, have encouraged investigators to develop alternatives. Alternatives based on microbial biopesticides tend to be safer and more environmentally benign than conventional pesticides. In recent years, formulations based on biopesticides have progressively increased in number and diversity and have attracted commercial interest. Understanding the mechanisms by which biopesticides control the disease is fundamental to achieving optimal disease control. Biocontrol mechanisms can be divided into two main categories: those related to the ability to inhibit pathogens or their virulence factors, and those that enhance host plant fitness and induce disease resistance. Here, the first type of strategy is reviewed, which is directly mediated by physical contact between biocontrol agents and pathogens or indirectly by exposure of a pathogen to antimicrobial or microbial-inhibiting compounds produced by the microbial antagonist. Mechanisms involving physical contact include mycophagy, destruction of pathogenic bacteria by bacteriophages or predation, and disease inhibition by topical applications of specific dsRNA. Indirect mechanisms that do not involve direct contact with a pathogen include the production of antimicrobial compounds, competition, and virulence factor suppression by quorum quenching. These topics are reviewed and discussed.

Keywords: biocontrol; biopesticides; food losses

1. Introduction

The reduction of food quantity and quality during their production or storage is associated with food losses [1]. These losses have a global impact on food security and health and often represent the main cause of hunger and malnutrition. In addition, prevention strategies designed to limit food losses are impacted by natural resources and can cause environmental deterioration [2,3].

Reductions in the supply and market value of fruits, vegetables, and cereals during production, postharvest storage, shipment, and marketing can reach up to 40% [1,4], depending on the type of crop and the economic and social conditions of a region. In all cases, significant amounts of human effort and valuable and often limited resources, such as soil and water, are invested in the process of producing and marketing agricultural products [5]. Biotic damage, caused by microorganisms (fungi, bacteria, and viruses), represents a major source of food loss [4,6], and agrochemical companies have developed and marketed numerous synthetic, chemical pesticides to manage and prevent these losses. The toxicity of these chemicals and reduced efficacy due to the appearance of resistant pathogens have driven research to identify and develop safer and more environmentally friendly alternatives, such as the use of biopesticides.

The United States Environmental Protection Agency [7] has defined biopesticides as naturally occurring substances (biochemical pesticides), microorganisms and their metabolic products (microbial pesticides), and substances produced by plants containing added genetic material (plant-incorporated protectants) that are able to control pests. Microbial biopesticides are often used in augmentative biocontrol strategies as a preventive measure to control pathogens. The microbial antagonists that form the basis of those biopesticide products are mass-produced by industrial fermentation and must be applied several times since their populations are generally self-sustaining for a limited time (partial or one growing season) [8]. They exert their disease control through different mechanisms. Understanding these mechanisms is fundamental to achieving optimal disease control, assessing their impact on non-target microbiota, and determining if their control potential can be potentiated. Biocontrol mechanisms can be divided into two main categories: those that involve the direct inhibition of pathogens or their virulence factors and those that enhance the fitness of a host plant by inducing disease resistance. In this review, we discuss several of the different modes of action of microbial control agents (bacteria, viruses, and fungi) that inhibit plant pathogens or their virulence factors. These mechanisms include those that are dependent on direct physical contact with a pathogen and those that act indirectly and do not involve physical contact, such as the production of antimicrobial compounds (Figure 1). We also review research on the use of RNA interference (RNAi)-based technologies for disease control as an alternative to the enhancement of host disease resistance by genetic modification [9]. We also present information on microbial biopesticides that have been successfully commercialized to prevent food and feed losses caused by plant pathogens.

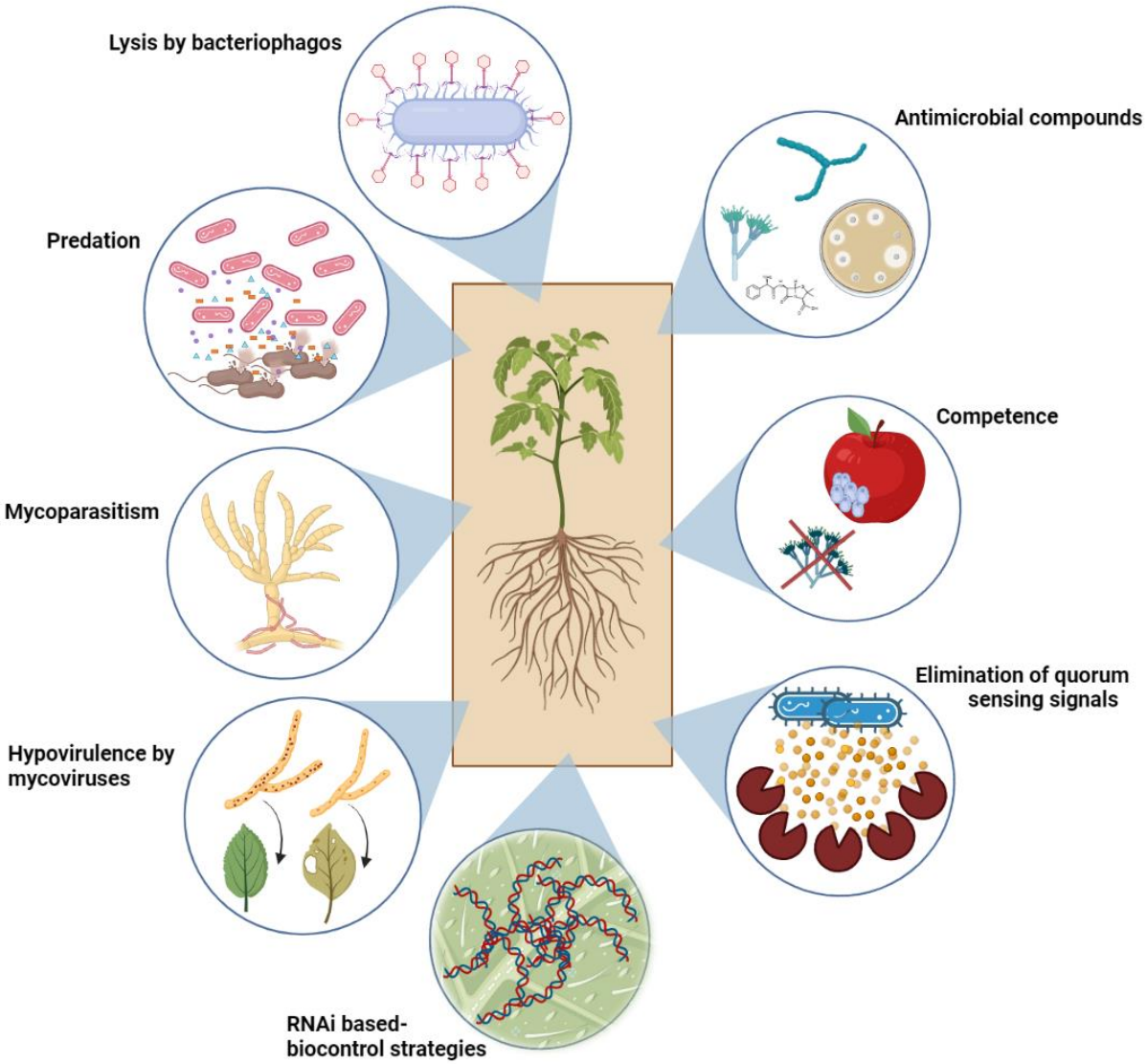

Figure 1. Different modes of action of biocontrol agents to inhibit plant pathogens. Mechanisms involving physical contact are on the left of the figure, and those in which physical contact is not a prerequisite are on the right. Created with Biorender (https://biorender.com/, accessed on 9 February 2023).

2. Direct Interaction between Pathogens and Biocontrol Agents through Physical Contact

Some biocontrol agents exert their action only when they come into close contact with a pathogen. Mechanisms involved in such interactions include mycophagy exerted by bacteria, yeasts, or fungi and the degradation of pathogenic bacteria by bacteriophages or predatory bacteria. We include in this category the actions of mycoviruses and RNAi that inhibit or minimize the expression of virulence factors produced by pathogenic fungi (Table 1).

Table 1. Modes of action that involve direct interaction and physical contact between the biological control agent and pathogen on different crops.

