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Review

Phytophthora Root Rot: Importance of the Disease, Current and Novel Methods of Control

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Abstract: *Phytophthora sojae* is a pathogen of major agricultural importance, responsible for *Phytophthora* root rot (PRR) in soybean crops, which can cause significant yield losses each year. The severity of the disease depends on the soybean cultivar, its growth stage at the time of pathogen infection, and the environmental conditions. High soil moisture and temperature around 25–30 °C are favorable conditions for the development of the disease. Consequently, cultural practices are mainly limited to avoiding bad weather (high moisture) during the sowing or to promoting soil drainage. The use of chemical fungicides is restricted to seed treatments when there is a high risk of disease development. Currently the most economical option for controlling *P. sojae* is the use of host resistance. However, even if breeding is the main control strategy of PRR, the use of resistant cultivars leads to selection pressure on *P. sojae* populations, which can lead to high variability of the pathogen and therefore to its adaptation to overcome plant resistance. New strategies are therefore needed, including the use of biological control agents (BCAs). The use of BCAs (i.e., microorganisms or their metabolites) is a promising and sustainable alternative to PRR control that should be strengthened. Therefore, this review addresses the *P. sojae*–soybean interaction, mechanisms of pathogenicity and host resistance, as well as current and new management strategies with emphasis on the biological control of *P. sojae* and its associated mechanisms.

Keywords: biological control agents; *Phytophthora* root rot; *Phytophthora sojae*; soybean

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1. Introduction

Fungi and oomycetes are the most important soilborne pathogens responsible for several diseases on agronomically important crops, which can lead to severe limitations in production [1]. Within the oomycetes, the genera *Phytophthora*, *Hyaloperonospora*, *Plasmopara*, *Pythium,* and *Albugo* are the most devastating, with *Phytophthora* being by far the genus with the largest number of pathogenic species under study [2], representing one of the biggest threats to global food security. One of the most iconic *Phytophthora* species is *Phytophthora sojae*, responsible for root rot in soybean, resulting in billions of dollars in yield losses each year [3]. Several studies have already documented *P. sojae* pathology, life cycle, host resistance, and disease control strategies [4–6]. In general, chemical control is limited to systemic fungicides and may not be effective due to the pathogen adaptation and the subsequent fungicide tolerance development of the pathogen. Breeding for resistant cultivars therefore remains the main strategy for managing the disease, although this is threatened by the high variability of the pathogen [7]. Novel strategies are therefore required, among which are the use of biological control agents (BCAs), which have become more and more popular for the control of pests and diseases in several crops [8–10]. The use of these alternative biocontrol strategies is in line with the objectives of the 2030 Agenda

for Sustainable Development adopted by the United Nations in 2015, to support the needs of the present and future generations via sustainable consumption and production (https://sdgs.un.org/2030agenda, accessed on 20 November 2021). Therefore, the aim of this review is to understand the complexity of the *P. sojae*–soybean interaction, addressing aspects related to the mechanisms of pathogenicity and host resistance and summarizing the current and novel management strategies for the (bio-)control of this major pathogen.

2. *Phytophthora sojae*: General Characteristics

2.1. The Genus Phytophthora in Brief

Phytophthora (from Greek φυτόν (*phytón*), "plant" and φθορά (*phthorá*), "destruction"; "the plant-destroyer") is a genus that morphologically resemble fungi, but that belong to the Oomycota in the species-rich group of Stramenopiles, constituted by more than 100 species assembled in 10 clades [11,12]. Unlike true fungi, their cell wall contain cellulose instead of chitin, their growth is by means of filamentous hyphae lacking cross-walls and they produce sexual spores called oospores and swimming asexual spores called zoospores. The zoospores are motile by two flagella for locomotion and dispersion under high moisture conditions. Meanwhile, oospores are thick-walled sexual spores produced by homothallic or heterothallic fertilization. Within the genus, there is a diversity between species related to host plants, infected tissues, genome size, etc. [13]. Several members of this genus can cause important plant diseases worldwide, resulting in a complete loss of production. The most iconic example is the Irish potato famine in 1845–1852 by *Phytophthora infestans* [14]. Other important diseases caused by *Phytophthora* sp. are tomato late blight (*P. infestans*), cocoa black pod and papaya blight (*P. palmivora*), stripe canker on the cinnamon tree and other ornamental and forest trees diseases (*P. cinnamomi*) and soybean root rot *(P. sojae*) [15].

2.2. Phytophthora Root Rot

Unlike other species of *Phytophthora*, *P. sojae* (syn. *Phytophthora megasperma* f. sp. *glycinea*) has a narrow host range [16]. Although the lupins (*Lupinus*), lima bean (*Phaseolus lunatus*), string bean (*Phaseolus vulgaris*), and cranesbill (*Geranium carolinianum*) have also been reported as susceptible hosts [2,16], soybean is the primary host of *P. sojae* [5].

