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REVIEW

A systematic review about biological control of phytopathogenic *Phytophthora cinnamomi*

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Abstract
The oomycetes of the genus *Phytophthora* have the most aggressive species for agriculture and forestry, such as *Phytophthora sojae* which is responsible for soybean root rot, *Phytophthora infestans* responsible for the potato downy mildew that caused the diaspora in Ireland in the nineteenth-century, and *Phytophthora cinnamomi* that affects a wide variety of tree species, from avocado in America, trees in Oceania to European chestnut trees. *P. cinnamomi* reproduces either sexually or asexually and asexual zoospores can live as saprotrophs and subsist in the soil long after death and removal of host plants. Controlling this organism is very challenging for researchers due to the limited range of effective chemical inhibitors. In this work, we present a systematic review of alternatives for biocontrol of *Phytophthora* in general and *P. cinnamomi* in particular. Our literature review indicates that *Trichoderma spp*., mainly *Trichoderma harzianum*, *T. virens*, and *T. asperellum* are very promising fungal species in the control of different *Phytophthora spp*. The Bacillus genus is also very promising in the control and inhibition of several *Phytophthoras spp*.

Keywords Biocontrol · Ecofriendly management · *Phytophthora* root rot · Anti-*Phytophthora* activity · Fungicide

Introduction

Phytophthora cinnamomi is a soil-borne pathogen responsible for root rot diseases in a vast diversity of plant species worldwide [1]. Economically important plants are among the host of *P. cinnamomi*, such as ornamental crops, avocado, and chestnut trees. The avocado cultivars are highly susceptible to pathogen infection and, historically, cause economic losses linked to a decline in quality and production (reviewed in Belisle et al. 2019; Sumida et al. 2020). Similarly, the European chestnut tree crop is hugely affected by the chestnut ink disease, caused by *P. cinnamomi* infection, which represents a concerning economic problem, mainly in Portugal [2].

The current management strategies for *P. cinnamomi* are limited due to the difficulty in diagnosis, as the plants remain symptomless until the late stages of the infection [3]. The prevention of soil flood and excessive moisture is a control strategy for this oomycete insofar as high soil moisture provides favorable conditions for *P. cinnamomi* to produce and increase the dispersal of zoospores [3, 4]. The use of convenient irrigation and drainage techniques is used to avoid the growth of the soil-borne pathogen; however, they are effective only when the soil is not contaminated with zoospores. In this particular scenario, the soil needs to be cleaned with fumigation and other appropriate agrochemicals, to purge the *P. cinnamomi* [1, 5]. Further management techniques include the use of seed treatments and resistant cultivars in zoospores-free soil and crop rotation. Whereas the first offers some flexibility to the producers, the last one is not widely used due to limitations of planting lands and the long-term survival of *P. cinnamomi* zoospores [6, 7].

The most commonly used management strategies for *P. cinnamomi* are phosphonate-based chemical fungicides (e.g. potassium phosphite) and phenylamide compounds (e.g. mefenoxam) [1, 8]. Both of these fungicides are effective

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in managing *P. cinnamomi* infection; mefenoxam possesses a single-site mechanism of action, by strongly inhibiting mycelial growth and sporulation through the blockage of RNA synthesis [9], and the phosphonate-based ones act in several pathways, however, the exact mode of action is still unknown [8]. Despite the effectiveness of both approaches, the use of these chemical fungicides raises some concerns: (i) due to the single-site mechanism of action of mefenoxam, *P. infestans*, *P. citricola*, *P. megasperma*, and *P. nicotianae* have already developed resistance to its action, and (ii) several *Phytophthora* species, such as *P. cinnamomi, P. capsici*, *P. citrophthora*, and *P. infestans*, present reduced *in vitro* sensitivity to phosphonate fungicides [10, 11].

Additionally, regarding the resistance problems, the wide use of agrochemical fungicides also raises environmental and human health concerns. The overuse of such products has threatened soil health given that it causes soil degradation and infertility, which is a current global problem, besides affecting negatively non-target organisms, such as beneficial microorganisms [12]. Moreover, the application of agrochemicals often results in heavy metal contamination, degradation of beneficial microorganisms, and leaching into the water, becoming a water pollutant. Mefenoxam, for example, decreases microbial biomass and inhibits nitrogen-fixing bacteria [12–14].

Biological control is an adequate, promising, and sustainable solution to these addressed problems and effective management of *P. cinnamomi*. Biological control of plant diseases is the inhibition of populations of plant pathogens by living organisms, such as bacteria, fungi, and protozoa, or metabolites derived from these microorganisms [15]. Currently, a few biofungicides, i.e., microorganisms with actions against fungi, are available for inhibition of *P. cinnamomi* growth. Brown et al. (2019b) [5], reported the short effectiveness of RootShield Plus^{+} (based on *T. harzianum*

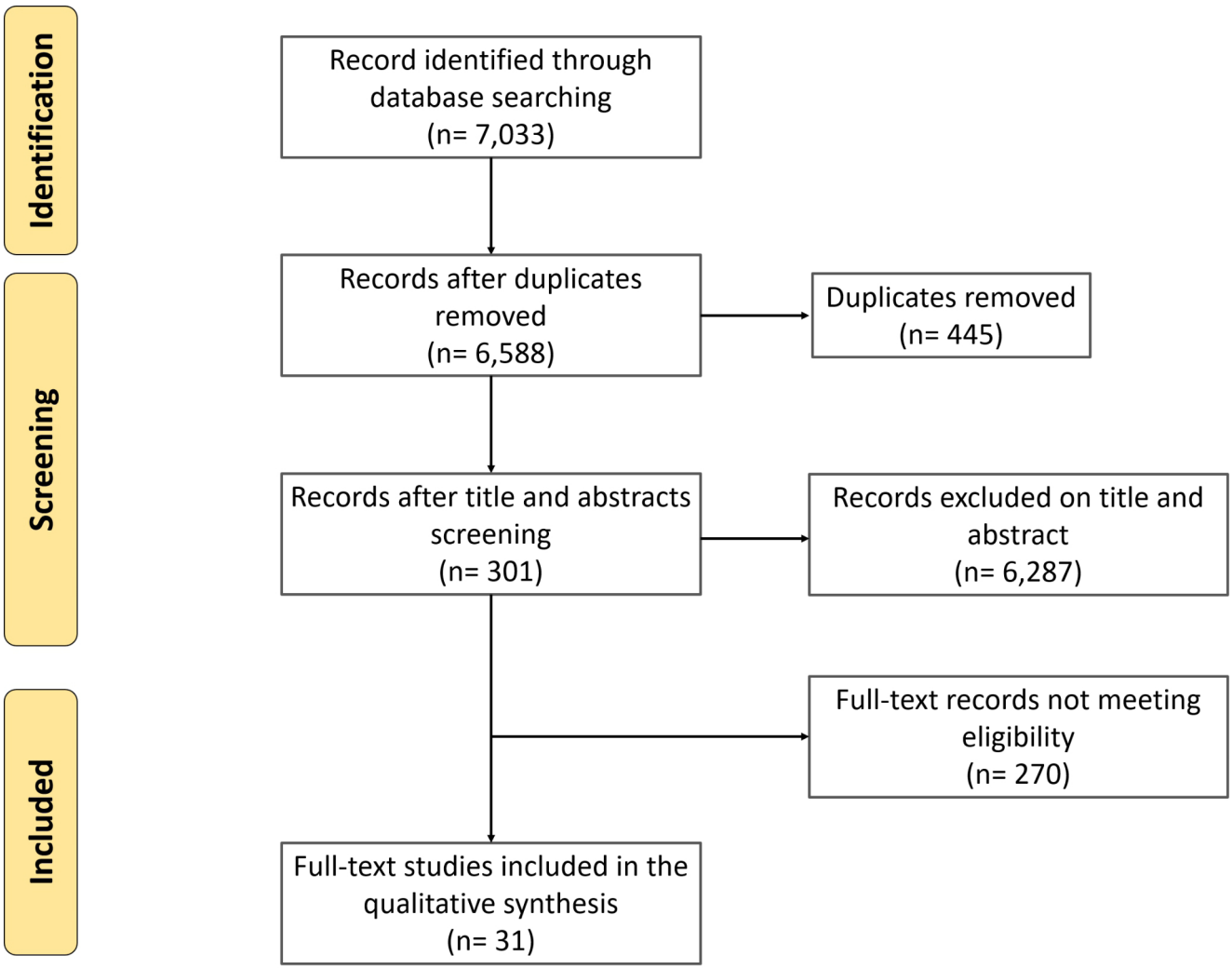

Fig. 1 PRISMA flow diagram

Rifai strain T-22 and *T. virens* strain G-41) to control *P. cinnamomi* root rot.

