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Review

Cell-Free Supernatants of Plant Growth-Promoting Bacteria: A Review of Their Use as Biostimulant and Microbial Biocontrol Agents in Sustainable Agriculture

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Abstract: Plant growth-promoting bacteria (PGPB) afford plants several advantages (i.e., improvement of nutrient acquisition, growth, and development; induction of abiotic and biotic stress tolerance). Numerous PGPB strains have been isolated and studied over the years. However, only a few of them are available on the market, mainly due to the failed bacterial survival within the formulations and after application inside agroecosystems. PGPB strains with these challenging limitations can be used for the formulation of cell-free supernatants (CFSs), broth cultures processed through several mechanical and physical processes for cell removal. In the scientific literature there are diverse reviews and updates on PGPB in agriculture. However, no review deals with CFSs and the CFS metabolites obtainable by PGPB. The main objective of this review is to provide useful information for future research on CFSs as biostimulant and biocontrol agents in sustainable agriculture. Studies on CFS agricultural applications, both for biostimulant and biocontrol applications, have been reviewed, presenting limitations and advantages. Among the 109 articles selected and examined, the *Bacillus* genus seems to be the most promising due to the numerous articles that support its biostimulant and biocontrol potentialities. The present review underlines that research about this topic needs to be encouraged; evidence so far obtained has demonstrated that PGPB could be a valid source of secondary metabolites useful in sustainable agriculture.

Keywords: plant growth-promoting bacteria; cell-free supernatants; cell-free metabolites; spent cultures; exopolymers; biofertilization; phytopathogenic microorganism inhibition

1. Introduction

Plant growth-promoting bacteria (PGPB) are a widespread group of bacteria generally living in association with plants, having several beneficial effects related to (i) improvement of plant nutrient acquisition [1], (ii) promotion of plant growth and development [2], and (iii) induction of tolerance towards abiotic and biotic stress [3]. Although the mechanisms behind these effects are complex and not fully known, most of the effects can be ascribed to the bacterial ability to produce metabolites with stimulant and/or protective effects.

Among stimulant molecules, a meaningful role is played by phytohormones (i.e., abscisic acid, auxins, cytokinins, ethylene, and gibberellins). These substances regulate plant growth at all stages of development, by stimulating growth, coordination between cells, tissues and organs, and by

preserving certain functions [4]. Stimulant effects are also ascribed to organic acids, which induce the release of nutrients from insoluble complexes by lowering soil pH, chelation, and mineralization [5,6]. The promotion of plant growth and development are also induced by several other secondary metabolites, volatile compounds, and exopolysaccharides [2,7].

Phytohormones, organic acids, secondary metabolites, volatile organic compounds, and exopolysaccharides also provide protection/tolerance against several stresses, both abiotic (e.g., salt and drought) and biotic (e.g., bacterial and fungal pathogens).

Due to the above characteristics and their sustainability, PGPB have received increasing attention in recent decades and their use is highly regulated by the European Parliament and by the European Council by the Regulation (EU) 2019/1009. However, formulation and effectiveness of PGPB cells present challenges. The main limit for bacterial cell suspension without an adequate carrier or formulation is that, after inoculation in the soil, there is a decrease in bacterial population for most of the PGPB species. This low persistence, combined with low production of bacterial biomass, makes it difficult to support the activity in the rhizosphere. The non-optimal bacterial physiological status at the time of application can prevent the accumulation of a sufficiently large PGPB population in the rhizosphere. Besides, these bacteria must compete with the adapted native microbial community and resist predation by soil microfauna [8]. In the scientific literature, many potential PGPB strains are described; however, only a few are on the market. This situation is mainly due to low bacterial survival during product shelf life and, once applied, inside the agroecosystems.

PGPB strains with these challenging limitations can be used for the formulation of a cell-free supernatant (CFS). CFSs, are mixtures derived from broth cultures by several mechanical and physical processes that allow the removal of cells. CFSs can be obtained through two main unit operations, centrifugation, and filtration (i.e., microfiltration, ultrafiltration, nanofiltration, inverse osmosis). These techniques can be applied individually or in combination with other technologies according to the desired final product. Several other downstream processes can be applied to isolate and purify target metabolites, also from the inside of cells [9].