Phytophthora root rot (PRR) is one of the major diseases of soybeans. This monocyclic disease appears after heavy rains under high soil moisture and warm conditions, which are optimal situations for oospore germination. The infection can occur at any stage of soybean growth [5], and according to this, the severity of symptoms can vary markedly. This pathogen principally infects soybean at pre-emergence, being able to cause seed decay and seedling damping-off. When the infection appears at the later stage of growth, the symptoms include root rot, brown stem lesions, leaf yellowing, wilting, and finally, plant death.

The severity of the disease also depends on the level of resistance of the soybean cultivar that can vary from partial resistance to root resistance and R-gene mediated resistance [17]. The first two types of resistance are quantitatively inherited as a multigenic trait, whereby several genes contribute to the level of resistance; while the R-gene mediated resistance is a race specific resistance that is qualitatively inherited. In highly susceptible soybean cultivars, *P. sojae* colonize roots and stems, becoming chocolate brown. The leaves turn yellow and wilt. In these cultivars, practically every single plant in the field may be killed. As partial resistance increases, the damage caused by the disease decreases. Thus, the losses generated in cultivars with moderate to low partial resistance generally do not exceed 50%, while in cultivars with higher partial resistance, the roots are infected but do not develop stem rot. In these cases, the roots are light brown in color. Cultivars with high levels of partial resistance carry no visible symptoms and show a reduced yield loss. The specific resistance that gives R-genes generally is a complete resistance, since it is conditioned by single dominant Rps genes. However, this type of resistance is not effective for all populations of *P. sojae* given that it varies according to the geographical regions [5].

2.3. Phytophthora sojae Life Cycle

P. sojae forms two types of spores: oospores and zoospores. The oospores are sexual thick-walled cells that can germinate into hyphae under high soil moisture conditions (generally in compacted soil) and temperature around 25–30 °C. From these hyphae, two types of asexual cells can be formed: zoosporangia and zoospores [18]. Zoosporangia give rise to zoospores that can germinate and infect the host tissues directly. Zoospores have two flagella that allow them to swim for several hours. It has been observed that the severity of the disease correlates with the amount of water in the soil, suggesting that zoospores are the principal source of propagation of this pathogen. Zoospores move towards the root by recognizing chemical signals (i.e., isoflavones) of the host. Once they find the surface of the root, they adhere as a cyst and penetrate the cell through a germ tube, giving rise to the infection. This chemotactic attraction is highly specific to soybean–*P. sojae* interaction because *P. sojae* is attracted by isoflavones (daidzein and genistein) that are released by soybean plants [19,20]. These isoflavones are present in the seeds and root exudates of soybean. Since other *Phytophthora* species do not show the same attraction for these compounds, it has been suggested that the sensitive attraction of *P. sojae* zoospores to these isoflavones may be the main mechanism that determines host range [19]. During compatible interaction, *P sojae* colonizes the root and stem tissues giving rise to characteristic symptoms of *Phytophthora* root rot. The oospores are produced in large numbers in infected plant tissue under unfavorable conditions (low humidity and temperature). These sexual spores can survive for a long time in the soil and plant debris, awaiting favorable conditions for germination and the initiation of a new disease cycle.

2.4. Phytophthora sojae Variability

P. sojae draft genome sequence was first published by Tyler et al. (2006) [13]. The final assembly contained 79.3 Mb and 26,584 predicted genes. This genome has a bipartite organization, with conserved and highly dynamic regions [4,13,21]. Later, the *P. sojae* genome project was completed by using modern sequencing tools that revealed genomic variations [22].

The first report of the pathogenic variability of *P. sojae* was observed in Illinois in 1955 [23]. Since then, the disease was reported in all soybean-producing regions [24]. Recently, a variability in the number of pathotypes of *P. sojae* was observed in different soybean areas (e.g., Canada, USA, Argentina), indicating that the complexity of this pathogen has increased in this population [7,25]. Although the use of soybean cultivars with single dominant resistance genes to *P. sojae* (Rps) has allowed them to control the disease for years, the massive deployment of Rps genes in soybean has caused a rapid evolution of the virulence of *P. sojae.* Fields with years of soybean cultivation show a greater diversity of pathotypes than fields where soybean cultivation is recent. New pathotypes of the pathogen continuously appear worldwide. Thus, *P. sojae* is considered a highly variable pathogen [26]. Currently, at least 200 pathotypes of the pathogen have been reported [27]. It is important to know the complexity of *P. sojae* pathotypes found in each soybean region as this allows for better decision-making regarding which Rps-resistant soybean genotype to use to avoid PRR losses.