However, the search for new biofungicides is justified. Numerous research groups have been working on this topic for many years, thus, this systematic review aims to present a qualitative discussion regarding microbial biological control agents, mainly for *P. cinnamomi*, but biological strategies for controlling other *Phytophthora* spp. are also discussed.

Methods

Study design

The present systematic review was conducted based on Chaps. 1–7 of the Cochrane Handbook for Systematic Reviews of Interventions [16] to provide an overview of the best evidence in biological control approaches towards *P. cinnamomi* or, at least, directed to the *Phytophthora* genus.

Information source and search strategy

This study is reported per Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [17]. We searched relevant articles published between 1st January 2016 and March 2021 in PubMed (www.pubmed.ncbi.nlm.nih.gov/), Scopus (www.scopus.com), and Science Direct (www.sciencedirect.com/) databases on 30th March 2021. The keywords used in the search were optimized with the binary operators as following "biological control" OR "biocontrol" AND "*Phytophthora cinnamomi*" OR "root rot". The studies found in the initial search (714 in PubMed, 413 in Scopus, and 5,846 in Science Direct) were retrieved and transferred to Mendeley, which further removed the duplicated papers. Gray literature was not assessed for this review.

Eligibility criteria, study selection, and data extraction and synthesis

After the removal of duplicates, two independent investigators screened all titles and abstracts against the following eligibility criteria: (i) published between the period determined; (ii) population included: *P. cinnamomi* and other species from the *Phytophthora* genus; (iii) outcomes: biological control and biocontrol for synonyms, and antifungal. The investigators evaluated the titles and abstracts with "yes" for inclusion, "no" for exclusion, and "unclear" for full-text analysis. The mutual consensus was used for discrepancies. The last stage was the full-text screening and, disagreements were resolved with mutual consensus. The results were described by a narrative approach and grouped accordingly to the microorganism tested for biological control of *Phytophthora* spp.

Results

A total of 6,588 articles were identified after duplicate removal. Of these, 6,287 were excluded during the title and abstract screening. The full-text analysis included 31 studies meeting the eligibility criteria for the qualitative synthesis (Fig. 1). The following results are presented by grouping studies accordingly to the nature of the microorganism investigated as a possible biocontrol agent against *Phytophthora* spp. using a narrative approach.

The fungal approach in the biological control of *Phytophthora* spp

Entomopathogenic microbes, such as fungi, bacteria, viruses, and protozoa have been studied for more than 100 years as a form of biological control for plant pests. They play important roles in the environment as plant disease antagonists, rhizosphere colonizers, and plant growth-promoting [18, 19]. In recent years, the interest in the use of entomopathogenic fungi as fungal endophytes has increased due to the necessity of effective eco-friendly agents as phytopathogen antagonists. This subsection will discuss the fungal approaches tested against *Phytophthora* genus oomycetes.

Trichoderma spp

In 2016, there was no knowledge of pepper cultivars resistant to *P. capsici*, the infectious agent of the pepper *Phytophthora* blight, and the use of *Trichoderma* spp. as an efficient approach to controlling plant diseases in several horticultural crops was already established [20]. Yao and colleagues (2016) [20] tested the antagonistic activities of 325 *Trichoderma* spp. isolates obtained from pepper, potato plant, and potato tubers, against *P. capsici* isolates obtained from pepper plant stems infected in *in vitro* dual culture, *in planta*, and the field. They reported that the isolate HNA12, identified as *T. harzianum*, showed the highest inhibition rate (62.3%) and reduced the growth of *P. capsici* at its minimum (31.5%) on the *in vitro* assay. The isolate HNA12 also reduced disease severity on pepper seedlings to the lowest disease index (15.5, ranging from 0 to 60), demonstrating a protective activity. The 2-year field evaluations showed that the treatment with *T. harzianum* (HNA12) reduced the disease severity index similar to the positive control, the fungicide Thiram, besides promoting the pepper plant's growth.

The production of mycoparasitic non-volatile metabolites is the mechanism of action proposed by the authors for the action of *T. harzianum* against *P. capsici* [20].

Consistent with the work of Yao and colleagues (2016), Nawaz et al. (2018) [21] studied the diversity of *Trichoderma* species obtained from chili farms, searching for antagonistic activities towards *P. capsici* strains. Thirty-three *Trichoderma* species were isolated and they found that *T. harzianum* was one of the most abundant, together with *T. virens*, *T. viride*, and *T. reesei*. Their results showed antagonistic potential against *P. capsici* in 9 *Trichoderma* species: *T. harzianum*, *T. viride*, *T. reesei*, *T. longibrachiatum*, *T. hamatum*, *T. koningii*, *T. pseudokoningii*, *T. longipile*, and *T. virens*. In agreement with [20], *T. harzianum* was one of the most effective species to inhibit the mycelial growth of *P. capsici* strains in an *in vitro* assay of dual culture with a range of 81.27–86.3%, followed by *T. viride* (82.66–85.53%) and *T. reesei* (81.93–84.27%). However, the experiments *in planta* under greenhouse conditions showed that the most effective performance in controlling root rot disease was *T. viride* (10.5%), followed by *T. reesei* (11.45%), and *T. virens* (13.2%), and *T. harzianum* (15.45%). The results reported by Nawaz and colleagues [21] regarding the *in planta* experiments are similar to that previously reported by [20], although there are differences in the methodological design. Lastly, they found that the application of *T. reesei*, *T. viride*, and *T. harzianum* also promoted plant growth, increasing root weight and length.

As pepper blight remains a destructive disease on pepper crops, Tomah and collaborators [7] also screened for *Trichoderma* spp. isolates from the rhizosphere of pepper plants (chili and bell) with antagonistic activities against *P. capsici*. A total of 77 isolates were obtained and 15 showed high antagonistic activity against the oomycete, and one isolate, identified as *T. virens* HZA14, demonstrated an ability to interact with the colony of *P. capsici*, leading to the disintegration of its hyphae. Among the 15 species tested, one was a new species of *Trichoderma*, described by Tomah and colleagues and named *T. dorothopsis*. Despite their discovery, this new species was not effective as *T. virens* HZA14 inhibits the growth of *P. capsici* both *in vitro* and *in vivo*. Further *in vitro* assays showed that *T. virens* HZA14 produces a compound with high activity, responsible for degrading the *P. capsici* hyphae, identified as gliotoxin. Evaluations in seedlings of chili pepper demonstrated that despite *T. virens* HZA14 substantially reducing the disease incidence and disease severity (62.64% and 64.2, respectively), 15 days after inoculation with zoospores of *P. capsici*, lesions on stem bases of plants were observed.

Das and colleagues [22] also searched for microbial agents with effective control of the main pathogens of black pepper and ginger, namely, *Fusarium oxysporum*, *Rhizoctonia solani*, and *P. capsici*. Rhizosphere soil samples of pepper and ginger fields were collected and four different strains of *Trichoderma* were isolated. Morphological characterization and molecular sequencing identified the strains as *T. asperellum* AFP, *T. asperellum* MC1, *T. brevicompactum* MF1, and *T. harzianum* CH1. The results obtained from the growth inhibition assay showed that all *Trichoderma* strains had significant antagonistic activity against all the pathogens tested using the dual culture technique. Nevertheless, *T. harzianum* CH1 was the most effective in inhibiting the mycelial growth of *P. capsici* (65.3%), followed by *T. asperellum* MC1 (53.1%). The culture filtrate assay showed that metabolites present in *T. asperellum* AFP and *T. harzianum* CH1 at 25 mg/µL totally inhibited the growth of *P. capsici*, and the growth inhibition by a volatile metabolites assay indicated a strong inhibition of the pathogen by *T. asperellum* strains (49.8% AFP and 42.3% MC1), followed by *T. harzianum* CH1 (40.8%) [22]. Although the authors did not identify the metabolites present on the culture filtrates, their results are in agreement with those previously reported by other researchers.