Many studies of CFSs deal with metabolites utilized in medical and food sectors; studies on the biostimulant and biocontrol properties of these formulations in plants are limited to in vitro tests, controlled conditions experiments, and/or addressed to the characterization of target metabolites.

Numerous reviews and updates concerning PGPB in agriculture, from their isolation to their formulation, can be found in the literature. However, as far as we know, there are no reviews dealing with applications of CFSs obtained by PGPB. The present review aimed at summarizing studies concerning PGPB CFSs and their metabolites as biostimulant and biocontrol agents. Several databases have been used to create a collection of articles. After article screening, a total of 109 valid published works has been selected. Data organization allowed the discussion of CFSs' and their metabolites' biostimulant and soil-borne pathogen control applications (i.e., of bacteria, fungi, oomycetes). This review provides useful information for future research on CFSs as biostimulant and biocontrol agents in sustainable agriculture.

2. Methods

To find relevant publications on CFSs and their metabolites an online literature search was conducted. The following databases were employed in the search:

- CAB Direct (cabdirect.org)
- Google scholar (scholar.google.com)
- Science Direct (sciencedirect.com)
- Scopus (scopus.com)
- Springer Link (springerlink.com)
- Taylor and Francis (tandfonline.com)
- Web of Science (webofknowledge.com)
- Wiley Online Library (onlinelibrary.wiley.com)

Several combinations of search terms were attempted in each database. The terms "cell-free supernatant", "spent supernatant", "bacterial broth", "bacterial culture", and "bacterial metabolites" were combined with "biostimulant", "biocontrol", "phytopathogens", "fungi", "bacteria" "oomycetes", and "sustainable agriculture". The search was extended to all manuscript sections.

The online literature search produced a large collection of articles that have been screened according to Title and Abstract contents (Initial check). Then, articles were read completely and related papers were included in the collection if they were not already present (Related paper check). The reading and screening allowed us to discard irrelevant papers from the collection and to find a total of 109 relevant articles. The complete reading of the articles also allowed the organization of the collection based on two main categories: "biostimulant" and "biocontrol". The Biostimulant category was organized based on details about PGPB strain, compound, production technique utilized to obtain CFS/metabolites (C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes), crop, and experiment (P, in vitro growth; G, greenhouse growth; O, open field growth). The Biocontrol category was organized depending on the type of phytopathogen (i.e., bacteria, fungi and oomycetes) and based on details about PGPB strain, pathogen, compound, production technique utilized to obtain CFS/metabolites (C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes), and experiment (V, in vitro antagonism; X, ex vivo antagonism; P, in vitro growth; G, greenhouse/pot growth). For each category, tables were prepared to provide these details per reference.

3. CFSs as Biostimulant Agents

Over the years, the application of synthetic fertilizers in agriculture has increased to the maximum requested by global demand–crop yield [10]. Continuous fertilization campaigns repeated over the years involve considerable production costs, environmental pollution and soil degradation [11,12]. The use of PGPB-CFSs and isolated metabolites can represent an alternative sustainable technique to synthetic fertilizers. Table 1 summarizes details of the studies concerning the application of CFSs and their metabolites as biostimulant agents. These studies reported interesting biostimulant properties of CFSs in vitro and in planta (both in greenhouse and in open field experiments).