The pathogenic variants of *P. sojae* are evaluated according to the response to soybean cultivars with different Rps. There are more than 33 Rps genes/alleles located on nine soybean chromosomes (chromosomes 2, 3, 7, 10, 13, 16, 17, and 18) that confer specific resistance for each race of *P. sojae* [28]. Among them, Rps1 (alleles Rps1a, Rps1b, Rps1c, Rps1d, Rps1k), Rps2, Rps3 (alleles Rps3a, Rps3b, Rps3c), Rps4, Rps5, Rps6, Rps7, Rps8, Rps9, RpsSu, Rps10 [29], Rps11, Rps12, RpsZS18, RpsYu25, RpsHN, RpsQ, RpsX, RpsYD29 [30], RpsWY, RpsHC18 [31], RpsSN10, RpsUN1, RpsUN2, RpsJS, RpsYB30, RpsZS18, and RpsSu have been identified and mapped [32–42].

2.5. *Phytophthora sojae* Pathogenicity

Many studies have focused their attention on characterizing and comparing the diversity of *P. sojae* pathotypes to predict which Rps genes are the most effective for breeding programs [43–45]. Furthermore, specific and global transcriptional studies of *P. sojae* have been carried out to identify genes involved in pathogenesis [46,47], in particular genes coding for effectors that interfere with the soybean immune system [48–50]. The knowledge about *P. sojae* secreted effectors is vast [51]. Some of these effectors act outside (apoplastic) and others inside the host cells (cytoplasmic) to suppress soybean immunity, favoring pathogen development. Among them, the *P. sojae* genome contains several necrosis- and ethylene-inducing-like proteins (NLP), genes, and pseudogenes. NLPs are conserved apoplastic effectors widely distributed in eukaryotic and prokaryotic plant pathogens. It is known that the majority of *P. sojae* NLPs do not cause visible necrotic symptoms in plant tissues and are supposed to have various functional roles [52]. Another apoplastic effector with hydrolytic activity toward xyloglucan, xyloglucan-specific endoglucanase 1 (PsXEG1) has been reported to be highly expressed during the first steps of infection [53]. Even though this effector can be blocked by a soybean glucanase inhibitor protein (GmGIP1), *P. sojae* can protect PsXEG1 by a paralogous known as PsXLP1. This "pseudo-effector" has no enzyme activity but has higher binding affinity to GmGIP1, thus freeing the PsXEG1 [54].

Most of the cytoplasmic effectors are RxLR, and thus have two conserved N-terminal motifs (RxLR and dEER) for entry into host cells. These proteins with RXLR or dEER motifs are recognized by R genes in a gene-for-gene manner in the cytoplasm of the host plant and can eventually manipulate its defense in favor of infection, and even suppress plant programmed cell death (PCD). Another class of cytoplasmic effectors with a conserved motif, FLAK (F, Phe; L, Leu; A, Ala; and K, Lys), are Crinklers (CRNs). For example, *P. sojae* CRN78 acts suppressing host immune signaling by targeting phosphorylation and degradation of plant aquaporin proteins [55]. Other CRN effectors can reprogram host gene expression by targeting their promoters [56]. In addition, data suggest that *P. sojae* secretes effectors with opposite functions in the host cell death modulation that are jointly required for full virulence [48]. Finally, there is a cytoplasmic effector with the non-classical signal peptide (i.e., PsISC) that can reprogram the host salicylate metabolism pathway by hydrolyzing its precursor [57]. Interestingly, a protocol for implementing the CRISPR/Cas9 technology in *P. sojae* has been developed [58]. This novel tool allows to create heritable genome modification and deepen our understanding of *P. sojae* pathogenesis for cultivar breeding and other disease control strategies as well. Recently, the use of this gene editing technology has elucidated the biological functions of a *P. sojae* glycosyl hydrolase (PsGRGH). Results showed that PsGRGH was associated with the mycelial morphology, sporangium development, and virulence of *P. sojae*. Additionally, this protein seems to be essential for tolerance to biological control strains (*Bacillus*) and abiotic stresses [59].