Following similar methodologies, Sanchez and collaborators [23] investigated the antagonistic activity of *Trichoderma* strains isolated from soil and roots of pear orchards against several *Phytophthora* strains. From 88 isolates, only one *Trichoderma* isolate (1384), identified as *T. guizhouense*, controlled the mycelial growth of all *Phytophthora* strains tested using the dual culture technique, namely *P. cactorum* 1378 (52.63%), *P. inundata* 1353 (62.19%), *P. rosacearum* 1315 (58.18%), and *P. lacustris* 1378 (50%), and 18 isolates of *Trichoderma* spp. reduced the mycelial growth by more than 45% in, at least, two species of *Phytophthora*. This result agrees with that previously reported, since *T. guizhouense* is a recently named species derived from *T. harzianum* and belonging to the *Harzianum* clade [24, 25]. They also showed that 81% of the *Trichoderma* isolates presented the highest level (4) of mycoparasitic activity, colonizing the *Phytophthora* colonies and sporulating on them. The inhibitory potential of the secondary metabolites of sixteen *Trichoderma* isolates was tested against *P. cactorum* only and the results ranged from 2.2 to 24.2%, with the highest value from *T. harzianum* 1367. They also tested *in vitro* growth promotion on tomato seedlings. Eleven isolates promoted root length and plant growth, among these, *T. harzianum* 1367, *T. harzianum* 1322, and *T. deliquescens* 1343 (also in the *Harzianum* clade) also were able to colonize the roots of the tomato seedlings. Moreover, they evaluated the *in vitro* fungicide tolerance of the six *Trichoderma* isolates selected against a commercial formulation of potassium phosphite (PHI K) used in pear orchards. Only three regional strains of *T. harzianum* (1330, 1367, 1371) were capable of growing at all the concentrations evaluated (0, 0.1, 1.0,

10.0, 50.0, and 100.0 ppm). Lastly, and most importantly, Sanchez and colleagues evaluated the semi-commercial biocontrol efficacy of *T. harzianum* (1330, 1367, 1371) against *P. cactorum* in a two-year experiment on pear orchards. The experimental design used the commercial dose of PHI K as chemical control, and a conidial aqueous suspension (10^6 conidia/mL) of the *T. harzianum* strain and the commercial *T. atroviride* isolate as the *Trichoderma* treatment in a preventive experiment and a curative experiment. The biocontrol effect was evaluated by the extension of the necrotic lesion (cm^2). The results showed that the regional *Trichoderma* isolates presented an elevated antagonistic effect by decreasing to a large extent the lesions on pear plants in the first (90.74–97.13%) and second (84-96.8%) year when applied preventively. In the curative evaluation, *T. harzianum* 1330 showed a biocontrol effect of 82.65%, and *T. harzianum* 1371 and *T. harzianum* 1367 presented 85.48% and 96.53% of biocontrol effect, respectively [23].

The last work with *T. harzianum* included in this subsection was carried out by Umadevi and Anadaraj [26] and reported a deep investigation of the molecular mechanisms involved in the interaction between black pepper, and *T. harzianum*, and *P. capsici* through label-free quantitative proteomic analysis of black pepper leaves. Their results showed that the number of proteins up-regulated in the tripartite interaction between black pepper, *P. capsici*, and *T. harzianum* was larger than in the bipartite interactions. These up-regulated proteins were described as *Trichoderma*-induced systemic resistance proteins (T-ISR), and the majority are related to defense against reactive oxygen species (ROS). The group of ROS-scavenging proteins is a marker of T-ISR, and the up-regulated expression of monodehydroascorbate reductase (MDAR) indicated that this enzyme is related to the early involvement of T-ISR. The alterations in superoxide dismutases (SOD) are also highlighted since it is up-regulated as a T-ISR in all tripartite interactions but it is down-regulated in the black pepper, *P. capsici*, bipartite interaction. Further altered proteins included the down-regulation of catalase isozymes in black pepper × *P. capsici* interaction and their up-regulation in the black pepper × *P. capsici* × *T. harzianum* interaction. Glutathione S-transferases (GSTs) were up-regulated in black pepper × *P. capsici* interaction but not in black pepper × *T. harzianum* interaction, indicating that GSTs are induced by the pathogen but not by the beneficial fungus. However, in the tripartite interaction, the up-regulation of GSTs was much higher, suggesting the GSTs also are T-ISR proteins in an infection condition. Additionally, other T-ISR proteins of the antioxidant defense system include the dehydrogenase family protein, peroxidase isoenzymes, reactive intermediate deaminase A chloroplastic (RidA), and ascorbate peroxidase isozymes, and 2-Cys peroxiredoxin BAS1 [26].

Moreover, they reported T-ISR expression alterations in other defense-related proteins and isolated proteins (i.e., are not included in the main categories) in the tripartite interaction. To summarise the work of Umadevi and Anandaraj (2019), a brief description follows. The proteins functionally annotated are from biological process (BP), cellular component (CC), and molecular functions (MF). The most interesting is the T-ISR proteins in the two main categories: the ROS-related proteins and other defense-related proteins. Additionally, other T-ISR proteins are in the isoflavonoid pathway, lignin synthesis, and ethylene synthesis pathways [26].

Furthermore, some works investigated the ability of *T. asperellum* to control *Phytophthora ramorum*, a great concern for ornamental nurseries. In line with this, Widmer and Shishkoff (2017) conducted a study using the patented *T. asperellum* strain 04–22 (Ta 04–22) (US Patent No. 9,320,283) for the control of *P. ramorum* in *Viburnum tinus* roots. The results showed that the incorporation of Ta 04–22 into the potting mix reduces the number of plants with *P. ramorum*-infected root systems in a dose-dependent way. This result was found with *P. ramorum* chlamydospores as inoculum propagule, but not with sporangia, indicating a dependence on the pathogen propagule type at the inoculation. Although the number of plants with root systems infected by *P. ramorum* reduced after the last Ta 04–22 application, the final populations of chlamydospores or sporangia from *P. ramorum* in the potting mix did not significantly decline. They also reported that independent of concentration and inoculum type, the *T. asperellum* does not affect total root length [27]. Despite some limitations in the experimental design, Widmer and Shishkoff (2017) also reported that the use of Ta 04–22 applied as wheat bran top-dressing reduced the *P. ramorum* inoculum, while the formulation of Ta 04–22 as a wettable powder and applied as root drench reduced the inoculum better than the commercial product Rootshield® Plus (*T. harzianum* Rifai strain T-22 and *T. virens* G-41) [27]. To further investigate the biological control effect of Ta 04–22 in field conditions, Widmer and colleagues [28] formulated the *T. asperellum* as wheat bran and as a wettable powder (Ta 04-22WP) in several final concentrations and tested it against soil artificially and naturally infected with *P. ramorum*, but with no plants. They reported that Ta 04–22, in both formulations and without the interference of seasons, reduced *P. ramorum* to non-detectable levels in the two trials. However, their methodology was very limited and the data was very heterogeneous. Nevertheless, their result is in agreement with previous studies using the *Trichoderma* spp. as an effective agent in controlling infections caused by *Phytophthora* spp.

Fungal agents specifically against *P. cinnamomi*

This subsubsection is dedicated to discussing works that include fungal agents tested to control *P. cinnamomi*. Trzewik and colleagues (2020) [29] tested the ability of *Piriformospora indica* to confer resistance to two rhododendron cultivars against *P. cinnamomi* and *P. plurivora*. The *in vitro* results from the dual-culture experiments showed that the presence of *P. indica* in the growth substrate is harmless for *Phytophthora* spp tested, and *P. cinnamomi* significantly inhibited the growth of mycelium of *P. indica* without affecting mycelial morphology on Käfer agar (KM) medium, which is in agreement with the ambiguous conclusions in the current literature. They also reported that *P. indica* has a bio-protective effect on 'Nova Zembla' and 'Alfred' rhododendron cultivars when applied to the peat substrate where young plants grew, and 21 days before the inoculation of the pathogens *P. cinnamomi* and *P. plurivora*. The application of *P. indica* in these conditions protected the plants against the development of disease symptoms, wilting of leaves, and root and stem necrosis. One year after the beginning of the experiment, 50% or more of plants bio-protected with *P. indica* and infected with *P. cinnamomi* or *P. plurivora* were asymptomatic [29].

Brown and colleagues (2019) [3] carried out a comparative study among fungicides, biofungicides, and host plant defense inducers abilities against *P. cinnamomi* artificially inoculated on flowering dogwood seedlings (3-to-4-month old) under greenhouse conditions during simulated root flooding events, which creates a favorable condition for *P. cinnamomi* infection. As this systematic review focus on biological control agents, here will be discussed only the findings related to the biofungicides tested. They used the commercial biofuncigides MBI-110 (*Bacillus amyloliquefaciens*

Table 1 – Fungi species with antagonistic effects against *Phytophthora cinnamomi*