The capability of CFSs to stimulate in vitro growth of seedlings has been reported for *Medicago polymorpha* [13], *Oryza sativa* [14], *Glycine max* [15,16], *Zea mays* [17], *Lemna minor* [18], *Solanum lycopersicum* [19], *Glycine max*, and *Triticum aestivum* [20]. The CFS obtained from *A. brasilense* Cd strain has been reported to be able to promote growth in an *M. polymorpha* seedling inoculated with *Rhizobium meliloti* RT1 early nodulation and changes in root morphology and function by ethylene production [13]. An 8% (*v*/*v*) CFS-based formulation obtained from *A. brasilense* Cd strain showed a good capability to increase in vitro *O. sativa* growth. In particular, the presence of CFS in the culture medium promoted better elongation, root surface area, root dry matter, and development of lateral roots of *O. sativa* seedlings than those grown on culture media without CFSs addition [14]. Idris et al. also described concentration-related positive effects of *Bacillus* spp. CFSs in *Z. mays* L. in a coleoptiles cylinder test [17] and in *L. minor* in 48-well microtiter plates growth [18]. *Bacillus amyloliquefaciens* KPS46 CFS metabolites positively affected growth and development of *G. max* under gnotobiotic condition [15]. The CFSs obtained from *Burkholderia seminalis* (an isolated strain selected for high levels of Indole-3-Acetic Acid (IAA) production) showed a positive impact on in vitro germination of tomato seeds [19]. Ethyl acetate extract of *Methylobacterium* spp. CFSs, composed mostly of cytokinins, demonstrated positive effects on *Triticum aestivum* L. seed germination and seedling growth [20]. To assess the actual capability of a certain compound to stimulate plant growth, in vitro experiments should be followed by in planta ones. However, among the above mentioned reports, only a few studies [13,15] confirmed in planta effectiveness in greenhouse experiments.

Effectiveness of CFSs' biostimulant properties in greenhouse experiments was also reported for *Manihot esculenta* [21], *Musa* spp. [22], *Vigna unguiculata* [23], *Pisum sativum* [24], *Vicia villosa* [24], *G. max* [16,25,26], and *M. sativa* [27]. *Bacillus* sp. CaSUT007 CFS solvent extracts containing lipo-chittin

oligosaccharides (LCOs), phytohormone and extracellular proteins promoted the growth of *M. esculenta* Crantz [21]. Posada et al. [22] reported that CFSs of *Bacillus subtilis* EA-CB0575, either from vegetative cells or from spores, significantly increased shoot length and total dry weight of *Musa* plants compared with control. CFSs of *Streptomyces acidiscabies*, containing siderophores and auxins, were able to promote growth and alleviate metal toxicity in *Vigna unguiculata* L. [23]. *Rhizobium leguminosarum* bv. *viciae* CFSs rich in LCOs were able to ameliorate *Pisum sativum* and *Vicia villosa* growth [24]. *G. max* was positively affected by treatment with *A. brasilense* Sp7 CFSs, inducing better root growth than experimental condition treated with the bacterial inoculum [25]. For this plant, the enhancement of biostimulant effectiveness has been reported when a combination of different treatments was tested. The application of CFSs of *A. brasilense* strains Ab-V5 (CNPSo 2083) and Ab-V6 (CNPSo 2084) via seeds improved root morphology and nodulation in *G. max* inoculated with *Bradyrhizobium* spp. [16]. However, the efficacy was lower than co-inoculation with *Bradyrhizobium* spp. single strains. Positive effects on *G. max* were reported by Moretti et al. [26]. In their work the best results were obtained with a combination of (i) *Bradyrhizobium diazoefficiens* (USDA 110) and *Rhizobium tropici* (CIAT 889) metabolites enriched in LCO seed treatment, (ii) *Bradyrhizobium japonicum* (SEMIA 5079) and *B. diazoefficiens* (SEMIA 5080) inoculation; and (iii) *A. brasilense* (Ab-V5 and Ab-V6) foliar application. Efficient combination was also reported by Morel et al. [27]. These authors indicated that hydroponic solution added with bacterial and root-secreted molecules (i.e., flavonoids, phytohormones, and lipophilic chitin oligosaccharides obtained during a co-inoculation of *Medicago sativa* L. with *Sinorhizobium* and *Delftia* strains) increased growth of *M. sativa*. Overall, this combination was the most effective in terms of root development, activity (i.e., greater exploitation of the soil), nodulation, and crop grain yield (+10%) compared with plants inoculated only with *Bradyrhizobium* strains and other formulations.