2.6. Molecular Response of Soybean to *Phytophthora sojae*

During the Soybean–*P. sojae* recognition stage, root exudates (i.e., the isoflavones daidzein and genistein) attract the pathogen zoospores and stimulate the encystment and germination [19]. Following infection, the soybean transcriptome is remodeled and its response differs according to genotypic differences and *Phytophthora* infection (Figure 1) [60]. During susceptible interactions, soybean induces a wide array of biological processes after *P. sojae* infection, including up-regulation of the jasmonic acid (JA) pathway, suppression of ethylene (ET) pathway, and no significant changes in salicylic acid (SA) and brassinosteroids (BR) pathways [61]. Gene expression analysis reflects changes during the infection progress. During the initial biotrophic phase, few changes are detectable, and they mainly concern phytoalexin metabolism and the induction of defense and signaling proteins (e.g., protein kinase, peroxidase, calmodulin). Meanwhile, 24 h post-infection, a high number of expression changes are observed and coincide with the pathogen necrotrophic phase transition. During the *P. sojae* necrotrophic phase, soybean transcriptome shows a set of down-regulated genes (e.g., lipoxygenases and peroxidases) and a strong induction

of glycolysis and citric acid and glyoxylate cycle and phytoalexin biosynthesis related genes [62]. In addition, microRNAs associated with *P. sojae* infection have been characterized. Among them miR1507, miR1508, miR1510, miR159, miR319, miR396, and miR482 families were negatively regulated, whereas families of miR156, miR166, and miR171 were positively regulated. The potential targets of these microRNAs are defense-related kinase and transcriptional factors [63].

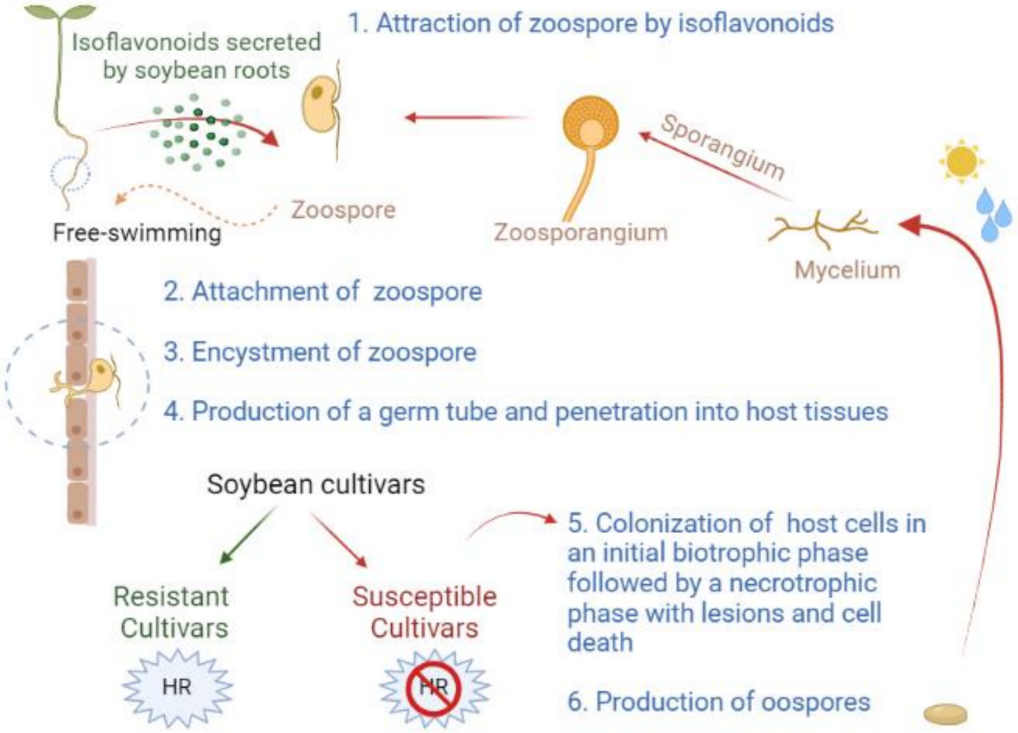

Figure 1. Process of *P. sojae* infection and response of soybean according to susceptible and resistant cultivars. The zoospores are attracted by root exudates (isoflavones daidzein and genistein), attach to the root surface and encyst before producing a germination tube entering the plant cells. If the host is a resistant cultivar, it induces hypersensitive reaction giving an incompatible interaction. Conversely, if the host is a susceptible cultivar, it triggers a wide array of biological processes following infection. The pathogen colonizes host cells in an initial biotrophic phase followed by a necrotrophic phase with necrotrophic lesions resulting in host cells death. Finally, under unfavorable conditions (low humidity and temperature) oospores are produced. These sexual spore can survive for a long time in the soil and plant debris. They can germinate and initiate a new disease cycle if the conditions are favorable for the disease development (high moisture and temperature around 25–30 °C).

Transcriptomic studies in resistant cultivars showed the up-regulation of cDNAs encoding enzymes of phytoalexin biosynthesis and pathogenesis-related proteins (Pru ar 1 gene belonging to PR-10 family) potentially involved in resistance to PRR [64]. In addition, Narayanan et al. (2009) [65] identified signaling genes (up and down-regulated) in the incompatible interaction. Among them are the down-regulation of genes encoding regulators of the chromosome condensation (RCC1) family protein. Even though it is known that PRR incompatibility is controlled by Rps (Resistance to *P. sojae*) genes, and there are huge variations in the molecular response between soybean near isogenic lines (NILs). It seems Rps genes/alleles have distinct timing and robustness in defense signaling [61].