Mechanism of Action	Biocontrol Agent	Pathogen	Crop	Reference
Lysis of phytopathogenic bacteria	Bacteriophages	*Pectobacterium* spp.	Potato	Zaczek-Moczydłowska et al., 2020 [10]
		Pectobacterium spp. and *Dickeya* spp.	Potato	Czajkowski et al., 2015; Zaczek-Moczydłowska et al., 2020 [10,11]
		Pseudomonas syringae pv. *actinidiae*	Leaves of kiwifruit	Pinheiro et al., 2020 [12]
		Pseudomonas syringae pv. *syringae*	Cherry leaves Sweet cherry plantlets	Rabiey et al., 2020; Akbaba and Ozaktan, 2021 [13,14]
		Pseudomonas syringae pv. *tomato*	Tomato seedlings	Hernandez et al., 2020 [15]
		Streptomyces scabies	Potato	Goyer, 2005 [16]
		Clavibacter michiganensis	Maize seeds	Kimmelshue et al., 2019 [17]
Destruction of bacterial pathogens by predatory bacteria	*Vampirovibrio chlorellavorus* (Epibiotic strategy)	*Chlorella vulgaris*	-	Soo et al., 2015 [18]
	Bdellovibrio bacteriovorus strain SOIR-1 (Endobiotic strategy)	*Xanthomonas campestris* *Pantoea* sp. *Pectobacterium carotovorum* subsp. *brasilense*	Potato slices Onion bulbs Potato slices	Odooli et al. (2020) [19] Youdkes et al. (2020) [20]
	Myxococcus xanthus R31 *Myxococcus* sp. strain BS (Group attack)	*Ralstonia solanacearum* *Pectobacterium carotovorum*	Tomato Calla lily	Dong et al., 2022 [21] Li et al., 2018 [22]
Mycophagy	*Saccharomycopsis schoenii* *Wickerhamomyces anomalus* *LBCM1105*	*Penicillium digitatum* *Penicillium expansum* *Moniliophthora perniciosa*	Oranges Apples Cacao	Pimenta et al., 2018 [23] Ferraz et al., 2021 [24]
Mycoparasitism	*Ampelomyces quisqualis* (Biotrophic mycoparasitism) *Trichoderma* spp. (Necrotrophic mycoparasitism)	*Pseudoidium neolycopersici* *Rhizoctonia solani*, *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Alternaria alternata*, *Fusarium* spp., and oomycetes such as *Pythium ultimum*	Tomato/powdery mildew Many crops	Németh et al., 2021 [25] Druzhinina et al., 2011 [26]
Hypovirulence of fungal pathogens	Mycoviruses: SsHV1 and SsHV2	*Sclerotinia sclerotiorum*	-	Xie et al., 2014 [27,28]
Silencing target genes in plant pathogens by RNA interference (RNAi)	Specific dsRNA	*Botrytis cinerea*	Tomato leaves	Niño-Sánchez, J. et al., 2022 [29]

2.1. Lysis of Phytopathogenic Bacteria by Bacteriophages

Bacteriophages or phages are viruses that infect and replicate in living prokaryote cells (Archaea and Bacteria) [30]. Depending on their life cycle, phages can be lytic (virulent) or lysogenic (temperate) [31].

Lytic phages infect and ultimately kill bacterial cells to release their own progeny to infect other cells. The duration of the infection-replication-release cycle is dependent on the phage type but typically is around 1 or 2 h [32].

Temperate phages infect their hosts and establish a long-term stable relationship in which the viral genome is replicated synchronously with the bacterial DNA and passed to daughter cells. The lysogenic state is regulated by environmental conditions, and, in some cases, a lytic cycle can be induced after a lysogenic period.

Lytic phages were reported to effectively control bacterial spoilage in foods and bacterial infections in plants [33,34]. They are active against multidrug-resistant bacteria and effective in removing bacterial biofilms [35]. Since phages can only infect prokaryotic cells, they are considered non-toxic and harmless to humans, animals, and plants. Thus, their use to control pathogens has been considered safe [33]. Some phages can be highly specific in their hosts, infecting only particular strains within a bacterial species, which represents a constraint when considering the use of phages as biopesticides. Notably, however, phage cocktails have been successfully used to overcome this limitation. For example, Zaczek-Moczydłowska et al. [10] reported that the application of a mixture of six phages was more effective than monophage applications in suppressing the soft rot of potatoes caused by *Pectobacterium* spp.

Other phages have a broad host range and are able to infect many species within a genus or even bacteria from different genera. For example, Buttimer et al. [36] described a phage belonging to the family Myoviridae that is able to infect different species in the genera *Erwinia*, *Cronobacter*, and *Pectobacterium*. Determining the host range for a particular phage is necessary to determine the range of pathogenic bacteria it could affect and assess its potential impact on beneficial microbiota.

Many studies have been published on the ability of phages to control various bacterial plant pathogens, such as *Pectobacterium* spp. and *Dickeya* spp., which are the major causes of postharvest losses in potatoes [10,11]. Successful examples of phage therapy against different pathovarieties of *Pseudomonas syringae* on various crops have also been reported, such as the control of *P. syringae* pv. *actinidiae* on kiwifruit leaves [12], *P. syringae* pv. *syringae* on cherry leaves [13] and sweet cherry plantlets [14], and *P. syringae* pv. *tomato* on tomato seedlings [15]. The control of other Gram-negative bacteria, such as *Ralstonia solanacearum* [37,38], various species of *Xanthomonas* [39,40], *Erwinia* [41,42], and *Xyllela fastidiosa* [43], on different crops was accomplished by different phages. Phages also have been effective in controlling some Gram-positive phytopathogenic bacteria, such as *Streptomyces scabies* on potatoes [16] and *Clavibacter michiganensis* in maize seeds [17].

Biocontrol products based on phages have also been commercialized. The AgriPhage™ product line (Omnilytics, Sandy, UT, USA) includes four commercial products based on bacteriophages that control bacterial spots and specks caused by *Xanthomonas campestris* pv. *vesicatoria* and *Pseudomonas syringae* pv. *tomato*, tomato bacterial canker caused by *Clavibacter michiganensis* subsp. *michiganensis*, fire blight caused by *Erwinia amylovora*, and citrus canker caused by *Xanthomonas citri* subsp. *citri*. Erwiphage Plus™ (Enviroinvest, Pécs Hungary) is another commercial product based on bacteriophages. It contains a mixture of bacteriophages for controlling fire blight in apple trees. Biolyse-PB™ from APS biocontrol is another commercial product based on a mixture of different bacteriophages designed to control f soft-rot bacteria in potatoes.

Using phages to control bacterial diseases in plants and foodborne bacteria is an emerging technology. Despite the advantages that phage therapy presents, some problems that limit the effective control of plant diseases have been reported. These limitations include the sensitivity of phages to UV light and other environmental factors, the likelihood of phages encountering and infecting susceptible hosts, and the possible negative impact on beneficial bacteria, which should be considered in each specific case when designing an effective and stable formulation.

2.2. Destruction of Bacterial Pathogens by Predatory Bacteria

Predation is one of the most common forms of antagonism between microorganisms in nature [44]. Some bacteria behave as microbial predators, killing others and using their remains for nutrition. Predatory bacteria belong to a variety of phyla (mainly Proteobacteria,

Bacteroidetes, and Cyanobacteria) and have been isolated from diverse environments [45]. Three main predatory strategies have been described for these bacteria: epibiotic, endobiotic, and group attack.

The first group includes bacteria that attach to the cell walls of their prey and feed from nutrients present in the periplasm or cytoplasm. *Vampirovibrio chlorellavorus*, a non-photosynthetic *Cyanobacteria*, is an example of this class of predatory bacteria. Its prey is the microalga *Chlorella vulgaris*, to which it remains attached and feeds until binary division occurs [18].

The second group of predatory bacteria is composed of endobiotic predators that penetrate the cells of their prey, occupy their cytoplasm, consume the cell contents, and then replicate. The prey cell is then lysed, and the predator's progeny are released into the environment. Bacteria from the genera *Daptobacter* and *Bdellovibrio* are examples of cytoplasmatic and periplasmatic endobiotic predators, respectively. *Bdellovibrio* and similar organisms (BALOs) can invade other living Gram-negative bacteria, including various phytopathogenic bacteria. The range of prey for these bacteria is dependent on the specific species and strains of each predatory bacterium. For example, eight strains of *B. bacteriovorus* isolated from rice ecosystems exhibited different prey ranges when co-cultured with different species of rice pathogenic bacteria in vitro [46]. Studies have also assessed the biocontrol efficiency of these types of predatory bacteria using in situ assays. Odooli et al. [19] reported the predatory activity of *Bdellovibrio bacteriovorus* strain SOIR-1 on *Xanthomonas campestris* and *Pantoea* sp. and the effective control of rots caused by both pathogens on potato slices and onion bulbs, respectively. Another example of the biocontrol efficacy of *B. bacteriovorus* was reported by Youdkes et al. [20], who demonstrated that two strains of this species preyed on *Pectobacterium carotovorum* subsp. *brasilense* and could effectively control rot caused by this bacterium on potato slices.