The final confirmation of the effectiveness of a formulation can be reached in open-field experiments, where the environmental conditions are extremely variable. Open-field studies of CFS biostimulant activity are few. Marks et al. [28] reported the enhancement of grain yields of *Glycine max* L. and *Zea mays* L. when rhizobial metabolites (exopolysaccharides, phytohormones, and LCOs) were co-inoculated with both *Bradyrhizobium* spp. and *Azospirillum* spp. Similar trends were also obtained by adding *Bacillus subtilis* QST 713 to this combination within the foliar application. The recent article by Tewari et al. [29] indicated that a combined formulation of *Bradyrhizobium* sp. IC-4059, its CFSs, and exopolysaccharides (EPS) increased the productivity and nodulation of *Cajanus cajan* in the field, compared to both bacterial inoculum and CFS applied alone.

From all these reports it is evident that further processing of CFSs provides several metabolites with interesting stimulant properties. Among these metabolites, LCOs are the most tested. Lesueur et al. [30] summarize the effective applications of different LCOs on legume–rhizobia symbiosis, with positive outcomes on plant growth. Positive LCO application effects have also been recorded for non-leguminous plants, e.g., *Zea mais*, *Solanum lycopersicum*, *Picea abies*, *Daucus carota*, *Arabidopsis thaliana* [31]. Biostimulant PGPB metabolites can also be obtained from lactic acid bacteria (LABs). In addition to their probiotic properties, metabolites of these strains showed interesting biostimulant and biocontrol potential in agriculture [32]. Rodríguez-Morgado et al. [33] reported that L-lactic acid obtained from *Lactobacillus rhamnosus* whey-waste stimulated soil microbial activity and release of soluble phosphates. PGPB inoculation enriched with lactic acid was also involved in shaping the composition of soil bacterial communities. In a second study, the same research team published similar results on metabolites isolated by *L. rhamnosus* whey fermentation and separated by physicochemical processes [34]. The protein hydrolysates and the lactic acid-induces soil microbial activity. Lactic acid also positively influenced microbial biodiversity, favoring some plant growth promoter families (i.e., Bacilliaceae and Veillonellaceae family). Several PGPB strains can also be exploited to produce biosurfactants (BFs) and bacteriocins. Positive outcomes on soil quality and plant growth promotion have been extensively reviewed both for BFs [35–37] and for bacteriocins [38,39].

Table 1. Studies of stimulant properties of plant growth-promoting bacteria (PGPB) cell-free supernatants (CFSs) and CFS metabolites.

PGPB Strain	Compound	PT	Crop/Experiment	Ref.
Azospirillum brasilense Cd	IAA	C	*Medicago polymorpha* – P+G	[13]
Azospirillum brasilense Cd	IAA	C+F	*Oryza sativa* – P	[14]
Bacillus amyloliquefaciens KPS46	EP; LP; indoles	C+F	*Glycine max* – P+G	[15]
Bacillus amyloliquefaciens FZB24, FZB42, FZB45	IAA	F	*Zea mays* – P	[17]
Bacillus subtilis FZB37	IAA	F	*Zea mays* – P	[17]
Bacillus amyloliquefaciens FZB42	IAA	F	*Lemna minor* – P	[18]
Burkholderia seminalis	IAA	C	*Solanum lycopersicum* – P	[19]
Methylobacterium spp.	LCO	C+E	*Triticum aestivum*– P	[20]
Azospirillum brasilense Sp7	IAA, ILA and GA	C+F	*Glycine max* – G	[25]
Azospirillum brasilense Ab–V5, Ab–V6	Indolic compounds	C+F	*Glycine max* – G	[16]
Bacillus sp. CaSUT007	EP and indoles	C+E	*Manihot esculenta* – G	[21]
Bacillus subtilis EA–CB0575	IAA, Siderophores	C+F	*Musa* spp. – G	[22]
Streptomyces acidiscabies E13	Siderophores	DP	*Vigna unguiculata* – G	[23]
Rhizobium leguminosarum bv. *viciae* GR09	LCO	E	*Pisum sativum, Vicia villosa* – G	[24]
Sinorhizobium meliloti U143	Flav, IAA, Trp	C+F	*Medicago sativa*– G	[27]
Delftia sp. JD2	Flav, IAA, Trp	C+F	*Medicago sativa*– G	[27]
Bradyrhizobium diazoefficiens USDA100 + *R. tropici* CIAT889	LCO	C+F	*Glycine max* – G	[26]
Rhizobium tropici CIAT 899	Flav	C+F+E	*Zea mays* – O	[28]
Bradyrhizobium diazoefficiens USDA 110	Flav	C+F+E	*Zea mays, Glycine max* – O	[28]
Bradyrhizobium sp. IC–4059	EPS	C+DP	*Cajanus cajan* – O	[29]
Lactobacillus rhamnosus	LLA	F+E	soil properties	[33]
Lactobacillus rhamnosus	LLA, peptides, AA	F+E	microbial growth	[34]