Microorganism	*In vitro* method	% inhibition (*in vitro*)	*In planta* method	*In planta* results	Reference
Piriformospora indica	Dual-culture	0%	Bio-protective effect on 'Nova Zembla' and 'Alfred' rhododendron cultivars	*P. indica* protected against the development of disease symptoms, wilting of leaves, and root and stem necrosis. One year after the inoculation, 50% of plants bio-protected and infected with *P. cinnamomi* were asymptomatic	Trzewik et al., 2020
MBI-110 biofungicide (*Bacillus amyloliquefaciens* strain F727; Marrone) RootShielPlus^{+}WP biofungicide (*Trichoderma harzianum* Rifai strain T-22 (1.15%) + *T. virens* strain G-41 (0.61%); BioWorks)	-	-	Protection against *P. cinnamomi* on flowering dogwood seedlings (3-to-4-months old) under greenhouse conditions during simulated root flooding events	MBI-110 treatment presented a reduction of disease severity compared to the positive control of only 1 day of flooding. MBI-110 had a smaller percent recovery of *P. cinnamomi* from root samples at 3 and 7 days of flooding. RootShielPlus^{+}WP treatment showed a decline in *Trichoderma* colony numbers declined with increased flooding duration.	Brown et al., 2019
RootShielPlus^{+}WP biofungicide (BioWorks) RootShielPlus^{+}WP biofungicides + ON-Gard 5-0-0 (5% total nitrogen, BioWorks)	-	-	Protection against *P. cinnamomi* and ambrosia beetles attacks on flowering dogwood seedlings (3-to-4-months old) under greenhouse conditions during simulated root flooding events	RootShielPlus^{+}WP *per se* treatment prevented the disease severity at 1 (both trials) and 3 (trial 1) days of flooding and did not reduce the percentage of infected roots. *Trichoderma* root colonization was higher on plants flooded for 1 or 3 days. RootShielPlus^{+}WP + ON-Gard 5-0-0 treatment prevented the disease severity at 1 (both trials) and 3 (trial 2) days of flooding and had a lower percentage of infected roots than the positive control only in trial 2. *Trichoderma* root colonization also was higher on plants flooded for 1 or 3 days.	Brown et al., 2019b
Aspergillus flavipes	Dual-culture	20%	-	-	El-Sayed & Ali, 2020
Trichoderma spp. (Maize DP5 and Maize CP4 isolates)	Dual-culture	73.3% (Maize DP5) and 73.3% (Maize CP4 73.3%)	-	-	Sumida et al., 2020

strain F727; Marrone) and RootShielPlus^{+}WP (*T. harzianum* Rifai strain T-22 (1.15%) + *T. virens* strain G-41 (0.61%); BioWorks) applied only as preventive drench applications 7 days before the flooding events. All treatments were flooded for 1, 3, or 7 days in two separate trials. Their results showed seedlings that were preventively treated with MBI-110 or with RootShielPlus^{+}WP had reduced disease severity compared to the positive control only at 1 day of flooding. Moreover, plants treated with MBI-110 had a smaller percent recovery of *P. cinnamomi* from root samples at 3 and 7 days of flooding, and in plants treated with RootShielPlus^{+}WP, the *Trichoderma* colony numbers declined with increased flooding duration. However, the study had some limitations, such as differences in days in the greenhouse and the single applications of the products [3].

In another set of trials in a separate study, Brown, and collaborators [5] investigated the ability of RootShielPlus^{+}WP *per se* and combined with ON-Gard 5-0-0 (5% total nitrogen, BioWorks) fertilizer program in controlling the *Phytophthora* root rot and ambrosia beetles attacks on flowering dogwoods exposed to simulated flood events under field conditions. They performed two trials with flooding durations of 1, 3, or 7 days and applied the biofungicide treatments 7 days before flooding (preventive). Their results showed that the flooding events did not interfere with the plant growth parameters in both trials, and the preventive treatment only with RootShielPlus^{+}WP was effective in preventing the disease severity at 1 (both trials) and 3 (trial 1) days of flooding and did not reduce the percentage of infected roots. The preventive treatment with RootShielPlus^{+}WP + ON-Gard 5-0-0 was effective in preventing disease severity at 1 (both trials) and 3 (trial 2) days of flooding and had a lower percentage of infected roots than the positive control only in trial 2. Regarding the *Trichoderma* root colonization, both treatments presented a higher number of colonies on plants flooded for 1 or 3 days when compared to 7 days of flooding [5]. In summary, the results of both works of Brown and colleagues indicate that the commercial biofungicide RootShielPlus^{+}WP is only effective against *P. cinnamomi* at shorter flooding durations. A summary of the main fungal species with anti-*P. cinnamomi* activity discussed in this revision is presented in Table 1.

Other endophytic species against *Phytophthora* spp. infection

Phytophthora spp. is a big concern for several commercial species such as Norway spruce, which is susceptible to *P. plurivora* and *P. pini*. In line with this, Terhonen, Sipari, and Asiegbu (2016) [30] investigated the potential inhibitory effects of the two root endophytes previously isolated against *P. pini* and two other Norway spruce pathogens (*Heterobasidion parviporum* and *Botrytis cinerea*). The two endophytes were identified as *Phialocephala sphareoides* and *Cryptosporiopsis* sp. The dual-culture *in vitro* results showed that the growth of *P. pini* decreased significantly after 14 days in presence of *Cryptosporiosis* sp. and after 15 days in presence of *P. sphareoides*. The analysis with the secreted metabolites showed that *P. pini* decreased after 14 days in contact with crude extracts from *Cryptosporiosis* sp., but no morphological change was observed in hyphal growth. *P. sphareoides* did not decrease the growth of the pathogens tested. Terhonen and co-authors tested both endophytes in Norway spruce seedlings using only *H. parsivoporum* as the pathogen, and they found that the *Cryptosporiosis* sp. caused detrimental effects in the seedlings, despite its extremely effective antagonistic activity. However, results showed that *P. sphareoides* had inhibitory effects on the growth of the pathogens, besides improving the root shoot ratio and occupying the newly growing roots, a form of preventing future infections [30].

Furthermore, Di Francesco and colleagues (2017) [31] tested two strains of *Aureobasidium pullulans* (L1 and L8) already used as biological control agents (BCAs) for post-harvest pathogens in several fruits, such as apple, against *P. infestans*, the causal agent of tomato late blight. They sprayed both surfaces of the leaves of tomatoes with the yeast's suspensions 24 h before or 16 h after inoculation with *P. infestans* for the *in vivo* experiments, which resulted in a protective (24 h before inoculation) effect similar to the positive control and higher effectiveness of L1, reducing the disease by 60%, while L8 reduced by 36.7%. The curative treatments reduced the disease by 43.9%, indicating that *A. pullulans* are more effective as a preventive treatment. The yeast population on leaves presented a small variation through the observed period but stayed at acceptable levels. Also, the leaves treated with both strains of *A. pullulans* presented a significant increase in β-1,3-glucanase activity, a plant defense enzyme capable of hydrolyzing *Phytophthora* spp. cell walls. Regarding the *in vitro* results of co-cultures and exposure to non-volatile and volatile metabolites produced by L1 and L8, both strains reduced the colony growth of *P. infestans* by 62.1% in the direct interaction. Non-volatile metabolites also inhibited the colony growth with L8 presenting the highest inhibition (35.3%), however volatile metabolites were more effective than non-volatile in inhibiting the colony growth, with an average of 44.1% [31].

Lastly, El-Sayed and Ali (2020) [32] investigated the antagonistic effect of *Aspergillus flavipes*, a fungus with a high diversity of secondary bioactive metabolites, against several species within the *Phytophthora* genus. The results of the co-culture assay showed that *P. parasitica* and *P. arecae* are the species more sensitive to *A. flavipes*, with an average of 35% of growth inhibition. *P. cinnamomi* was

not very sensitive to the fungus, with growth inhibition of around 20%, however, the data also presented deviation. Further experiments were conducted with *P. parasitica*, which presented high susceptibility to the whole organic solvent layer, indicating that the biologically active compounds of *A. flavipes* are located intracellularly. The extracted compounds exerted strong inhibition of the growth of *P. parasitica*, as well as inhibition of spore germination and hyphal anomalies. These compounds were evaluated and classified as putative and identified as 3-Hydroxy-2′,4,4′,6′-tetramethoxychalocone, isovitexin, amodiaquine, and flavanone with concentrations of 35.8%, 26.4%, 11.47%, and 9.16%, respectively. They also tested the potential pathogenicity of *A. flavipes* and its compounds to *Nicotiana benthamiana* and *Solanum lycopersicum*, and the results showed that, possibly, the *A. flavipes* and its extracts presented no sign of toxicity to the tested plants [32].

The bacterial approach with antagonistic activity against *Phytophthora* spp

This subsection is dedicated to presenting and discussing the bacteria tested as biocontrol agents against *Phytophthora* species.

Bacillus spp as biological control agents against *Phytophthora* spp

Rajaofera and colleagues (2018) [33] studied the antifungal activity of *Bacillus atrophaeus* HAB-5 isolated against 22 plant pathogenic fungi, including *P. nicotianae*, in *in vitro* dual culture. The inhibition rates of mycelial growth ranged from 21.07 to 67.23%, and the *B. atrophaeus* inhibited *P. nicotianae* growth by 34.38%. They also tested substances of the crude extract of HAB-5 isolated against *P. nicotianae* disease suppression in tobacco (*Nicotiana tabacum cv.* Samsun-NN) plant seedlings as a preventive treatment. The control group presented severe disease symptoms, in contrast, the HAB-5 inoculated seedlings did not present disease symptoms. Further analysis included the toxicity evaluations of the heat-stable crude extract compound produced by *B. atrophaeus* HAB-5 in *Danio rerio* embryos. Their results indicated that the bioactive substance tested was moderately toxic to zebrafish. The composition of the crude extract of HAB-5 showed the presence of chitinase and protease, which are consistent with the pattern of growth inhibitory biological agents. Moreover, *B. atrophaeus* HAB-5 was demonstrated to be a phosphate solubilizing bacteria and siderophore producer, providing plant-absorbable forms of phosphate and inhibiting the growth of plant pathogens, respectively [33].