Interestingly, several soybean genes, e.g., those encoding for pathogenesis-related protein (GmPR10), dirigent protein (GmDRR1), isoflavone reductase (GmIFR), a novel pathogenesis-related protein (GmPRP), chalcone Isomerase (GmCHI), and WRKY transcription factors (GmWRKY31, GmWRKY40), have been reported to play an important role in soybean resistance to *P. sojae* [66–72].

Furthermore, proteomic studies provided additional information about soybean defense against *P. sojae*. In fact, it has been proposed that the main mechanism during incompatible interaction is a local response with a H_2O_2 accumulation, the induction of salicylic acid (SA) signal pathway and the biosynthesis of high levels of isoflavones [73]. Moreover, elevated levels of ascorbate peroxidase suggested their potential role in reactive oxygen species (ROS) scavenging for the cellular homeostasis maintenance [74].

Other studies, using proteomic approaches, have focused on the exogenous application of BRs and their capacity to mediate response to *P. sojae* in soybean. BRs significantly enriched the lignin biosynthesis, which was consistent with the resistance phenotype [75].

Particular metabolites, such as the auxin IAA (indole-3-acetic acid), increase in susceptible soybean roots in the presence of the pathogen. Indeed, better modulation of auxin levels is associated with resistance to PRR [76]. Moreover, transcriptional and metabolic studies allowed the identification of groups of metabolites potentially involved in resistance to PRR (i.e., sugars, organic acids, amino acid derivatives and secondary metabolites). However, only a few differentially expressed genes, such as those encoding invertases, chalcone synthases, 2-hydroxyisoflavanone synthases, and xanthine dehydrogenase/oxidase, were involved in the regulation of potential resistant substances [77]. The integration of these transcriptomic and metabolomic data illustrates the limitation of the omics application separately, since some modifications in the transcriptome do not necessarily have an absolute correlation downstream.

3. Control Strategies of *Phytophthora* Root Rot

Currently, control of soybean PRR include the use of resistant cultivars, soil drainage, and seed treatment with fungicides [5]. Although these strategies are widely used and effective in limiting crop productivity losses, their intensive use can produce potential negative effects that must be taken into account. In recent years, the use of biocontrol strategies has grown substantially as a promising alternative to reduce pathogen resistance or environmental pollution. Among them, the use of microorganisms or their metabolites as well as plant extracts, minerals, and ions are considered in disease management programs [78,79].

3.1. Host Resistance

The most economical option for controlling *P. sojae* is the use of resistant soybean cultivars [80]. Backcross (BC) breeding is the most commonly used method for the secure production of plant resistance. This methodology consists in crossing an agronomically adapted genotype (GA) with another genotype carrying a gene of interest (e.g., resistance gene). The resulting progeny is then crossed with the GA for several generations, selecting at each cycle of BC breeding the gene of interest [81]. The complete genome sequence of the soybean [82] has allowed genetic breeding programs to select genes of interest through genetic markers. The most commonly used molecular markers (MM) for gene mapping and assisted selection are simple sequence repeat (SSRs), sequence characterized amplified region (SCAR), and sequence tagged site (STS). These markers are easily reproduced in laboratory via the use of the polymerase chain reaction (PCR). Although these MM are still used in classic genetic breeding programs, the new technologies of massive DNA sequencing (next-generation sequencing NGS) have become the main strategy for the discovery of single nucleotide polymorphisms (SNPs) and genotyping in large populations. Among the used methods are the restriction site-associated DNA tag sequencing (RAD-seq), genotyping by-sequencing (GBS), 2b-RAD, and specific length amplified fragment sequencing (SLAF-seq) [75].

Currently, there are more than 33 Rps genes reported in soybean, several of which are commercially used to protect plants against *P. sojae*. The gene Rps1 encoding six alleles is the most widely used in breeding programs as a source of resistance to *P. sojae*, particularly Rps1k [83]. However, the utilization of resistant cultivars causes a selection pressure over *P. sojae* populations that may lead to Rps gene adaptation, consequently requiring the

development of alternative control strategies. The capability of the pathogen to overcome the plant resistance depends on its capacity to suppress or alter the initial stage of the plant-pathogen interaction (recognition stage), allowing its growth and reproduction. This virulence gain can be accomplished by several mechanisms. The pathogen avirulence genes (Avr) are located in repetitive regions of the genome, where mutation or recombination events are more likely to occur, leading to modifications or complete losses of these genes. Moreover, the pathogen can acquire an additional epistatic effector that suppresses the immune response. In fact, avirulent genes could be regulated at the transcriptional level, as the result of a mutation in the regulatory regions or by the differential expression of sequence-identical epialleles [84].