The third group of predatory bacteria includes those that attack prey cells using a collective strategy. In this case, predatory bacteria approach the prey in swarming groups using gliding motility and produce hydrolytic enzymes and secondary metabolites that degrade and kill the prey cells. The contents of prey cells are then released into the environment and used as nutrients by the predatory bacteria and other microorganisms present in the surroundings. The close proximity between the predator and prey is needed for this process, and the efficiency of such a strategy seems to be dependent on the density of the predatory bacteria's population [47]. *Myxobacteria* (Deltaproteobacteria) and *Lysobacter* spp. (Gammaproteobacteria) are representatives of this type of predatory bacteria. *Myxobacteria* are Gram-negative bacteria that are widely distributed in soil and capable of multicellular morphogenesis. They can function as collective predators of many phytopathogenic bacteria and fungi and have strong resistance to environmental stresses, so their potential as biocontrol agents of plant diseases is currently being explored. For example, *Myxococcus xanthus* R31, a predatory myxobacterium, has been reported to have strong antagonistic activity against *R. solanacearum* and control tomato wilt caused by this pathogen in pot experiments [21].

2.3. Mycophagy

2.3.1. Mycophagous Bacteria

Several species of bacteria exhibit mycophagous activity, defined as the ability to use living fungi as a nutritional source. *Corallococcus* sp. strain EGB is an example of a bacterium that exhibits mycophagy against a variety of phytopathogenic fungi, including *Verticillium dahliae*, *Fusarium oxysporum*, and *Magnaporthe oryzae* [48]. Its mycophagous ability seems to rely on a β-1,6-glucanase localized in its outer membrane. Similarly, *Collimonas fungivorans*, a chitinolytic bacteria, was shown to grow in sterile sand only when mycelia from live fungi were added to the sand medium [49]. Kamilova et al. [50] also reported the ability of an isolate of *C. fungivorans* to colonize hyphae of *Fusarium oxysporum* f. sp. *radicis-lycopersici* in vitro when both species were cultured on agar lacking a carbon source but not when co-cultured on a nutrient medium. They also observed that the

bacterial isolate effectively controlled the development of foot and root rot caused by this fungal pathogen on tomato plants in pots under greenhouse conditions. *C. fungivorans* colonized tomato roots under these conditions but did not attach to the fungal hyphae of the pathogen. Therefore, the authors postulated that the biocontrol activity was due to niche competition rather than mycophagous activity. Other mechanisms, such as nutrient competition, mineral weathering, or the production of antifungal compounds, have also been suggested to be involved in fungal inhibition by *Collimonas* spp. [51]. Mycophagous activity seems to be expressed only when nutrients are scarce, so the role of this ability in the biocontrol of fungal pathogens requires research in each particular case. Moreover, the influence of mycophagous bacteria on beneficial fungi, such as mycorrhizal fungi, also needs to be evaluated.

2.3.2. Mycophagous Yeasts

Some yeasts have also been reported to exhibit mycophagy of other yeasts and filamentous fungi. The predatory activity of yeasts over yeasts has been reported in species of the genus *Saccharomycopsis* [52]. In that study, direct contact between predatory yeasts and prey cells was observed to be mediated by haustoria or pegs emitted by the former. Pimenta et al. [23] explored the ability of *Saccharomycopsis schoenii*, a predatory yeast, to control the incidence of fungal rots in oranges and apples during postharvest storage. They reported a significant reduction in the incidence and severity of rot caused by *P. digitatum* in oranges and *P. expansum* in apples by this yeast. Microscopic observations indicated that hyphae and spores of pathogens were preyed upon by the yeast and that mycophagy was typically initiated via the adhesion of the predatory yeast cells to the surface of the fungal hyphae. Recently, Ferraz et al. [24] reported the ability of the yeast *Wickerhamomyces anomalus* LBCM1105 to inhibit *Moniliophthora perniciosa*, the causal agent of Witches' Broom Disease, in a manner that resembled predation. They suggested a collective action of yeast occurs, forming a network of interconnected cells that adhere to hyphae and then feed upon their cellular content.

The use of predatory yeasts as biocontrol agents for microbial diseases of plants is an interesting strategy that needs further investigation. The lack of involvement in the production of antimicrobial compounds is notable as it precludes concerns about the contamination of vegetable products with toxic, allergenic, or antibiotic substances.

2.3.3. Mycoparasitism

Mycoparasitism, also known as fungal mycophagy [53], is a lifestyle in which fungi parasitize other fungi. In this type of interaction, which can be biotrophic or necrotrophic, one living fungus acts directly as a nutrient source for another [54].

Biotrophic Mycoparasitism

In biotrophic mycoparasitism, the parasite depends on a living host and obtains nutrients from host cells without killing them. Both host and parasitic fungi interact in a stable and balanced manner [55]. The best-known biotrophic mycoparasites are *Ampelomyces* spp. [56]. The ability of these fungi to control powdery mildews, caused by different species in the family Erysiphaceae, on economically important crops has been extensively reported. Many examples of the biocontrol activity of *Ampelomyces* spp. have been reviewed by Manjunatha et al. [57].

Ampelomyces spp. is a safe biocontrol agent with no antagonist effects on beneficial microbiota since it has a unique and specific mode of action (biotrophic mycoparasitism). This mycoparasite requires a pre-existing infection of plant tissues by the pathogen in order to parasitize it. This is a notable characteristic since most biopesticides do not exhibit curative properties and must be applied prior to the occurrence of an infection to be effective. Notably, in the case of biotrophic mycoparasites, the risk of the development of resistant pathogenic strains is reduced. At present, several biofungicide products based on *Ampelomyces* spp. strains, such as AQ10® (Ecogen Inc., Langhome, PA, USA) and Q-fect®

(Green Biotech, Paju-si, Korea), have been commercialized and are available in several countries [58].

Necrotrophic Mycoparasitism

In contrast to biotrophic mycoparasites, necrotrophic parasites invade host spores or hyphal cells after killing them. They usually have a wide host range, often including a variety of fungal plant pathogens.

Certain genera of Hypocreales (class Sordariomycetes), especially *Trichoderma* and *Clonostachys* (formerly *Gliocladium*), are among the best-studied mycoparasitic fungi. These fungal genera are the active ingredients in several commercial formulations developed for the biocontrol of a variety of fungal plant pathogens. The products include Promot WP® (JH BiotechInc., Ventura, CA, USA) and Trichosoil® (Lage y CIA, S.A., Montevideo, Uruguay), among several others, with *Trichoderma* spp. as the active ingredient, and Lalstop G46® WG (Lallemand Plant Care, Milwaukee, WI, USA) with *Clonostachys* spp. as the active ingredient. *T. virens*, *T. atroviride*, and *T. asperellum*, species from the *T. harzianum* complex, as well as *Clonostachys rosea*, are highly efficient at overgrowing and killing their fungal prey. *Trichoderma* mycoparasites have wide host ranges that include plant pathogens such as the basidiomycete *Rhizoctonia solani*, ascomycetes such as *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Alternaria alternata*, and *Fusarium* spp., and also oomycetes such as *Pythium ultimum* [26]. *Trichoderma* spp. can also parasitize and degrade sclerotia of phytopathogens, such as *Sclerotinia sclerotiorum* and *Sclerotium rolfsii* [59,60]. *Trichoderma* species are relatively resistant to abiotic stress and also have the ability to colonize and degrade fungal structures other than hyphae, such as *Giberella zeae* perithecia in wheat straw, resulting in a reduction of the primary inoculum source of Fusarium head blight [61]. Another example of a parasite of sclerotia-forming plant pathogens is the fungus *Coniothyrium minitans*. It is considered an obligate mycoparasite since it cannot grow in soil as a saprotroph, although it can survive in a dormant state for several years [62]. A commercial product, Contans® WG (Bayer), based on this mycoparasite has been developed [58]. Mycotrophic properties of *Trichoderma* and *C. rosea* [63] are similar; however, they have developed different strategies. *Trichoderma* species are invasive mycoparasites that attach to their prey, coil around their hyphae, and form appressoria-like structures to penetrate them [64,65]. While *C. rosea* has a similar strategy, the formation of appressoria by *C. rosea* has not been verified [66–68].

Mycoparasitism is a complex, multistage process, which, in the case of *Trichoderma* spp., has been extensively studied. The parasite is attracted by the prey, probably through chemotropism [69]. Once in contact with the prey, specific lectins from the cell surface of the prey foster parasite attachment and its coiling around the prey hyphae [70,71]. Hydrolytic enzymes, such as chitinases, β-1,3-glucanases, and proteases are then produced by the parasite to permeabilize and degrade the fungal cell wall of the prey. The parasite then penetrates the prey cells and utilizes its intracellular content as nutrients [72].