Aiming at a biocontrol approach to tobacco black shank disease, caused by *P. nicotianae*, and in line with Rajaofera et al. (2018), Guo and colleagues (2020) studied the Ba168 isolated from plant growth-promoting rhizobacteria (PGPR), further identified as *Bacillus velezensis*. The *B. velezensis* Ba168 presented the highest inhibition diameter in dual culture (28.42 mm) than the other isolates tested. The ammonium sulfate precipitation of Ba168 (ASPBa) was more effective in suppressing *P. nicotianae* mycelial growth than the Ba168 culture with complete inhibition at 5 µg/mL. The antagonistic effect of ASPBa may be associated with irreversible damage to the cytoplasmic membranes and cell walls. Analysis of the composition of ASPBa mainly identified the presence of antifungal polypeptides, antimicrobial peptide LCI, and cellulose degradation enzymes (CDEs) among several proteins/peptides, indicating multiple pathways of biocontrol. Guo et al., (2020) [34] also tested the *B. velezensis* Ba168 in 2 consecutive years of field trials using the tobacco varieties *N. tabacum* QinYan96 and NC89. Their results showed that *B. velezensis* Ba168 exerted a disease control efficacy in QinYan96 of 78.45% in the first year and 77.26% in the second year, and in NC89 of 67% in the first year and 66.01% in the second year. Both results were lower than Azoxystrobin (MPA) but higher than Dimethomorph preparations, which are chemicals that have been applied to control tobacco black shank disease [34].

As many studies have reported some promising species of Actinobacteria with antagonistic activity against *P. cinnamomi*, the causal agent of Phytophthora root rot, Méndez-Bravo and colleagues (2018) [35] focused on investigating the potential of rhizobacterial volatile compounds for the suppression of *P. cinnamomi*. They isolated rhizosphere soil samples from symptomatic and asymptomatic avocado trees for Phytophthora root rot, one of the species of plants most affected by *P. cinnamomi* infections. Firstly, the 21 rhizobacterial isolates were screened to determine the possible plant growth-promoting activity on *Arabidopsis thaliana* seedlings. Seven isolates were chosen based on their capacity in stimulating primary root length and lateral root formation as well as fresh weight accumulation, however, only two isolates inhibited *P. cinnamomi* mycelial growth in dual culture *in vitro*. Isolates A4d and A8a were identified as belonging to the genus *Bacillus* and the second was determined as phylogenetically close to *B. acidiceler*. The antifungal activity of volatile compounds emitted by isolate A8a (*B. acidiceler*) was stronger than in the dual culture, reaching 76% and 46% of mycelial growth inhibition, respectively. Scanning electron microscopy showed that the bacterial volatile compounds induced multiple degenerative alterations in the hyphal morphology of *P. cinnamomi*. The most abundant volatiles were tentatively identified as

2,3,5-trimethylpyrazine (28.86%), 3-amino-1,3-oxazolidine-2-one (22.80%) and 6,10-dimethyl-5,9-undecadien-2-one (15.95%) [35].

In line with previous studies, Syed-Ab-Rahman and colleagues (2018) [36] screened microbial biocontrol agents from *(A) thaliana* rhizosphere grown in a potting mix against several *Phytophthora* spp, namely *P. citricola*, *P. palmivora*, *P. cinnamomi*, and *P. capsici*. They identified 48 isolates in which the genera *Pseudomonas* was the most prevalent. The isolates were screened in biochemical microbiological *in vitro* assays for growth-promoting and biocontrol properties. The strongest inhibitory activity for mycelial growth of the four *Phytophthora* spp. in dual culture *in vitro* assay was observed for *Bacillus amyloliquefaciens* (UQ154), *(B) velezensis* (UQ156), and *Acinetobacter* sp. (UQ202), that also induced abnormal hyphae morphology in *P. citricola*. Regarding the plant growth-promoting traits *B. amyloliquefaciens* (UQ154) and *B. velezensis* (UQ156) are nitrogen-fixing bacteria, but *Acinetobacter* sp. (UQ202) is not. All three isolates, UQ154, UQ156, and UQ202, are phosphate solubilizing bacteria with similar efficiencies, and they also can produce siderophores and indole acetic acid (IAA). Biofilm production was confirmed only for *B. velezensis* (UQ156) and *Acinetobacter* sp. (UQ202). The assay for cell wall-degrading enzyme activities showed that none of the three strains synthesized chitinase, while an indicator of protease production was found only in *B. amyloliquefaciens* (UQ154). *B. amyloliquefaciens* (UQ154) and *B. velezensis* (UQ156) were found to produce cellulose, however, *B. velezensis* (UQ156) and *Acinetobacter* sp. (UQ202) did not produce cellulases. Syed-Ab-Rahman et al. (2018) [36] also tested the selected isolates in lettuce seeds, in which the inoculation contributed to better seed vigor, enhanced the germination percentages between 9.33% and 18.67%, and seedling root growth ranging from 16 to 16.8%. The isolates also significantly increased the shoot length of lettuce seedlings and the plants inoculated with *B. amyloliquefaciens* (UQ154) presented the highest increase (32.26%). Lastly, they tested the biocontrol activity of the three bacterial isolates on chili-pepper plants infected with *P. capsici* in pot trials. The inoculation of the bacterial isolates increased photosynthetic carbon assimilation, leaf transpiration, and stomatal conductance in both *P. capsici*-infected and healthy plants. Plants inoculated with *B. amyloliquefaciens* (UQ154), *B. velezensis* (UQ156) and *Acinetobacter* sp. (UQ202) presented lower *P. capsici* DNA biomass (0.56, 1.56, 0.12 pg, respectively). The plants also had a reduced appearance of symptoms, indicating the reduction in the pathogen's population and disease severity on chili pepper plants, with an increase in higher root biomass. They also identified seven chemical compounds belonging to the diketopiperazines (DKPs) class, which are associated with strong inhibition of *Phytophthora* spp. Taken together, their findings indicated that *Acinetobacter* sp. (UQ202) could be tested in chili pepper fields as a biocontrol approach.

To clarify, the possible mechanisms of action of the strains *B. amyloliquefaciens* (UQ154), *B. velezensis* (UQ156), and *Acinetobacter* sp. (UQ202) against *Phytophthora* spp. and in the plant growth promotion, Syed-Ab-Rahman and colleagues (2019) [37] tested the involvement of the diffusible compounds and both non-volatile and volatile organic compounds (VOCs) in *A. thaliana* and *Capsicum annuum* L., cultivar Cayenne (chili pepper), and the *P. capsici* inhibition. The chili pepper seeds treated with the bacterial isolates presented enhanced growth, demonstrated by (i) an increase of 81.6% in total fresh weight of chili seedlings, (ii) increase of root length, (iii) improvement in seed vigor, and (iv) increase in seed germination from 7.2 to 21.4%. They also tested the potential of plant-growth promotion of the bacterial volatile compounds, which also promoted growth in chili, demonstrated by the increase in the development of chili primary root length and lateral roots, and total fresh weight. The highest increase in fresh weight, 196.9%, was achieved by plants inoculated with *Acinetobacter* sp. The potential of the diffusible compounds was evaluated with the co-inoculation between the bacterial isolates and chili pepper in controlled conditions and these compounds also induced significant increases in total fresh weight (71.33–103.96%) and increased primary root length (103.95–128.8%). An increase of > 100% in plant biomass and primary root lengths was observed in chili pepper plants inoculated with all bacterial isolates. An increase in the chili biomass (shoot and root fresh weights) and in the primary root length (32.1–87.9%) as well as in both hair growth and lateral root development, was observed on the plants grown with the bacterial isolates VOCs. Regarding *(A) thaliana*, the direct inoculation (analysis of diffusible compounds) with *(B) amyloliquefaciens* (UQ154) and with *Acinetobacter* sp. (UQ202) resulted in plants with longer primary root lengths. Plants exposed to VOCs presented greater primary root length (24.6–38.9%) and total biomass, increased by 388%. The diffusible compounds and VOCs exerted antagonistic activities against *P. capsici* in *in vitro* assay, whereas a stronger mycelial growth inhibition was observed in the presence of diffusible compounds, and those produced by *Acinetobacter* sp. (UQ202) had the highest inhibition percentage (49.4%), followed by *B. amyloliquefaciens* (UQ154) and *B. velezensis* (UQ156). In contrast, VOCs emitted by *B. amyloliquefaciens* (UQ154) presented the highest inhibitory activity (32.7%), followed by *Acinetobacter* sp. (UQ202) and *B. velezensis* (UQ156). The analysis of VOCs detected a total of 25 distinct chemical compounds, some species-specific, belonging to the group's aldehydes, alcohols, esters, carboxylic acids, and