3.2. Chemical Control

Chemical pesticides, from fungicides to algaecides, have been used for oomycetes control with varying degrees of success [85,86]. The efficacy of chemical formulations is associated to their mode of action, their persistence, and the biology of the target pathogen. Particularly, the chemical control of underground pathogens is restricted to the use of systemic fungicides that are absorbed by the plant. Among them, the use of metalaxyl-based formulations is used to control *P. sojae* [87]. Seed treatment with this substance has been shown to be beneficial when there is a high risk of disease development [88,89]. However, the flexibility of *P. sojae* to adapt and overcome chemical control methods and the increasing public concern on the intensive use of agrochemicals demand the consideration of more sustainable alternatives (as nano-fungicides or bio-pesticides) to ensure the success of environment protection and food safety.

3.3. Agronomic Practices

PRR control through cultural practices is mainly limited to avoiding bad weather (high moisture) during the sowing or through soil drainage [5]. No-tillage, which has shown many advantages for agricultural systems [90], can lead to PRR development since the presence of a higher level of *P. sojae* inoculum has been observed during this practice as compared to conventional tillage [91]. Similarly, fertilization with potassium chloride can potentially increase the incidence of PRR on soybean seedlings [92]. Crop rotation is not an effective option due to the ability of oospores to survive for long periods in the soil. However, it has been shown that it can contribute to maintaining a uniform diversity, in order to avoid a dominant race that leads to the loss of resistance of cultivars [93]. Interestingly, intercropping between soybean and maize could suppress *P. sojae* disease. Phenolic acids in maize rhizosphere have strong antimicrobial activity and interfere with zoospores chemotaxis [94]. Nevertheless, this practice requires attention, since during interspecies interactions, non-host roots can recruit many microbial species, which can be beneficial or harmful to the crop of interest.

3.4. Integrated Disease Management (IDM)

This disease management system consists in the combination, according their compatibility, of all suitable techniques and methods available in order to maintain the pathogen population at levels below those causing economic injury [95]. In the case of *P. sojae*, this approach may consist in combining some of the strategies presented above to increase the type of resistance (quantitative or qualitative) with the use of fungicides and agricultural practices.

3.5. Biological Control Agents (BCAs)

Soil contains a huge reservoir of microorganisms that comprise bacteria (4–20 $\times$ 10^9 cells cm^{-3}), protists (10^4–10^7 cells m^{-2}), fungi (10^6–10^9 cells g^{-1}), and viruses (up to 10^9 g^{-1} soil) with millions of species or ecotypes [96]. Within the plant rhizosphere, many of these microorganisms or even the metabolites that they produce can be used for biocontrol. In fact, most BCAs have been isolated from the rhizosphere or plant tissues,

since a large number of them are endophytic. Very recently, Bolivar-Anillo et al. (2020) [83] summarized all the studies in which endophytic bacteria and fungi had been used successfully against different species of *Phytophthora*. However, studies based on the use of BCAs to control PRR are few (see Figure 2).