The mycoparasitism of *Trichoderma* and *Clonostachys* species is at least partly effective because of the strong ability of these fungi to produce and release many antifungal secondary metabolites, which in several cases also exhibit plant growth-promoting and plant resistance-inducing activities [73]. Numerous secondary metabolites have been reported to be produced by *Trichoderma* species, including nonribosomal peptides, polyketides, terpenoids, steroids, and pyrones. Genome analyses have revealed that mycoparasitic *Trichoderma* species and *C. rosea* are especially enriched in secondary metabolism-related genes, relative to other filamentous ascomycetes [72].

During the mycoparasitic interaction, the fungal prey usually responds to the attack by secreting secondary metabolites, enzymes, and reactive oxygen species. Thus, a successful mycoparasite must be able to cope with this counterattack [26]. For example, *F. graminearum*, which causes Fusarium head blight and foot rot in wheat, produces zearalenone (ZEA), which has strong antifungal properties [74]. *C. rosea* has been shown to tolerate ZEA when interacting with *Fusarium graminearum* by producing a ZEA-detoxifying enzyme and ABC transporters that release ZEA and its degradation products from its fungal cell. Further,

a predator must protect itself against its own enzymes during the interaction with its host. For example, in *Trichoderma* cf. *harzianum*, the cell wall-bound protein Qid74 has an important role in cell protection. Mutants without a Qid74 gene are more sensitive to lytic enzymes. However, so far, the information is limited about the mechanisms involved [75].

2.4. Hypovirulence of Fungal Pathogens Caused by Mycoviruses

Mycoviruses are viruses that infect fungi and replicate only within the fungus' cells. Most mycoviruses lack an extracellular phase in their life cycles. They can be transmitted intracellularly during cell division or sporogenesis in the same thallus or via hyphal fusion between vegetatively compatible strains of the same species [76].

Mycoviruses are widely distributed throughout the major taxonomic groups of fungi. More than 300 genomes of mycoviruses have been sequenced and deposited in the NCBI database. Most of them have linear double-stranded RNA (dsRNA), some are made of positive linear single-stranded RNA, and only a few contain negative linear single-stranded RNA or circular single-strand DNA.

In most cases, mycoviral infections are symptomless, but sometimes they are associated with advantageous or deleterious phenotypic changes in the host fungus. The presence of certain mycoviruses in some phytopathogenic fungi results in hypovirulence. The best-studied examples of mycoviruses responsible for producing a hypovirulent phenotype in a plant pathogenic fungus are the hypoviruses of *Chryphonectria parasitica*, the causal agent of chestnut blight. In the early 1950s, chestnut trees infected by *C. parasitica* in Genoa, Italy, were observed not to be killed, and the lesions induced on the stems by the pathogen healed without additional treatment. It was found that the pathogen was restricted to the outer layer of the bark. Isolates obtained from those trees exhibited reduced virulence and were able to eliminate existing blight lesions and symptoms when inoculated into cankers [77]. Subsequently, these hypovirulent strains that were effective biocontrol agents of chestnut blight were found to harbor mycoviruses. Since then, considerable research has been conducted on mycoviruses, and fungi bearing them have been considered potential tools for biocontrol [78]. Many hypovirulence-associated mycoviruses have been described in diverse species of plant pathogenic fungi, such as *Fusarium graminearum* [79], *Magnaphorte oryzae* [80], *Rosellinia necatrix* [81], *Penicilliun digitatum* [82], *Alternaria alternata* [79], and *Botryosphaeria dothidea* [83]. Hypovirus FGHV2, a mycovirus inhabiting *F. graminearum*, reduces mycelial growth rate and the synthesis of deoxynivalenol [79], a mycotoxin frequently found in infected wheat grains. Hypoviruses, such as SsHV1 and SsHV2, have been found in strains of *Sclerotinia sclerotiorum* [27,28]. This is a fungal pathogen that infects more than 400 species of plants and also harbors a wide diversity of mycoviruses, including dsRNA and single-stranded RNA viruses and one single-stranded circular DNA virus [84]. SsBRD2 in the family *Botybirnaviridae* induces hypovirulence in its associated fungus, reduces fungal growth in the host, and prevents sclerotia production, which makes fungi harboring this virus great potential candidates for biocontrol agents [85].

The use of mycoviruses in the biocontrol of fungal plant pathogens involves their transmission from a hypovirulent (bearing the virus) to a virulent fungal strain. Mycoviruses do not generally have an extracellular phase and are transmitted by hyphal anastomosis, which only occurs between fungal strains of the same vegetative compatibility group. However, methods of artificial transfection between unrelated fungal species have been explored to overcome this limitation. Transfection of fungal protoplasts with purified virions obtained from a hypovirulent strain of a different vegetative compatibility group or even a different fungal species has been successful. For example, virions of a partitivirus obtained from a hypovirulent strain of *S. sclerotiorum* were transfected into *B. cinerea* protoplasts and reduced the virulence and conidial germination of *B. cinerea* in its host plant [86]. MyRV3, a mycoreovirus from *Rosellinia necatrix*, was successfully introduced into protoplasts of other phytopathogenic fungi, including *Diaporthe* sp., *C. parasitica*, and *V. ceratosperma*, conferring hypovirulence to the new hosts, as it did to *R. necatrix* [87]. A double-stranded RNA mycovirus associated with hypovirulence in *Fusarium boothi* was also transmitted

via protoplast fusion to *F. graminearum*, *F. asiaticum*, *F. oxysporum* f. sp. *lycopersici*, and *Cryphonectria parasitica* [88]. In all cases, the recipient strains exhibited reduced growth rates, altered pigmentation, and hypovirulence.

Currently, no biocontrol products based on hypovirulent strains bearing mycoviruses are commercially available [89]. However, continued advances in mycovirus research suggest that successful applications of mycoviruses for the biological control of plant diseases are feasible and that commercial products will be forthcoming.

2.5. RNAi-Based-Biocontrol Strategies

RNA interference (RNAi) has become a potential solution for creating biological control methods that are sustainable and have a high degree of specificity in targeting plant pests and pathogens. RNAi is a mechanism present in eukaryotes that can silence genes by breaking down messenger RNA (mRNA) through the interaction with double-stranded RNA (dsRNA) molecules. This process was first observed in *Caenorhabditis elegans* [90] and involves the processing of dsRNA by Dicer enzymes into short dsRNA molecules named small interfering RNAs (siRNAs). These siRNAs can either silence genes by blocking transcription or by breaking down mRNA, resulting in a loss of protein function that can lead to reduced growth or even the death of the organism. It has also been shown that RNAi can work across different species, including plants and animals [91,92]. Thus, RNAi-based control methods differ from traditional pesticides in that they exploit the molecular mechanisms of the targeted pests themselves to silence crucial genes and control their population rather than relying on external, less-specific chemicals to combat them.

There are two approaches used to take advantage of the RNAi mechanism in order to control plant pathogens in a targeted manner. The first one is called host-induced gene silencing (HIGS), which involves introducing specific interfering RNAs into the plant through genetic modification to provide resistance against a particular pathogen. The second approach is spray-induced gene silencing (SIGS), which uses dsRNA molecules applied to the plant to silence genes in the pathogen. HIGS makes use of RNAi across different kingdoms to manage plant diseases. This is achieved by genetically modifying plants so that they produce RNAs that target the genes of the pathogen, leading to the silencing of these genes and making the plant resistant to the disease [93]. Using HIGS provides durable protection to plants and enables the silencing of various genes from different pathogens that are significant to fungi and oomycetes, such as *Fusarium* [94], *Puccinia* [95], or *Phytophthora* [96]. However, this method can be difficult, time-consuming, and challenging to regulate, and its effectiveness is influenced by the host plant's ability to be modified. Due to these factors, only a few HIGS-based products are available in the crop protection market.

In contrast to HIGS, SIGS is a non-genetically modified method that is significantly faster, less expensive, and simpler to manage. This method is a safe and potent way to protect pre-harvest crops and post-harvest products against a wide range of pathogens, such as viruses [97,98], insects [99,100], fungi [101,102], and oomycetes [103] that efficiently incorporate dsRNA. One significant disadvantage of SIGS is the limited stability of RNA in the environment, particularly under field conditions where physical barriers such as UV light, rainfall, and high humidity hinder the entry of externally applied dsRNA into plant leaves. To address this problem, one approach is to attach RNAs to chemically modified substances. As a result, significant progress has been made in producing RNA sprays that are stable in the field and reduce the risk of unintended harm to non-target organisms. Various methods of applying exogenous foliar treatments have been tested and proven effective. These methods include delivering dsRNA using techniques such as liposomes [104], nanoparticles [105], and clay nanosheets (BioClay) [106,107].