IAA, 3-indoleacetic acid; ILA, indole-3-lactic acid; GA, Gibberellins; LP, lipopeptides; EP, extracellular proteins; LCO, lipo-chitin oligosaccharide; LLA, L-lactic acid; AA, amino acids; Trp, tryptophan; Flav, flavonoids; EPS, exopolysaccharides; PT, production technique utilized to obtain CFS/metabolites; C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes; P, in vitro growth; G, greenhouse growth; O, open field growth.

4. CFSs as Biocontrol Agents

Beyond biostimulant activity, CFSs and metabolites of PGPB can be used for the inhibition of microbial soil-borne pathogens. The strategies behind this antagonistic activity are mainly related to antibiosis and induction of plant defense response (i.e., induced systemic resistance - ISR) mechanisms [40]. The use of bioformulations in agriculture can be interesting, as it offers a valid tool for phytopathogen control whilst safeguarding ecosystems [40]. Pathogen control is a major concern in agriculture. Nowadays, the most effective strategy against plant pathogens is the use of resistant cultivars. However, due to its high costs, the application of agrochemicals remains one of the most utilized techniques [41]. Agrochemicals cause environmental pollution, with serious consequences for human health. These issues force agriculture towards effective and sustainable techniques to manage bacterial, fungal, and oomycete pathogens.

4.1. Bacterial Pathogen Control

Among soil-borne pathogens, phytopathogenic bacteria are one of the major threats for agriculture, due to the deficiency of effective agrochemicals, the absence of host plants' resistance or immunity, and the accidental and undetected spread or latency [42]. Plant bacterial diseases cause devastating damage to cultivation with huge economic losses [43].

Studies of CFSs and PGPB useful to counteract this risk are limited. In Table 2 details of the studies concerning the application of CFSs or their metabolites against bacterial phytopathogens are summarized.

Table 2. Studies of biocontrol properties of cell-free supernatants (CFS) and CFSs metabolites of plant growth-promoting bacteria (PGPB) against bacterial phytopathogens.