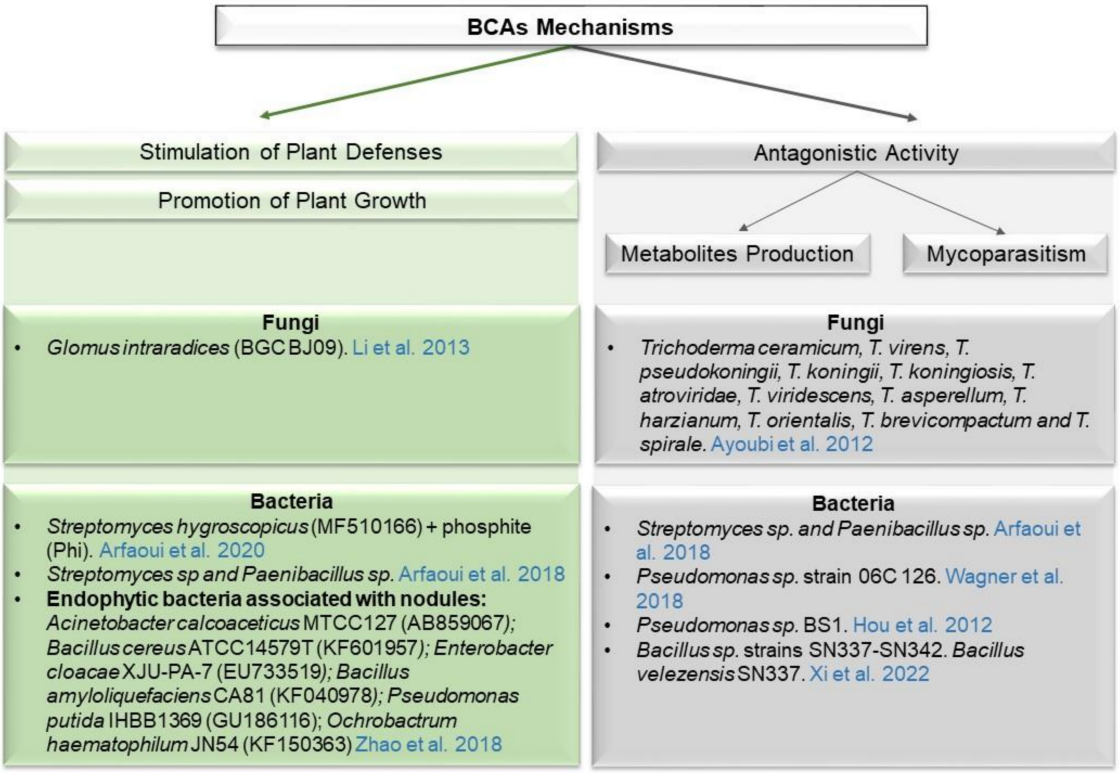

Figure 2. Biocontrol agents for the management of the *Phytophthora* root rot and the associated mechanisms. In green are BCAs (fungi and bacteria) associated to the promotion of plant growth and stimulation of plant defense. In grey are BCAs (fungi and bacteria) with antagonistic activity.

The most often reported mechanisms used by BCAs to protect the plant from pathogens include: competition for infection sites, competition for substrate, antibiosis, production of siderophores, mycoparasitism, production of cell wall degrading enzymes, and the induction of the plant immune resistance. In most of the cases, more than one of these mechanisms can act simultaneously [97]. However, the ability of the BCAs to control pathogens depends on various factors, such as their capacity to interact with the plants, the pathogen itself, the soil microbiome, and many other 'agro'-environmental factors.

3.5.1. Promotion of Plant Growth

A variety of bacteria and fungi isolated from the rhizosphere can improve plant growth through biological nitrogen fixation, mineral solubilization (P and Zn), and phytohormone production, at the same time resulting in plants more resistant to pathogens [98]. Bacteria belonging to *Paenibacillus*, *Bacillus*, and *Streptomyces* isolated from the soil (rhizoplane and rhizosphere) have shown antagonist activity against *P. sojae*. In particular, one strain of *Streptomyces hygroscopicus* S11 was reported to reduce by 50% the disease severity caused by *P. sojae* and to improve soybean shoot and root weight through auxin production, nitrogen fixation, and siderophore production [99]. Interestingly, the separate application of *S. hygroscopicus* S11 and potassium phosphite (Phi) solution reduced soybean root rot symptoms, and a synergic effect in the soybean plant growth was observed when both treatments were combined [100].

3.5.2. Stimulation of Plant Defenses

Plants are able to recognize the presence of microorganisms through pattern recognition receptors, and in consequence induce their defense. The recognition of pathogen-associated molecular patterns, PAMPs, or microbe-associated molecular patterns, MAMPs (i.e., non-pathogenic microorganism), triggers a cascade of cellular signals with a defense gene activation (antimicrobial compounds, resistant protein, phenolic compounds). Several beneficial microorganisms activate plant immunity via induced systemic resistance (ISR).

Arbuscular mycorrhizal fungi (AMF) and *Trichoderma* are the fungi most widely used for improving plant resistance to diseases. It has been shown that the use of AMF improves the resistance of host plants against different pathogens (virus, fungi, bacteria, nematodes), possibly because of better plant nutrition and the activation of the mycorrhizal induce resistance (MIR) [101]. Recent studies have shown that mycorrhizal soybean plantlets had a reduction in soilborne pathogen colonization and an important transcriptional reprogramming [102–104], suggesting an AMF regulation of the host defense response. Although mycorrhizal protection has been extensively studied, there are only a few studies that have demonstrated soybean protection against *P. sojae*. AMF enhanced the resistance of soybean plants against *P. sojae* through the release of H_2O_2 and jasmonic acid accumulation in response to infection [105]. Arfaoui et al. (2020) [100] tested the combined effect of *S. hygroscopicus* and phosphite (Phi) in susceptible and tolerant soybean cultivars. The effect of pre-treatment (*S. hygroscopicus* + Phi) was observed on defense responses and salicylic acid (SA) and jasmonic acid (JA) production. The susceptible cultivars showed higher levels of SA and JA than the tolerant cultivars after *P. sojae* infection. Soybean plants pre-treatment (*S. hygroscopicus* + Phi) showed a reduction of the level of SA and JA in response to *P. sojae*. The differential accumulation of these hormones in the time suggests a regulation of interaction by the temporal coordination of defense-related genes.