The wide spectrum of successful RNAi studies targeting plant pests indicates that dsRNA has the potential to address the limitations of controlling agricultural pests. However, there are additional challenges that need to be addressed, such as the efficiency of dsRNA uptake by plants, the practicality of field applications, environmental safety risks,

and the acceptance of spray-delivered RNAs by regulatory bodies and communities. These challenges require careful consideration and clarification before RNAi-based biocontrol strategies can be widely used commercially. Bayer Crop Science began the "BioDirect" program by creating RNA-based substances to manage insect pests such as the Colorado potato beetle, Brassica flea beetle, and Varroa mites, pathogens such as Tospovirus, and glyphosate-resistant weeds. In particular, the product formulated to tackle *Varroa destructor* was the first exogenously applied dsRNA biopesticide active ingredient submission made to the U.S. EPA in the industry. The commercial appeal of RNA applications to big companies has encouraged the emergence of start-ups that use new or existing biotechnology tools to develop platforms and technologies for the agriculture industry. For instance, companies such as Genolution or GreenLight Biosciences have created technologies that allow for the cost-effective mass production of dsRNA. In this sense, GreenLight Biosciences has successfully conducted large-scale assessments using its product Ledprona, which provides protection against the Colorado potato beetle, Leptinotarsa decemlineata. Thus, in the near future, it is expected that further products will be developed and sold to tackle other pests and pathogens.

3. Interaction between Pathogens and Biocontrol Agents without Physical Contact

Microbial antagonists can exert biocontrol activity by outcompeting pathogens for resources as well as indirectly inhibiting pathogen development or pathogen effectors. These activities involve competition for nutrients or space, the production of antimicrobial metabolites, and the suppression of virulence factors (Table 2).

Table 2. Different modes of action of biocontrol agents on different crops that do not involve direct physical contact with the pathogen.

Mechanism of Action	Biocontrol Agent	Pathogen	Crop	Reference
Pathogen inhibition by primary metabolites	Lactic acid produced by *Lactobacillus plantarum*	*Pseudomonas syringae* pv. *actinidiae* *Xanthomonas arboricola* pv. *pruni* *Xanthomonas fragariae* in strawberry	Kiwifruit Prunus Strawberries	Daranas et al., 2019 [108]
Pathogen inhibition by antibiotics	Pyoluteorin and 2,4-diacetylphloroglucinol produced by *Pseudomonas protegens*	*Botrytis cinerea*	Cannabis	Balthazar et al., 2022 [109]
	Phenazine-1-carboxylic acid (PCA) produced by *Pseudomonas fluorescens* LBUM223	*Streptomyces scabies*	Potato	Arseneault et al., 2015 [110]
Pathogen inhibition by bacteriocins	BacGM17 produced *by Bacillus clausii* GM17	*Agrobacterium tumefaciens*	-	Mouloud et al., 2013 [111]
	Thuricin Bn1 secreted by *Bacillus thuringiensis subsp. kurstaki Bn1*	*Pseudomonas savastanoi* and *Pseudomonas syringae*	-	Ugras et al., 2014 [112]
	Amylocyclicin produced by *Bacillus amyloliquefaciens subsp. plantarum* FZB42	*Clavibacter michiganensis*	-	Scholz et al., 2014 [113]
	Nisin produced by Lactic acid bacteria	*Clostridium botulinum*, *Bacillus cereus*, *Listeria monocytogenes*, and *Staphylococcus aureus*	-	Balciunas et al., 2013 [114]

Table 2. *Cont.*

Mechanism of Action	Biocontrol Agent	Pathogen	Crop	Reference
Pathogen inhibition by killer toxins	*Debaryomyces hansenii* MI1a, *D. hansenii* K12a and *Wickerhamomyces anomalus* BS91	*Monilinia fructigena* and *Monilinia fructicola*	Stone fruit	Grzergorczyk et al., 2017 [115]
	Schwanniomyces sp., *Galactomyces* sp., and *Rhodotorula* sp.	*Monilinia fructigena*, *Monilinia fructicola*, and *Aspergillus niger*	Apples	Madbouly et al., 2020 and Czarnecka et al., 2019 [116,117]
	Issatchenkia orientalis strains 17C2 and 16C2	*Aspegillus carbonarius* and *Aspergillus niger*	Grapes	Bleve et al., 2006 [118]
Pathogen inhibition by volatile organic compounds with antimicrobial activity	*Bacillus* sp. and *Enterobacter* sp.	*Botrytis cinerea*, *Colletotrichum heterostrophus*, and *Setosphaeria turcica*	Tobacco and maize plants	Chung et al., 2016; Vlassi et al., 2020 [119,120]
	Candida sake	*Penicillium expansum*, *Botrytis cinerea*, *Alternaria alternata*, *Alternaria tenuissima*, *and Alternaria arborescens*	Apples	Arrarte et al., 2017 [121]
	Vishniacozyma victoriae	*Phlyctema vagabunda*	Apples	Sepúlveda et al., 2022 [122]
Competition for resources	***Competition for*** *nitrogen:* *Cryptococcus laurentii* 317 and *Candida ciferrii* 283	*Penicillium expansum*	Apples	Vero, et al., 2002 [123]
	Competition for iron: rhodotorulic acid produced by *Rhodotorula glutinis*	*Penicillium expansum* *Botrytis cinerea*	Apples	Calvente et al., 2001 Sansone et al., 2005 [124,125]
	Competition for space: *Leucosporidium scottii*	*Penicillium expansum* *Botrytis cinerea*	Apple	Vero et al. 2013 [126]
Inhibition of virulence factors by elimination of quorum sensing signals	AHL lactonases produced by *Mesorhizobium* sp. and *Lysinibacillus* sp.	*Pectobacterium carotovorum* subsp. *carotovorum*	Potato, carrot, and cucumber	Mahmoudi et al.,2011; Garge and Nerurkar, 2016 [127,128]

3.1. Production of Antimicrobial Compounds

Microorganisms can produce diffusible or volatile metabolites that inhibit the growth of other bacteria and fungi, including plant pathogens. In some cases, primary metabolites such as ethanol, or lactic and acetic acid are responsible for inhibiting pathogens. Daranas et al. [108] demonstrated the role of lactic acid produced by a selected strain of *Lactobacillus plantarum* in the prevention of bacterial diseases in kiwifruit, *Prunus* species, and strawberries. Lactic acid bacteria have also been reported to be effective in the preservation of ensiled grains, partly due to the production of lactic and acetic acids and partly due to the production of bacteriocins and other secondary metabolites [129].

Notably, however, most antimicrobial compounds involved in biocontrol are secondary metabolites, produced once the growth of a microbial antagonist has reached a stationary phase. The presence of antimicrobial metabolites can be readily detected using dual cultures under laboratory conditions. Since the production and concentration of antimicrobial compounds are dependent on the growth conditions provided to the producing microorganism, their role in biocontrol activity should be verified at the site where biocontrol activity is expected to occur.

Antimicrobial compounds produced by biocontrol agents can be volatile or non-volatile. We present examples of both types of compounds and discuss their mode of action

and scope. Among non-volatile compounds, information on antibiotics, bacteriocins, and killer toxins is reviewed.

3.1.1. Non-Volatile Antimicrobial Compounds

Antibiotics

Antibiotics are low-molecular-weight organic compounds synthesized by microorganisms (bacteria or fungi) that, at low concentrations, kill or inhibit the growth of other microorganisms [130,131]. Peptides that are not ribosomally synthesized and contain a limited number of amino acids are also included in this category [132].

Many biocontrol agents have been selected for their ability to inhibit phytopathogens by producing antibiotics. Species in several genera of bacteria, mainly *Bacillus*, *Paenibacillus*, *Burkholderia*, *Pseudomonas*, *Pantoea*, and *Streptomyces*, have been shown to produce chemically diverse antibiotics with different scopes of action [133–135]. For example, *Pseudomonas* species can produce a variety of different antibiotics, including phenazines, phloroglucinols, dialkylresorcinols, pyoluteorin, and pyrrolnitrin [136]. Some species, such as *P. fluorescens*, can also produce non-ribosomally synthesized lipopeptides with antimicrobial and biosurfactant activity [137]. Several species of *Bacillus* and *Paenibacillus* can produce lipopeptides such as iturins, fengicins, surfactins, and polymyxins with antibacterial and antifungal activity [138]. These amphiphilic molecules damage the cell membranes of other microorganisms inducing the formation of pores that facilitate the leakage of intracellular contents and subsequent death. *Streptomyces* spp. have also been recognized as effective biocontrol agents for many fungal and bacterial phytopathogens. Their inhibitory activity involves the production of diverse antibiotics with a broad scope of action [139]. For example, Suarez-Moreno et al. [140] reported that an isolate closely related to *S. racemochromogenes* has a very wide range of activity, exhibiting antimicrobial activity against 20 bacterial species and 9 phytopathogenic fungi. They reported that the isolate produced several antimicrobial compounds with a molecular mass <3 kDa and identified three of them as streptotricins.