PGPB Strain	Pathogen	Compound	Pt – Experiment	Ref
Bacillus amyloliquefaciens strain FZB42	*Bacillus brevis; Bacillus subtilis; Paenibacillus granivorans; Micrococcus luteus*	Amylocyclicin	C+E+DP – V	[44]
Bacillus amyloliquefaciens strain RC-2	*Agrobacterium tumefaciens Xanthomonas campestris* pv. *campestris*	Iturin	C+F – X (*Morus alba*)	[45]
Bacillus amyloliquefaciens strain KM658175	*Clavibacter michiganensis* ssp. *michiganensis*	-	C – V	[46]
Bacillus amyloliquefaciens strain KPS46	*Xanthomonas axonopodis* pv. *glycines*	Surfactin	C+F – G (*Glycine max*)	[47]
Bacillus amyloliquefaciens (SS-12.6, SS-38.4); *Bacillus pumilus* SS-10.7	*Pseudomonas syringae* pv. *aptata*	Iturin	C+E – V+P (*Beta vulgaris*)	[48]
Bacillus amyloliquefaciens Bk7; *Brevibacillus laterosporus* spp. (B4, S5); *Alcaligenes faecalis* spp. (Bk1, P1)	*Xanthomonas oryzae* pv. *oryzae*	-	C+F – V	[49]
Bacillus licheniformis N1	*Xanthomonas oryzae* pv. *oryzae*	Iturin A, Surfactin	C+DP – V+G (*Oryza sativa*)	[50]
Bacillus sp. SS12.9	*Xanthomonas oryzae*	Iturins	C+E – V	[51]
Bacillus sp. EA-CB0959	*Ralstonia solanacearum*	Fengycin, Iturin, surfactin,	C/E/DP- V + G (*Musa*)	[52]
Bacillus subtilis NB22, UB24	*Xanthomonas oryzae; Pseudomonas lachrymans*	Iturin	C+F+E – V+X+G (*Oryza sativa; Cucumis sativus*)	[53]
Bacillus subtilis 14B	*Agrobacterium tumefaciens*	-	C+DP – V+G (*Solanum lycopersicum*)	[54]
Bacillus subtilis (ATCC 6633; BBG100)	*Erwinia chrysanthemi; Pseudomonas aeruginosa; Micrococcus luteus*	Mycosubtilin, surfactin, subtilin, subtilosin, rhizocticins	C+E – V	[55]
Bacillus subtilis IH7	*Agrobacterium tumefaciens*	Bac IH7	C+E+DP – V	[56]
Lactic acid bacteria	*Pseudomonas syringae* pv. *actinidiae; Xanthomonas arboricola* pv. *pruni; Xanthomonas fragariae*	D- and L-lactic acid	C+F – V	[57]
Pseudomonas aeruginosa RZS3; Alcaligenes sp. STC1	*Pseudomonas solanacerum*	*Siderophores*	C – V	[58]
Ochrobactrum lupini KUDC1013	*Pectobacterium carotovorum*	PAA, H, LA/LPs/Flagella	C+E/C+DP – P (*Nicotiana tabacum*)	[59]
Peanibacillus polymyxa	*Xanthomonas campestris* pv. *campestris*	-	C – V C+F – G (*Brassica oleracea* var. *acephala*)	[60]
Paenibacillus sp. B2	*Pseudomonas viridiflava; Erwinia carotovora;*	Polymyxin B	C+DP – V	[61]

PAA, Phenylacetic acid; H, 1-hexadecene; LA, Linoleic acid; LPs, lipopolysaccharides; PT, production technique utilized to obtain CFS/metabolites; C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes; V, in vitro antagonism; X, ex vivo antagonism; P, in vitro growth; G, greenhouse/pot growth.

Literature on bacterial biocontrol by CFSs/metabolites is mainly on tests carried out in vitro against pathogens belonging to *Bacillus*, *Clavibacter*, *Ralstonia*, *Erwinia*, *Micrococcus*, *Agrobacterium*, *Pectobacterium* and *Xanthomonas* genera. Several CFS/metabolites obtained from *Bacillus* spp. demonstrated activity against these pathogens. In particular, the *B. amyloliquefaciens* species is one of the most promising. The antagonistic capability of *B. amyloliquefaciens* CFSs was first reported by Yoshida et al. [45], who described good inhibition of *Agrobacterium tumefaciens* and *Xanthomonas campestris* pv. *campestris*

in ex situ *Morus alba* leaves. *B. amyloliquefaciens* Bk7, together with *Bacillus laterosporus* spp. (B4, S5), and *Alcaligenes faecalis* spp. (Bk1, P1), showed good in vitro biocontrol capabilities against *Xanthomonas oryzae* pv. *oryzae* [49]. Interesting results in planta biocontrol of *X. oryzae* pv. *oryzae* were reported by Kong et al. for CFS extracts (i.e., surfactin, iturin, and acid precipitate with a concentration of 500 μg mL^{-1}) obtained from *Bacillus licheniformis* N1 [50]. Among several PGPB strains isolated from the rhizosphere of three horticultural and tree crops (i.e., apple, apricot, and strawberry), biocontrol capabilities were showed by *B. amyloliquefaciens* KM658175 CFSs against *Clavibacter michiganensis* ssp. m*ichiganensis* [46]; best in vitro inhibition was achieved utilizing 1% (*v*/*v*) concentration of the CFS of this strain. Extracts of *B. subtilis* ATCC 6633 and BBG100 CFSs inhibited in vitro growth of *Erwinia chrysanthemi*, *Pseudomonas aeruginosa*, and *Micrococcus luteus* due to the presence of mycosubtilin, surfactin, subtilin, subtilosin, and rhizocticins [55]. CFS of *B. subtilis* 14B was able to reduce the *Agrobacterium tumefaciens* infection both in vitro and in planta in *Solanum lycopersicum* [54].