3.5.3. Antagonistic Activity

Many microbial species have been reported for their antagonistic activity, including *Trichoderma*, *Bacillus*, and *Pseudomonas* [78]. In general, antagonistic microorganisms have no unique mode of action. Some of them include metabolite production, mycoparasitism, antibiosis, and competition. Arfaoui et al. (2018) [99] isolated rhizospheric bacteria adhering to soybean roots and evaluated *in vitro* and under greenhouse conditions their potential biocontrol activity. Six isolates were efficient against *P. sojae* race 4 under *in vitro* conditions, while only two isolates belonging to the genera *Paenibacillus* and *Streptomyces*, had potential biocontrol properties for PRR. These observations are in agreement with numerous studies that have demonstrated the biocontrol potentials of bacteria and fungi against important phytopathogenic fungi [106,107].

A combined study involving antagonistic assays and whole genome analysis predicted that *Pseudomonas* isolated from aquatic ecosystems can produce a non-ribosomal peptide synthetase (NRPS) and two bacteriocin with the ability to inhibit oomycetes. Furthermore, authors identified 21 biosynthetic gene clusters with potential for antagonistic activity, suggesting that more than one inhibitory compound can be produced under different environmental conditions [108]. *Pseudomonas* capacity to produce compounds with potential for biological control has also been studied. For instance, Bi et al. (2012) [109] reported that *Pseudomonas sp*. BS1 produces rhamnolipids, metabolites obtained from fermentation filtrates, which have effects on the normal growth and development of the hyphal, zoosporangium, and zoospore of *P. sojae*.

Several endophytic bacteria associated with nitrogen-fixing nodules, including *Acinetobacter*, *Bacillus*, *Enterobacter*, *Ochrobactrum*, and *Pseudomonas*, can exert antagonistic activity against *P. sojae* through siderophores and lytic enzymes (chitinase and laminarinase) production [110].

The *Trichoderma* genus contains several antagonistic species that have been widely studied and commercially used due to their capacity to protect the plant and reduce the pathogen populations [111]. Ayoubi et al. (2012) [112] found that *Bradyrhizobium*

and *Trichoderma* dual inoculation could control *P. sojae* and promote the growth of soybean plants. Furthermore, different *Trichoderma* species isolated from fields in Iran in combination with commercial *B. japonicum* were tested for their biocontrol effects in soybean against *P. sojae*. Even though all the species of *Trichoderma* tested in this work reduced the pathogen growth by mycoparasitism and by the production of volatile and non-volatile metabolites, *T. brevicompactum* was the most effective against *P. sojae* and was proposed to be used in the management of PRR. Importantly, although all these studies were able to demonstrate biological control of *P. sojae*, there are only few works that evaluated the impact of BCAs in the field. Recently, Xi et al. (2022) [113] studied the specific effects of six bacteria selected from soybean rhizosphere in China. All the tested strains showed antagonistic activity against *P. sojae*. However, one of these strains, identified as *Bacillus velezensis* (SN337), was the most promising. Results suggested a reduction of severity in root rot incidence that could be explained by the antagonist effect of *Bacillus* SN337 over *P. sojae*, and by the improvement of the bacterial community structure in the soybean rhizosphere.

4. Concluding Remarks and Future Perspectives

One of the major concerns about PRR is the increasing variability of *P. sojae*, since genetic resistance mediated by Rps genes is the major mechanism of disease control. However, many other factors can influence the virulence activity of the pathogen [114]. Particularly, knowledge about how environmental conditions affect the pathogen fitness during its life cycle can help to integrate concepts for more efficient disease control. As was shown in this review, a diversity of microorganisms that coexist within the host or in the rhizosphere can increase or decrease the disease severity caused by *Phytophthora* species including *P. sojae*. Nevertheless, only a few studies have considered the use of BCAs as a sustainable management strategy of PRR. If the potential of these BCAs is thus undeniable, their effects can vary according to multiple factors, which makes them vulnerable to impractical use by the agricultural world compared to chemical pesticides. Moreover, it is important to remember that BCAs can enter into competition with established microbial communities and can spread to other cultures. Their safety for human/animal health must also be established before their use in agricultural systems. Therefore, in this review, we highlighted the need to study in detail how the application of BCAs can affect the pathogen and the rhizosphere microbiota, and if soil community modification can influence the plant–BCA interaction. In this sense, the challenge is the development of research with a combination of techniques that will allow to study the overall effect of the use of BCAs on the pathogen growth, disease development, and the environment. Knowledge about how these microorganisms behave in situ may allow human or environmental risk assessment. We are convinced that the combination of current management practices and the application of BCAs represents a promising approach for successful crop protection.

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