Fungi also produce antibiotics. Peptaibols produced by *Trichoderma* spp. are an example of antimicrobial compounds that contribute to the biocontrol of fungal plant pathogens. They are amphipathic, short, non-ribosomally synthesized peptides that also contain some non-proteinaceous amino acids. Their antimicrobial action is due to their ability to form ion channels and permeabilize the lipid bilayer membranes of cells [141]. Members of the genus *Clonostachys* also produce a diverse array of secondary metabolites with antimicrobial properties that have pharmaceutical and agrochemical applications [142]. For example, the role of non-volatile antimicrobial compounds produced by *C. rosea* to inhibit the fungus *B. cinerea* has been confirmed both in vitro and on tomato stems [143].

Antibiotics have lethal or inhibitory effects on target microorganisms at specific concentrations. Those concentrations can be easily achieved in culture media under laboratory conditions. Therefore, the selection of antibiotic-producing microorganisms active against phytopathogens in dual cultures is relatively simple. Antibiotic concentrations on plant surfaces or in the soil, however, are considerable if not exponentially lower than those obtained in culture media [144]. Despite this difference, the role of antibiotics produced by biocontrol agents in the suppression of many plant diseases *in planta* has been confirmed through the use of mutant strains that are unable to produce antibiotics and do not suppress disease symptoms [109].

Studies have shown that even subinhibitory concentrations of antibiotics can affect both the producer and target microorganisms. Low concentrations of antibiotics can enhance the fitness of the producing strains by regulating biofilm formation, cell differentiation, motility, and resistance to predation, as well as intra- and intersignaling and communication with plants [145–147]. In these situations, antibiotics do not have direct antimicrobial activity against the pathogen but rather promote plant health by stimulating the plant itself or by enhancing the growth of the antibiotic-producing bacterium, which may then exert biocontrol activity through other mechanisms. For example, surfactin, a cyclolipopeptide produced by *Bacillus subtilis*, induces the formation of biofilms that pro-

vide a survival advantage to the bacterium in natural habitats [148]. During the formation of biofilms, a subpopulation of *B. subtilis* cells differentiates and secretes toxins that are lethal to undifferentiated bacterial cells. The cellular contents of dead cells are then used as nutrients by the differentiated cells, which are resistant to toxins. These cells then secrete the extracellular matrix used to form the biofilm. Notably, the coordinated expression of cannibalism and matrix production in a subpopulation of cells is triggered by surfactin. Other antimicrobial metabolites, such as nystatin, amphotericin, valinomycin, and gramicidin, can also induce differentiation and biofilm production in *B. subtilis* [149]. Similar cannibalism-mediated biofilm formation has been detected in *Bacillus velezensis*, in which bacillunoic acid, an antimicrobial compound, plays an important functional role [150].

Sub-inhibitory concentrations of antibiotics can also reduce pathogen virulence. Arseneault et al. [110,151] demonstrated that sub-inhibitory concentrations of phenazine-1-carboxylic acid (PCA) produced by *P. flourescens* LBUM223 reduce the expression of thaxtomin A, a critical virulence factor of *Streptomyces scabies*, the causal agent of common scab of the potato. Arsenault and Filion [146] reported that the antibiotic reduces the appearance of disease symptoms and modulates the *S. scabies* transcriptome in the geocaulosphere relative to the transcriptome exposed to a non-producing PCA mutant of *P. flourescens* LBUM223.

Low concentrations of antibiotics can also enhance plant growth and the activity of beneficial bacteria. A secondary metabolite with antimicrobial properties, 2,4-diacetylphloroglucinol (DAPG), produced by fluorescent *Pseudomonas* spp., can induce systemic resistance in host plants [152], and stimulate root exudation of amino acids [153], as well as branching of the root system [154,155]. This metabolite also induces the expression of *Azospirillum* genes involved in root colonization and plant growth promotion [156].

Subinhibitory concentrations of antibiotics can also affect target microorganisms. Exposure of receiver microorganisms to subinhibitory concentrations can induce a stress-on-stress (SOS) response (a global response to DNA damage), which is associated with various antibiotic resistance mechanisms. As a result, antibiotic tolerance can be induced in the recipient microbial community [157].

As previously indicated, antibiotics can modulate the interaction between plants, pathogens, and biocontrol agents in many different ways, which may or may not benefit plant health. Selecting a biocontrol agent solely based on antibiotic production, however, may be shortsighted since selection pressure could result in the appearance of resistant pathogen strains.

The first case of the appearance of resistance to antibiotics produced by biocontrol agents was described in *Agrobacterium tumefacienes*, the causal agent of crown gall. This pathogen was successfully controlled using *A. radiobacter* strain K84, which produced the antibiotic agrocin. The biocontrol bacteria harbor a plasmid that encodes resistance to agrocin and the mobility of this plasmid to other bacteria. The plasmid was eventually transferred to plant-pathogenic strains of *Agrobacterium tumefaciens*, making them resistant to agrocin [158]. To address this problem, the biocontrol bacterium was subsequently genetically modified to prevent plasmid mobility. The modified strain was called K1026 and is used in commercial formulations that are currently available in many countries, including the USA [159]. Since this formulation contains genetically modified bacteria, however, its use is not allowed in many other countries, including those in the European Community and some countries in South America.

Ajouz et al. [160] obtained *B. cinerea* strains with reduced sensitivity to pyrrolnitrin after growing successive generations in the presence of sublethal concentrations of the antibiotic. Strains with resistance factors higher than 1000 were obtained using increasing concentrations of pyrrolnitrin. Loss of resistance did not occur even after growing ten generations of the resistant variants in the absence of pyrrolnitrin, indicating that the resistance was relatively stable. Notably, the resistant variants exhibited reduced growth in culture and decreased virulence in plants. The observed decrease in fitness indicates that

the resistant variants would be unlikely to prevail without selection pressure. The potential appearance of resistant variants, however, should not be neglected.

Many bacterial and fungal biocontrol agents that represent the active ingredient of commercial products approved by the EU and USA are antibiotic producers, but they also exhibit other mechanisms of action such as competition, defense induction in host plants, and mycoparasitism. *Bacillus amyloliquefaciens* strains D747 and MBI600, the active ingredients of Amylo-X® and Serifel® and *Trichoderma asperellum* T34 formulated as T34 Biocontrol® are examples of such microorganisms [58]. They have been classified by the Fungicide Resistance Action Committee (FRAC) as BM02 fungicides, which include microorganisms with multiple modes of action. Importantly, the existence of multiple modes of action lowers the risks associated with the appearance of resistant pathogen strains.

Bacteriocins

Bacteriocins are ribosomally synthesized peptides with antimicrobial activity secreted by a variety of Gram-positive and Gram-negative bacteria to eliminate other bacteria, especially closely related species [161,162]. Bacteriocins exhibit a variable spectrum of antimicrobial activity. Some are rather specific, while others have a broad spectrum of activity that includes activity against certain fungi and viruses [163,164] The mechanism of action of bacteriocins depends on their structure. Some bacteriocins exert their activity by disrupting the membrane integrity of sensitive bacteria, causing cell lysis, while others enter sensitive cells and affect specific intracellular targets [165].

Various members of *Bacillus* spp. are known to produce bacteriocins.; *B. clausii* GM17 produces BacGM17, a bacteriocin that inhibits *Agrobacterium tumefaciens* [111]; and *B. thuringiensis* subsp. *kurstaki* Bn1 secretes thuricin Bn1, which has inhibitory activity against *Pseudomonas savastanoi* and *Pseudomonas syringae* [112]. *B. amyloliquefaciens* subsp. plantarum FZB42, the active ingredient of AmyProtect 42®, produces the cyclic bacteriocin amylocyclicin, which has inhibitory activity against certain Gram-positive bacteria, including various subspecies of *Clavibacter michiganensis* that specifically infect the xylem vessels of economically important host plants [113]. Lactic acid bacteria are also able to produce bacteriocins, such as nisin, which is used as a food preservative. It has broad-spectrum antimicrobial activity against other Gram-positive bacteria, including *Clostridium botulinum*, *Bacillus cereus*, *Listeria monocytogenes*, and *Staphylococcus aureus*, among others [114].