ketones. The most abundant VOCs produced by the three bacterial isolates were 3-methylbutanol and methyl (Z)-N-hydroxybenzimidate, compounds already described as having antifungal and antibacterial activity. The application of each one of the VOCs purified on *P. capsici* inhibited the mycelial growth at different degrees and the most effective concentration was 10 $\mu g.mL^{-1}$. Moreover, the application of the pure VOCs in chili pepper seedlings showed that the 2-heptanone increased the root length, followed by 3-methylbutanol and benzyl alcohol at 10 $\mu g.mL^{-1}$, on the other hand, isovaleric acid inhibited the growth of seedlings at all concentrations. Finally, the tripartite assay chili peppers seedlings × *P. capsici* × VOCs demonstrated that inoculation with *Acinetobacter* sp. (UQ202) promoted increased root length and fresh weight of seedlings, and reduced the mycelial diameter, while in the absence of *P. capsici*, no effect on seedlings growth was observed [37]. In general, their results indicate the potential use of VOCs as biocontrol and plant-growth-promoting compounds.

In line with previous studies, Sagredo-Beltrán and colleagues (2018) [38] studied bacterial strains isolated from soil with antagonistic effects against some root rot phytopathogens, including *P. capsici*. The selected strain, identified as *Bacillus halotolerans* MS50-18 A, inhibited the growth of the pathogens by at least 60% in dual culture and presented unharmful or innocuous interaction with pepper plantlets in pots under *in vitro* conditions. Moreover, *B. halotolerans* MS50-18 A produces indoleacetic acid, an auxin-related phytohormone. They sequenced the bacterial genome and identified several proteins related to osmoregulation and the biosynthesis of glucosamine synthase [38]. Bhusal and Mmbaga (2020) [39] also screened *Bacillus* spp. isolates, namely *B. thuringiensis* (IMC8), *B. vallismortis* (Ps), and *B. amyloliquefaciens* (PsL) against *P. capsici* in *in vitro* and greenhouse conditions. In the dual culture assay, the percentual of mycelial growth inhibition indicated that the isolate PsL was the most effective (46.62%), followed by Ps (45.95%) and IMC8 (27.59%). For the greenhouse evaluations, they used a preventive approach, since the seeds of sweet pepper plants were treated with bacterial isolates and then grown in *P. capsici* infested soil in two distinct experiments. The PsL isolate was the most effective in inhibiting *P. capsici*, presenting a disease suppression of > 80%, followed by the Ps isolate, that was also highly effective in disease suppression and both PsL and Ps were more effective than the fungicide control (metalaxyl). The combination of the isolates PsL, Ps and IMC8 treatment was effective at the same level as the fungicide, but not as effectives the PsL and Ps isolates individually. Regarding the disease progress, plants treated with PsL and Ps individually, showed a very slow disease progression during the 35 days of analysis, with mild symptoms starting at day 29 (PsL) and 31 (Ps) and remained mild until day 35. In reference of the plant growth promoting effects of the bacterial isolates, PsL presented the best growth promotion, however all treatments, including the fungicide, presented significant improvements in plant weight, chlorophyll content and seedling root length [39]. Overall, their results indicate that *B. amyloliquefaciens* (PsL) has a promising antagonistic effect against *P. capsici* along with plant growth-promoting activity.

The last work in this subsection was carried out by Kumbar and colleagues (2019) [40], who investigated four *Bacillus subtilis* strains (KU936341, KU936344, KU936345, and MTCC-2422) against *P. infestans* in field applications with *Solanum tuberosum* (potato). The seed potatoes were drenched with the different treatments; however, it is not clear how the pathogen inoculations were conducted. The bacterial treatments reduced the disease incidence by 53.84–73.13% while the reduction in the fungicide control (Mancozeb & CURZATE®) ranged from 49.08 to 63.38%. The results of potato disease severity revealed no difference between the bacterial treatments (73.75–78.75%), fungicides (65%), and control (81.25%). Regarding the vegetative growth parameters before and after *P. infestans* infection indicates that the bacterial treatments improve the height of plants very slightly, as well as increasing the total commercial tuber weight [40].

Pseudomonas spp. with anti-phytophthora activity

The bacterial species from the *Pseudomonas* genera are among the most investigated agents with antagonistic effects against several plant pathogens, including *Phytophthora* spp. Looking for a biocontrol agent against *P. capsici*, Zohara and colleagues (2016) [41] isolated bacterial species from soil samples collected from rice fields contaminated with arsenic and tested their antagonistic activity against *P. capsici* in dual cultures assay. From 30 bacterial isolates, three showed the strongest levels of hyphal growth inhibition against *P. capsici*, and they were identified as *Pseudomonas aeruginosa* strain RHH13 (B-1), *P. aeruginosa* strain duan1 (B-10), and *P. aeruginosa* strain JBP-16 (B-17). These isolates caused hyphal alterations, at different levels, such as increased branching, swelling, cellular disintegration, and curly growth. *In vitro* assay showed that B-1 and B-10 isolates suppressed production of sporangia by 52% and 54%, respectively, while B-17 presented the lowest suppression of sporangia, by 42%. Regarding the production of zoospores, B-10 was the most effective, presenting the lowest rate of release of zoospore (29% in bacteria and 47% in cell-free culture filtrate), followed by B-17 (31% and 45%) and B-1 (45% and 62%). The use of the three bacterial culture supernatants impaired the motility of the zoospores similarly, when added to the suspension of *P. capsici*

zoospores, and lysed within 30–60 min. On the other hand, the B-17 isolate presented the lowest mycelial dry weight (0.313 ± 0.08 g), followed by B-1 (0.062 ± 0.0642 g) and B-10 (0.895 ± 0.09 g). Finally, they tested the three isolates on cucumber seedlings grown from seeds previously treated with the bacterial isolates, *in vitro* and net houses. None of the three isolates showed negative effects on the germination of cucumber seeds and the highest disease suppression was observed in plants treated with B-17 (60–65%), followed by B-1 and B-10 that both showed disease suppression > 43%. Regarding growth parameters, B-17 isolate also induced the highest level of seed germination, seedling vigor, and dry matter production in a petri dish [41]. Their results indicate that *Pseudomonas* spp. B-17 is a promising biocontrol agent for *P. capsici* and also contributes to the cucumber plant vigor and growth.

El-Sayed and colleagues (2018) [42] characterized bacterial isolates from root, leaves, and stems of *Smilax bona-nox* L, a wild plant with invasive growth habits, with antagonistic activity against *Phytophthora parasitica*. Forty distinct bacterial isolates were obtained belonging to thirteen different genera, the genus most frequently occurring was *Burkholderia* (> 30% of isolates), followed by *Pseudomonas* (18%). The antimicrobial activity by *in vitro* assay revealed that only two *Pseudomonas* spp. (EA6 and EA14), identified as belonging to the *P. fluorescence* subgroup, presented the strongest mycelial growth inhibition to four distinct isolates of *P. parasitica*, as well as against *P. cinnamomi*, *P. tropicalis*, *P. capsici*, and *P. palmivora.* The anti-*Phytophthora* activity mechanism was investigated through bioactivity assay. The *Pseudomonas* spp. EA6 and EA14 produce and emit hydrogen cyanide (HCN) and volatile sulfur compounds, which are involved in antimicrobial activities; however, HCN and these compounds individually did not inhibit the mycelial growth of *P. parasitica*. The biosurfactant activity of these isolates is similar to the other isolates tested. Both *Pseudomonas* sp. EA6 and EA14 secrete compounds with strong activity against the four *P. parasitica* isolates. However, only the ones secreted by EA6 could be partially identified as having a proteinaceous nature and presented elevated anti-*Phytophthora* activity. The authors identified glucanolytic enzymes produced and secreted by EA6 isolate with strong anti-*Phytophthora* activity, the fractions corresponding to the most biological activity are β-1,3 glucanase and β-1,4 glucanase, known as cell wall-degrading. Lastly, they tested crude protein extracts of β-1,3 glucanase from *Pseudomonas* sp. EA6 against *P. parasitica* and obtained a stronger inhibition of mycelial growth than the purified enzymes (> 75% at 0.1 U/mg of crude extract). The partially purified glucanase reduced the pathogen's growth by about 50% and the inhibition of mycelial growth was found to be concentration-dependent [42].