Gram-negative bacteria also produce bacteriocins that generally have a narrower spectrum of activity than bacteriocins produced by Gram-positive bacteria [166]. Among Gram-negative bacteria, members of *Pseudomonas* spp. are bacteriocin producers [133]. These bacteriocins, including different types of pyocins, have inhibitory activity against closely related species [133]. For example, Lavermicocca et al. [167] purified a bacteriocin produced by *P. syringae* pv. *ciccaronei*, which inhibited the growth in vitro and *in planta* of *P. syringae* subsp. *savastanoi*, the causal agent of olive knot disease. Additional studies on biocontrol activity using avirulent bacteriocin-producing strains of plant pathogenic bacteria have been reported. Chen and Echandi [168] used an avirulent strain of *Ralstonia solanacearum* that produced bacteriocins to reduce the bacterial wilt of tobacco. An avirulent bacteriocin-producing strain of *Xanthomonas campestris* pv. *oryzae* was reported to reduce the incidence of bacterial leaf streaks in rice plants caused by virulent strains of the same species [169].

Killer Toxins

Killer toxins are proteins secreted by some yeasts that are lethal to susceptible strains [170]. They were first described 60 years ago by Bevan and Makower [171]. Since that time, yeasts have been classified into three killer toxin modes of action classes: killer, sensitive, and neutral. Regarding genotype, initial studies suggested the role of cytoplasmic genetic determinants associated with the synthesis of these killer toxins; however, it has now been reported that a killer toxin can also be chromosomally encoded [172]. Most killer toxins that have been characterized are encoded by chromosomal genes [173]. For example,

toxins produced by killer strains of *Wickerhamomyces*, a widely studied genus in the field of biological control [115,174–177], are chromosomally encoded. Other chromosomally encoded killer toxins have been described in species belonging to the genera *Cyberlindnera*, *Pichia*, *Millerozyma*, *Kluyveromyces*, *Lachancea*, *Williopsis*, and *Tetrapisispora* [172,178]. Killer toxins produced in these genera are commonly associated with membrane permeabilization mechanisms, the production of glucanases, or the inhibition of glucan synthesis in sensitive microorganisms [179].

A well-known example of extra-chromosomally encoded killer toxins are those produced by *Sacharomyces cerevisiae* strains. Some *S. cerevisiae* strains can synthesize so-called K1, K2, or K28 killer toxins. These toxins were extensively researched due to their ability to permeabilize membranes and bind to intracellular targets to block DNA replication.

Killer toxins can be generally classified based on their cellular target. Four categories of killer toxins are recognized [180]. T1 and T2 toxins target cell walls and membrane structures, generating channels or disrupting membrane integrity. Types T3 and T4 act on intracellular targets. They can bind to membrane receptors and translocate into cells, where they inhibit replication or cleave RNAt, preventing its proper functioning. All four categories of killer phenotypes represent a key ecological factor, not only inhibiting but also killing competitive cells, providing a selective advantage to the killer toxin-producing species [172].

Initially, killer yeasts were reported to have a narrow scope of action. More recently, however, killer toxins have been shown to inhibit a wider range of microorganisms, including fungi and bacteria. Thus, the use of killer yeasts has been proposed for several applications, including combating human diseases and controlling fungal contamination of plants and food [180,181].

Killer yeasts have been reported as effective biocontrol agents against pre- and postharvest fungal pathogens. Effective preharvest applications include the work of Santos et al. [179], who isolated a killer toxin (CYC 1106) from *Pichia membranifaciens* that could be used to control *B. cinerea* in preharvest applications. More recently, Liu et al. [182] isolated three killer strains of *S. cerevisiae* from wine that effectively controlled *C. gloeosporioides*, the causal agent of pre-harvest anthracnose in grapes. Additionally, Lopes et al. [183] investigated the activity of killer yeast strains against *C. acutatum*, the causal agent of citrus post-bloom drop disease. They reported that the selected yeasts had both curative and preventive activity in plant assays.

Postharvest uses of killer yeasts as biocontrol agents are more common. Several reports have been published on the identification and application of killer yeasts as antagonists against *Penicillium digitatum* and *P. italicum*, postharvest pathogens of citrus fruit [175–177,184–186]. Killer yeast strains from different species (*Debaryomyces hansenii* MI1a, *D. hansenii* K12a, and *W. anomalus* BS91) have also been reported as effective biocontrol agents against *Monilinia fructigena* and *Monilinia fructicola*, which cause severe losses of stone fruit [115].

There is growing interest in the search for and identification of killer yeasts that can be used as biological control agents against different fungal phytopathogens. Genetic modifications that enhance their killer phenotype or the use of purified killer toxins may represent strategies that can be used to improve or broaden the use of killer yeasts.

3.1.2. Volatile Organic Compounds with Antimicrobial Activity

Volatile organic compounds (VOCs) are low molecular weight (<300 Da) organic molecules with a low polarity and a high vapor pressure ($\geq$0.01 kPa at 20 °C) [187–189]. VOCs include a panoply of molecular classes, including hydrocarbons, alcohols, thioalcohols, aldehydes, ketones, thioesters, alkanes, heterocyclic compounds, phenols, and benzene derivatives [190]. VOCs are produced by a wide range of microorganisms, including bacteria, fungi, and yeast [191]. The chemical composition of each blend of volatiles (the so-called volatilome) may change depending on the producing strain, its ecological niche, and its interactions with other organisms [192,193].

Many VOCs inhibit plant pathogens. In vitro studies on the effect of VOCs produced by bacteria confirmed their ability to inhibit the growth, spore germination, germ tube elongation, and growth of pathogenic fungi such as *Penicillium* spp., *B. cinerea*, and *F. oxyxporum* [194–197]. Chung et al. [119] and Vlassi et al. [120] reported that VOCs emitted by *Bacillus* sp. and *Enterobacter* sp. protected tobacco (*N. benthamiana* D.) and maize (*Zea mays* L.) plants from several pathogenic fungi, such as *Botrytis cinerea*, *Colletotrichum heterostrophus*, and *Setosphaeria turcica*, in greenhouses and open field trials. Bacterial VOCs represent an effective tool that can be used in the biocontrol of diseases caused by fungi on different commodities.

Antifungal VOCs produced by yeasts have also been extensively studied, especially in association with the biocontrol of fungal pathogens during postharvest storage. Arrarte et al. [121] reported that two Antarctic strains of *Candida sake* produced antifungal VOCs that inhibited the in vitro growth of five pathogens of apple (*P. expansum*, *B. cinerea*, *A. alternata*, *A. tenuissima*, and *A. arborescens*). VOCs produced by *C. sake* strains were also effective in controlling *P. expansum* growth in "Red Delicious" apple wounds. The antifungal activity of VOCs produced by the two yeast strains was different, confirming that the volatilome is strain-dependent. Sepúlveda et al. [122] evaluated the antifungal effect of VOCs produced by two *Vishniacozyma victoriae* isolates in dual cultures in different media against *Phlyctema vagabunda*, the causal agent of bull's eye rot in apples. They found that the chemical composition of the volatilome and the inhibitory effect of VOCs on the pathogen were dependent on the type of culture medium, confirming that the growth conditions of the microorganisms affect their volatilome. The chemical composition of volatilomes produced by many biocontrol yeasts growing under different conditions has been characterized. Lipophilic compounds of low molecular weight, mainly alcohols, esters, acids, or ketones derived from primary and secondary metabolism, have been identified [197]. One of those compounds, 2-phenylethanol, has been frequently identified in the volatilome of biocontrol yeasts [198]. Tilocca et al. [199] attempted to determine the specific role of 2-phenylethanol in reducing growth, sporulation, and ochratoxin A biosynthesis in *Aspergillus carbonarius*. They assessed the effect of the whole volatilome produced by the biocontrol yeast *Candida intermedia* 253 on the proteome of a target pathogen proteome compared to the proteome in the presence of just 2-phenylethanol. Yeast VOCs caused a marked reduction in protein biosynthesis, proliferative activity, mitochondrial metabolism, and the detoxification of toxic substances. Similar but milder effects on the proteome of the pathogen were observed in the presence of 2-phenylethanol alone, confirming that other VOCs produced by the yeast were also involved in pathogen inhibition.

Microbial VOCs can be involved in microbial interactions as signaling and quorum-sensing compounds [188]. They can also influence the plant growth-promoting (PGP) activity induced by certain bacteria [200]. Notably, the positive effect of the volatile dimethyl disulfide on plant health has been widely studied [201,202].

VOCs do not require direct contact with pathogens or the matrix that supports their growth to exert their impact; in that sense, they are considered potential safe biofumigants for foods by some authors [121]. However, some VOCs may be extremely hazardous and carcinogenic to human health [203], so they should be unequivocally identified before using VOC-producing microorganisms as biocontrol agents, especially in the postharvest stage. Greater technological improvements are needed to enable their application in preharvest and postharvest disease control.

3.2. Competition for Nutrients or Space So They Should Be Clearly Identified before

Microorganisms sharing the same ecological niche often need to compete for limited resources. This indirect interaction is known as exploitative competition [204].

Competition for limited nutrients and space is a common mode of action for many yeast and bacterial biocontrol agents against postharvest fungal pathogens in fruit wounds [205]. In many cases, nitrogen represents a limiting nutrient [206] and a source of competition. In this regard, Vero et al. [123] and Bencheqroun et al. [207] determined the effect of adding

amino acids to apple wounds on the efficacy of selected biocontrol yeasts against *Penicillium expansum*. They demonstrated that the exogenous addition of amino acids to apple wounds resulted in a significant decrease in biocontrol efficacy by the selected antagonists, thus providing evidence supporting the premise that competition for nutrients, especially amino acids, played a major role in determining biocontrol activity.

In addition to the competition for limited nitrogen, competition for other essential elements has also been reported [204]. Iron is an essential nutrient for all living organisms. While it is the fourth most abundant element in the earth's crust, it is not readily available to living organisms due to its low solubility at pH > 6 [208]. Many microorganisms that have a high affinity for ferric iron secrete iron chelators or siderophores in low-available iron environments [204,209]. In this regard, siderophores form complexes with iron once they are released into the extracellular environment. Such complexes are specifically recognized by receptor proteins within the membrane of the siderophore-producing microorganism, allowing for enhanced uptake of iron into the cell [210]. Siderophore-producing microorganisms should have a distinct advantage as a biocontrol agent in iron-deficient environments [208]. Several studies have reported iron competition by biocontrol agents as a mode of action in the inhibition of postharvest pathogens. For example, Calvente et al. [124] and Sansone et al. [125] reported that rhodotorulic acid, a siderophore produced by *Rhodotorula glutinis*, contributed to and enhanced the control of *P. expansum* and *B. cinerea* on apples.

Competition for space is another parameter that can be used to limit pathogen development. By completely colonizing an area of resource availability, a biocontrol agent can prevent pathogen establishment and infection by limiting resource allocation and by potentially blocking the pathogen from access to germination cues. The biocontrol activity of *Pseudomonas fluorescens* 2P24 on wheat take-all has been demonstrated to be principally controlled by the PcoI-PcoR quorum sensing system, which is involved in the regulation of biofilm formation [211]. Biofilm formation facilitates effective microbial colonization and persistence [204]. It also enhances the stress resistance of the microorganisms embedded in the biofilm, protecting them from adverse physical and chemical agents [212]. Notably, microbial communication is also enhanced in a biofilm, and communication mediated through signaling molecules can enhance biocontrol by inducing the synthesis of antimicrobial metabolites and/or enzymes. For example, a transcriptome analysis conducted by Kröber et al. [213] revealed that the production of an antimicrobial peptide by *Bacillus amyloliquefaciens* FZB42 was upregulated when the microbe had formed a biofilm. The collective evidence presented underscores why the ability to form a biofilm is a beneficial trait when selecting a biocontrol agent. In this regard, biofilm formation has frequently been observed in biocontrol agents selected to protect fruit wounds from pathogen colonization [126,214].

3.3. Inhibition of Virulence Factors of Pathogenic Bacteria by the Elimination of Quorum Sensing Signals

Quorum sensing (QS) is a communication process between microorganisms that involves the production, detection, and response to extracellular signaling molecules called autoinducers (AIs) [215,216]. Briefly, microorganisms produce and release AIs that accumulate outside the cell as the density of the microbial population increases. Microorganisms that produce AIs monitor the accumulation of these chemical signals through specific receptors [217,218]. Once a minimum threshold concentration of Ais is reached, gene expression in producer microbes is altered, and specific activities are induced [219]. Those activities can be associated with defense or attack mechanisms and include bioluminescence, sporulation, competence, antibiotic production, biofilm formation, and virulence factor secretion [220,221]. QS has been well described in bacteria, and more recently, it has also been reported in yeast and fungi. Gram-positive and Gram-negative bacteria utilize different QS systems [219]. Gram-positive bacteria utilize peptides as Ais, while Gram-negative bacteria use smaller molecules that are either acyl homoserine lactones (AHLs) or molecules whose synthesis is based on S-adenosylmethionine (SAM) [211]. In general, the

expression of virulence and pathogenicity factors is initiated as a result of QS; therefore, the disruption of QS represents a feasible strategy for protecting plant hosts against bacterial diseases. The interruption of QS and, thus, intercellular communication is called quorum quenching (QQ) [222], a mechanism that regulates interspecies and even cross-kingdom interactions [216]. QQ can be achieved by different mechanisms, such as inhibiting the synthesis or detection of AIs, enzymatic degradation or modification of signal molecules, or blocking the expression of target genes triggered by QS molecules [216,223,224]. The most studied QQ mechanism is the enzymatic degradation of AHLs (QS molecules). These molecules are highly conserved, exhibiting the same homoserine lactone but differing in the length and structure of the acyl chain [225]. Several enzymes have been reported to facilitate the degradation of AHLs, including AHL acylases, AHL lactonases, AHL oxidoreductases, and AHL oxidases [226,227]. AHL lactonases, which are produced by several microorganisms, have been the most studied [216]. AHL-degrading enzymes have been reported to reduce the virulence of *Pectobacterium carotovorum* subsp. *carotovorum* (Pcc). This Gram-negative bacterium is the causal agent of soft rot and wilt in several crops, including potatoes, carrots, tomatoes, onions, and cucumbers [228]. The pathogenicity of Pcc is dependent on the abundance of plant cell wall-degrading exoenzymes, including pectate lyase (Pel), pectin lyase (Pnl), polygalacturonase (Peh), cellulase (Cel), and protease (Prt) [229]. The production of these exoenzymes is controlled by QS, mainly through AHLs [230]. In this regard, many QQ strains of microorganisms and their AHL-degrading enzymes have been reported to prevent or inhibit the synthesis and accumulation of cell wall-degrading exoenzymes by degrading the quorum signals that induce their production in the pathogen. For example, *Mesorhizobium* sp. and *Lysinibacillus* sp. significantly reduce Pcc pathogenicity and suppress tissue maceration [127,128] through the production of AHL lactonases.

QS have also been described in yeast species, such as *Candida albicans*, *Saccharomyces cerevisiae*, and *Debaryomyces hansenii*, and in filamentous fungi, including some species of *Aspergillus* and *Penicillium* [231]. Farnesol, tyrosol, phenylethanol, and tryptophol have been reported to function as QS signaling molecules in fungi and have been associated with various developmental processes, such as dimorphic changes, spore germination, and biofilm formation [232]. Lactone-containing molecules have also been reported to function as QS molecules in filamentous fungi. For example, *G*-heptalactone has been reported to regulate growth and secondary metabolite production in *A. nidulans* [233]. Fungi can also produce metabolites that interfere with QS in bacteria. In this regard, patulin and penicillic acid produced by fungi have been identified as QS inhibitors in *Pseudomonas aeruginosa*. [234]. Continued research on this topic is needed to further elucidate the QS signals involved in plant pathogen virulence and potential strategies that can be used to block them.

QS and QQ can also modulate communication between bacteria and fungi. Dor et al. [235] demonstrated that an AHL lactonase can degrade patulin, a mycotoxin produced by *P. expansum*, the fungal agent that causes blue mold rot in apples. The AHL lactonase also inhibited the fungal colonization of apple wounds, thus preventing the development of fruit rot. It also inhibited gene expression in patulin and fungal cell wall biosynthesis. Therefore, the use of QQ lactonases represents a potentially novel method for controlling blue mold in apples during postharvest storage.

4. Conclusions

On average, 20–40% of global crop production, including food crops, is lost annually due to pests and diseases [1]. Therefore, strategies that can be employed to provide crop protection are continually being investigated and assessed. In particular, methods that support sustainable agricultural production are receiving greater attention. In this regard, interest in biopesticides has grown exponentially. In recent years, formulations based on these biopesticides have steadily increased in number and diversity and have received greater support from large chemical companies.

Biopesticides achieve their protection through various mechanisms. These mechanisms can be highly specific, such as biotrophic mycoparasitism, or have a broader spectrum of activity, as is the case with certain antibiotics that can also impact microorganisms that may benefit host plants. Understanding the modes of action of biopesticides is fundamental to assessing their spectrum of activity and predicting their potential impact on beneficial microbiota. Comprehensive knowledge of a biocontrol agent and its mode of action can also provide insight into its performance under variable environmental conditions. Collectively, this knowledge can facilitate biocontrol strain improvement, formulation, and its proper and effective application. Preferences for certain mechanisms of biocontrol will have an impact on the screening methods utilized when searching for a new biocontrol agent [236]. Importantly, however, it should be recognized that most microbial biocontrol agents exert their antagonistic activity through more than one mechanism. Thus, both primary and secondary modes of action should be assessed to identify any potentially harmful impact on human health (producers, harvesters, processors, and consumers), the environment, other crops, and beneficial microorganisms.

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