Streptomyces spp. as a Phytophthora spp. inhibitor

In the search for biocontrol solutions against *P. capsici* and *Sclerotium rolfsii*, the main pathogens of black pepper (*Piper nigrum* L.), Thampi and Bhai (2017) [43] investigated actinomycetes present in the rhizosphere of healthy black pepper. Seven out of 50 isolates showed more than 90% inhibition against *P. capsici* in dual culture *in vitro* assay. The three isolates with a strong ability to inhibit the mycelial growth of both pathogens were found to belong to the genus *Streptomyces* (IISRBPAct1 presented 91.80% inhibition, IISRBPAct25 and IISRBPAct42 presented 86.30% and 68.80%, respectively). The functional characterization of plant growth promotion showed that the three *Streptomyces* isolates presented siderophore production and zinc solubilization, but only IISRBPAct42 presented phosphate solubilization. None of the isolates produce HCN and only IISRBPAct1 produces indole acetic acid (IAA). Regarding the production of the hydrolytic enzymes, all the three isolates produce, in different levels, protease, cellulase, amylase, and lipase. The IISRBPAct42 isolate produces the four enzymes analyzed at high levels. The analysis of growth promotion *in planta* using black pepper plants showed that all three isolates induced better height of plants, fresh dry root and shoot biomass, and the number of nodes and laterals. IISRBPAct1 increased fresh root weight, shoot height, and the number of nodes, and IISRBPAct42 induced a good development and extensive root system, with the maximum increase in fresh and dry root biomass. Regarding biocontrol efficacy, the treatments with the three isolates were tested in a protection experiment. The IISRBPAct25 isolate showed the maximum reduction of *P. capsici* infection (80.73%), followed by IISRBPAct1 (72.13%), and IISRBPAct42, which presented the least disease reduction (35.85%) [43]. In general, their results indicate that the IISRBPAct1 isolate is the most promising.

Arfaoui and colleagues (2018) [44] screened bacterial isolates from rhizosphere and rhizoplane of healthy soybeans and their ability to reduce *P. sojae* infection in soybeans. Nine out of one hundred bacterial isolates inhibited the mycelial growth of *P. sojae* isolates and were identified as belonging to the genera *Paenibacillus* sp. (S1), *Bacillus* sp. (S2, S3, S4, and S5), *Streptomyces* sp. (S9, S10, and S11), and *Lysobacter* sp. (S16). An inhibition rate of more than 50% was found in six isolates as follows: *Paenibacillus* (S1), *Bacillus* (S2, S4, and S5), and *Streptomyces* (S10 and S11). The assessment of growth-promoting parameters showed that (i) S3 and S1 produce siderophores, (ii) S3, S4, S9, S10, and S11 are phosphate solubilizer bacteria, (iii) S2, S3, S5, and S16 produce HCN, and (iv) all nine bacteria isolates produce ammonia and auxin, and the highest auxin production was observed in S3 and S9. The biocontrol

activity of S1, S9, S10, and S11 bacteria isolates were tested in soybean inoculated with *P. sojae* race 4 under greenhouse conditions. The highest reduction in disease severity was found in *Paenibacillus* (S1) and *Streptomyces* (S11) isolates. The four bacterial isolates tested increased root and shoot fresh weight and length in both healthy and inoculated plants; treatment with S11 was the most effective in increasing the soybean biomass, followed by S1 and S3 [44]. Taken together, their results indicate that the bacterial isolate S11, which belongs to the genus *Streptomyces* is a promising bacterium for biocontrol of *P. sojae*.

Burkholderia cenocepacia suppresses P. cinnamomi

Colavolpe and colleagues (2020) [45] screened the bacterial strains present in the rhizosphere of *Lotus corniculatus* to find isolates with strong antagonistic effects on *P. cinnamomi* and in *Trifolium subterraneum* infected by *P. cinnamomi*. A total of 172 strains were found, but only the B2Ri29 isolate was selected due to the potent inhibition of mycelial growth in the dual culture assay. This isolate presented high homology with *Burkholderia cenocepacia*. The B2Ri29 isolate presented cellulase activity *in vitro*, however, this activity was detected in other strains that did not inhibit *P. cinnamomi*, indicating that it is not the only mechanism for the *B. cenocepacia* anti-*Phytophthora* effect. The evaluation of *T. subterraneum* seedlings treated with B2Ri29 strain and inoculated with *P. cinnamomi* showed that seedlings presented higher dry weight than the seedlings treated only with *P. cinnamomi*, suggesting a protective effect of *B. cenocepacia* [45]. Although presenting promising results, the disease severity was not evaluated as well as the plant growth-promoting traits, which are important analyses considering that *B. cenocepacia* is an opportunistic pathogen of animals and humans. A summary of the main bacteria species with anti-*P. cinnamomi* activity discussed in this revision is presented in Table 2.

Studies with both fungi and bacteria as biocontrol agents against *Phytophthora* spp

This subsection will present some works investigating the use of bacteria and fungi tested as biocontrol agents against *Phytophthora* species. Looking for biological approaches to control the root rot of muskmelon caused by *Phytophthora drechsleri* (Tucker), Anjum and colleagues (2019) [46] obtained *Trichoderma* isolates (*T. harzianum* HM, *T. harzianum* HK, and *T. asperellum* TH) and isolated *B. subtilis* from soil samples collected at the Research Area of the University of Sargodha. All biocontrol agents tested showed mycelial inhibition against *P. drechsleri* to some degree in dual culture *in vitro* assays. The strongest inhibition was provided by *T. asperellum* TH, followed by *T. harzianum* HK, *T. harzianum* HM, and *B. subtilis.* The

Table 2 – Bacteria species with antagonistic effects against *Phytophthora cinnamomi*

Microorganism	*In vitro* method	% inhibition (*in vitro*)	*In planta* method	*In planta* results	Reference
Bacillus acidiceler	Volatile compounds Dual-culture	76% 46%	-	-	Méndez-Bravo et al., 2018
Burkholderia cenocepacia (B2Ri29 strain)	Dual-culture	100%	*Trifolium subterraneum* seedlings treated with B2Ri29 strain and inoculated with *P. cinnamomi*	Seedlings presented higher dry weight	Colavolpe et al., 2020
Pseudomonas fluorescens (C1 and C2 strains)	Dual-culture Non-autoclaved metabolites Autoclaved metabolites	40% (C1) and 44% (C2) ≥ 90% (both) 39% (C1) and 60% (C2)	Application of *P. fluorescens* treatments in avocado seedlings inoculated with *P. cinnamomi*	Plants are symptomless in both root and aerial parts with C1 and C2 treatments. Plants treated with *P. fluorescens* C1 isolate remained symptomless and presented enhanced length and weight of dry matter in the aerial portion	Sumida et al., 2020

non-volatile metabolites of the four microorganisms were evaluated and presented mycelial growth inhibition of *P. drechsleri*. The non-volatile metabolites from *T. asperellum* TH presented the maximum mycelial growth inhibition (46.8%). The volatile metabolites of *T. asperellum* TH also presented the highest mycelial growth inhibition (35.02%), however, the non-volatile metabolites represent the strong potential against *P. drechsleri*. The results under field conditions in muskmelon plants in two growing seasons indicate that all treatments, when applied individually, reduced the disease incidence and increased plant survival rate. Moreover, these treatments also presented plant growth-promotion traits, demonstrated by the increase in dry root and dry shoot weights. However, the most efficient treatment was the combination of all biocontrol agents, which showed the minimum percent of disease incidence (20%) and the highest survival rate of plants (80%), as well as the higher dry root and dry shoot weight [46]. Their results suggest that *Trichoderma* spp. and *B. subtilis* isolate have the potential to inhibit the mycelial growth of *P. drechsleri* at a low inoculum level.

Considering the ability of *P. capsici* to be spread through water and the limited synthetic fungicides for soilless systems, Gilardi and colleagues (2020) [47] investigated the efficacy of experimental BCA (alone or in a mixture) for the control of *P. capsici* on zucchini in a soilless system under controlled conditions. The BCAs used were: *Pseudomonas* sp. PB26, *Fusarium solani* FUS25, *Trichoderma* sp. TW2, and a mixture of three *Pseudomonas* spp. strains, *Pseudomonas* sp. FC7B, *P. putida* FC8B, and *Pseudomonas* sp. FC9B. The BCAs were applied to a pot and then 15 days-old seedlings were planted. The BCAs were re-applied six times to the growing medium at 5 day-intervals. The results obtained regarding the disease severity and efficacy were inconsistent throughout four trials, but the disease severity ranged from 30 to 47.9%. Moreover, the BCA mixture tested did not enhance the disease control efficacy compared to the efficacy of each BCA individually. Their results indicate that the BCAs tested are promising because they induced a certain degree of control of *P. capsici* and presented results compared with the commercial formulation mixture *Trichoderma gamsii* + *T. asperellum* [47].

Also focusing on the crown and root rot of zucchini (*Cucurbita pepo* L.) caused by *P. capsici*, Cucu, and colleagues (2020) [48] assessed the biocontrol effectiveness of the commercially available BCAs Serenade max - SM (*B. subtilis* QST713) and Remedier - RM (*T. gamsii* ICC 012 + *T. asperellum* ICC 080) and experimental (*Trichoderma* sp. TW2 plus a mixture of *Trichoderma* sp. FC7 and FC8). They conducted two field trials over two consecutive years (2016 and 2017) in two different sites (Moretta and Carmagola) to evaluate the efficacy of pre-planting soil treatments against *P. capsici*. In the first trial (2016) all BCAs treatments significantly reduced the disease severity ranging between 19.2 and 21.2 (0-100 index) at the Carmagnola site, and between 8.8 and 12.5 at the Moretta site. In the second trial (2017), the disease severity in the Carmagnola site was slightly reduced (50 and 63.9), while in the Moretta site the reduction was very expressive (11.3 and 18.8). All treatments tested did not affect the resident microbiota and mycobiota diversity in the two sites for the two different years. Moreover, all treatments reduced *P. capsici* abundance in the rhizosphere samples at different levels, indicating a direct pathogen-BCAs interaction. In general, their results reaffirmed the potential of *B. subtilis* and *Trichoderma* spp. as biocontrol agents for controlling *P. capsici* [48].

P. cinnamomi Rands infection is a destructive disease in avocado (*Persea americana* Mill.) crop, and to assess the potential of biological agents against *P. cinnamomi*, Sumida and colleagues (2020) [49] evaluated the effects of *Trichoderma* spp. and *Pseudomonas fluorescens* and their metabolites. The highest mycelial growth inhibition was promoted by Maize DP5 (73.3%) and Maize CP4 (73.3%) *Trichoderma* spp. isolates, followed by the commercial products tested. The two *P. fluorescens* isolates produced 40% (C1) and 44% (C2) inhibition and the lowest level of inhibition was observed in *Trichoderma* spp. isolated from coffee and sugarcane. The non-autoclaved metabolites from *P. fluorescens* C1, C2, and a mixture of C1 + C2 inhibited the mycelial growth of *P. cinnamomi* by more than 90%, meanwhile, the autoclaved metabolites of C1 presented only 39% of inhibition, and C2 and C1 + C2 inhibited by 60%. The experiments in avocado seedlings investigating the application of treatments after *P. cinnamomi* inoculation showed that the chemical compounds presented the most efficient control of the pathogen and the plants were symptomless in both root and aerial parts, but promising results were observed in the plants treated with *P. fluorescens* C1 isolate since plants remained symptomless and presented enhanced length and weight of dry matter in the aerial portion [49].

Discussion

To our knowledge, this is the first systematic review to gather data from the most recent works that aimed to find effective biological control solutions for species of the genus *Phytophthora*. Our search methodology retrieved a large number of studies, and this probably occurred due to (i) the generalized keywords used for the searches and (ii) the lack of use of a system similar to the Medical Subject Headings (MeSH). All studies included were published

between 2016 and 2022 in indexed journals. The gray literature was not searched.

Of the 31 scientific articles included, 14 presented data on the use of fungi for the biological control of *Phytophthora* species, 13 presented data on the use of bacteria, and 4 presented data on fungi and bacteria in the same methodological design. Furthermore, we found 2 papers addressing data on the use of plants of the genus *Brassica* for the control of *P. cinnamomi* and *P. nicotianae*, however, they did not meet the eligibility criteria. Despite aiming at the biological control of *P. cinnamomi*, the most of papers used in this review are related to several species of the *Phytophthora* genus. For a better understanding, the fungal and bacterial approaches tested against *P. cinnamomi* are summarized in Tables 1 and 2, respectively.

In the last few decades, a strong intensification of agricultural practices has occurred to attend to the global necessities, but this comes with negative aspects, mainly for biodiversity and the environment. The wide use of chemical compounds to control pests is effective but detrimental since it is one of the main drivers of air, water, and soil pollution. In this context, biological control has been considered an underlying pillar of integrated disease management [50, 51].

Our literature search revealed some methodological limitations, mainly regarding the studies of fungal isolates with antagonistic effects against *P. capsici.* In the five years of 2016 to 2020, four studies followed a very similar methodology that consisted in isolating an elevated number of fungi from pepper plant rhizosphere and assessing their anti-*P. capsici in vitro* and *planta* experiments. Taken together, the results reported by Yao et al. (2016), Nawaz et al. (2018), Mousumi Das et al. (2019), and Tomah et al. (2020) are in agreement that *T. harzianum*, *T. asperellum*, and *T. virens* are promising species in controlling the *P. capsici* and also present growth-promoting characteristics. In line with this, the study developed by Umadevi and Anandaraj (2019), which evaluated the mechanism of interaction between black pepper, *T. harzianum*, and *P. capsici* through proteomic analysis, reported interesting molecular results. *T. harzianum* also presented strong inhibition *in vitro* against *P. cactorum*, *P. inundata*, *P. rosacearum*, and *P. lacustris*, and good results in field studies, presenting plant growth-promoting traits to pear orchards and antagonistic activity in soil against *P. cactorum*, as reported by Sanchez et al. (2019). The works reported by Brown et al. (2019a, b) revised the efficacy of two commercial biofungicides against *P. cinnamomi* and their results indicate that these products present some limitations, mainly when flooded soil is considered. Moreover, some included studies presented methodological and statistical problems, which were discussed in the results section.

Furthermore, the studies reporting bacteria with antagonistic activity against *Phytophthora* spp. highlight the wide promising use of *Bacillus* spp. The results of Rajaofera et al. (2018) and Guo et al. (2020) showed the strong ability of *B. atropheus* and *B. velezensis* in inhibiting *P. nicotianae* in direct contact and their extracts *in vitro* and field experiments. Six out of 13 studies in this group studied biocontrol agents against *P. capsici*, demonstrating the importance of controlling this soil-borne pathogen. Works developed by Syed-Ab-Rahman et al. (2018, 2019) demonstrated the very promising effects of *Acinetobacter* sp., followed by *B. amyloliquefaciens* and *B. velezensis* against *P. cinnamomi* as well as against *P. citricola*, *P. palmivora*, and *P. capsici* in experiments *in vitro* and *planta*, and these species also presented plant-growth traits. They also reported the effects of the volatile organic compounds produced by these bacteria against *P. capsici* and the results were promising. This group of results is also composed of a high number of studies with very similar methodologies, based on the isolation of bacteria from the rhizosphere of selected plants.

Regarding *P. cinnamomi*, Méndez-Bravo et al. (2018) reported very good results using *B. acidiceler* isolates from avocado trees, including the strong potential of *P. cinnamomi* inhibition presented by the volatile compounds of *B. acidiceler*. As stated previously, *Acinetobacter* sp., *B. amyloliquefaciens*, and *B. velezensis* also showed mycelial growth inhibition of *P. cinnamomi* in dual culture *in vitro* assay. Colavolpe et al. (2020) focused only on *P. cinnamomi* and reported that *Burkholderia cenocepacia* is a potent inhibitor of this pathogen *in vitro*, however, as this bacterium is opportunistic for humans and animals, more studies must be conducted. The results presented by Sumida et al. (2020) indicate the use of *P. fluorescens* against *P. cinnamomi*, however, the study is very limited. Biofumigation also is considered a natural agent against pests and in line with this, Ríos et al. (2016) reported a very consistent, strong, and promising study using *Brassica* spp. genotypes to control *P. cinnamomi* in different stages of the life-cycle. Their results pointed to *B. carinata* genotype Bc-IAS119 as a promising biofumigant, and the results of Serrano-Pérez et al. (2017) are consistent with the use of *B. carinata* for controlling *Phytophthora* spp. infections and its associated diseases.

Ultimately, our study has some limitations mainly related to the selected studies due to the search terms used and to the size and quality of studies included. We are aware of the risk of bias, potentiated by the studies with poor methodological quality.

Conclusions

Collectively, our literature review indicates that *Trichoderma* spp., mainly *T. harzianum*, *T. virens*, and *T. asperellum* are

very promising fungi species for controlling different *Phytophthora* spp. in several conditions and promoting plant growth. Moreover, the *Bacillus* genus also is very promising in controlling and inhibiting several *Phytophthoras* spp. and promoting plant growth and better plant vigor. The biofumigant *B. carinata* is a potent inhibitor of *P. cinnamomi* and *P. nicotianae* and also promotes plant growth. Subsequent research should focus on elucidating the mechanisms behind each promising and potent biocontrol agent against *Phytophthora* spp. and to study methods to transfer these technologies to the agroindustry.

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