The main active compounds identified in *Bacillus* CFSs are iturins. Iturins extracted from *Bacillus* sp. SS12.9 CFSs showed effective antagonism against *X. oryzae* pv. *oryzae* in in vitro experiment [51]. Iturins were also found in CFSs successfully applied in *Beta vulgaris*, *Oryza sativa*, and *Cucumis sativus*, in which they were able to inhibit several bacterial phytopathogens. CFSs of *B. amyloliquefaciens* and *Bacillus pumilus* inhibited *Pseudomonas syringae* pv. *apta* pathogenic activity in *B. vulgaris* in vitro cultivation [48]. CFS of *B. subtilis* NB22 and UB24 counteracted infections of *X. oryzae* and *Pseudomonas lachrymans* in *O. sativa* and *C. sativus*, respectively, during ex vivo and in planta experiments [53].

Other studies demonstrated the capability of different compounds to counteract several bacterial diseases. The ability of *B. amyloliquefaciens* CFSs to decrease *Glycine max* pustule disease severity caused by *Xanthomonas axonopodis* pv. *glycines* in a greenhouse experiment to surfactin has been ascribed [47]. Inhibition capabilities of *Bacillus brevis*, *B. subtilis*, *Paenibacillus granivorans*, and *M. luteus* strains to amylocyclicin isolated by *B. amyloliquefaciens* FZB42 has been recognized [44]. The ability of a lipopeptide mixture from *Bacillus* sp. EA-CB0959 to decrease the incidence of *R. solanacearum* disease in *Musa* plants to fengycin, and in a lesser extent to surfactin and iturin, has been ascribed [52]. In vitro antibacterial properties against *A. tumefaciens* to the bacteriocin BAC IH7, isolated from *B. subtilis* IH7, have been recognized [56].

In addition to the *Bacillus* genus, several CFSs obtained by LABs, showed significant in vitro inhibition against *P. syringae* pv. *actinidiae*, *Xanthomonas arboricola* pv. *pruni* and *Xanthomonas. fragariae* [57], thanks to the presence of organic acids. Antibacterial effects have been inactivated by pH neutralization of CFS. CFSs containing siderophores produced by *P. aeruginosa* RZS3 and *Alcaligenes* sp. STC1 strains efficiently inhibited in vitro growth of *Pseudomonas solanacerum* [58]. Metabolites present in the culture supernatant of *Ochrobactrum lupini* KUDC1013 were able to elicit ISR against *Pectobacterium carotovorum* ssp. *carotovorum* in *Nicotiana* leaves [59]. Several CFSs of bacterial strains isolated from suppressive soils showed in vitro antagonistic activity against *X. campestris.* Among them, CFSs from *Peanibacillus polymyxa* also revealed a strong in vivo inhibition activity against this black rot causal agent [60]. Interesting results were also reported for the purified CFS of *Paenibacillus* sp. strain B2; superdex-purified CFS, constituted mainly by polymyxin B, inhibited in vitro growth of *Pseudomonas viridiflava* and *Erwinia carotovora* pathogens with minimal inhibitory concentrations (MICs) of 0.6 and 6.7 μg mL^{-1}, respectively [61].

4.2. Fungal Pathogens Control

In addition to bacteria, phytopathogenic fungi are one of the other major microbial soil-borne pathogens that threaten productive landscapes. Fungal plant pathogens cause enormous losses in yield and quality of plants [62]. A broad-spectrum antifungal activity has been observed for diverse CFSs against the genera *Fusarium*, *Rhizoctonia*, *Botrytis*, *Sclerotinia*, *Colletrotrichum*, and *Ralstonia*. However, the majority of the studies report results on in vitro assays. Most of the studies are on *Bacillus*. Table 3 summarizes studies on CFS and extracted metabolites from this genus.

Table 3. Studies of biocontrol properties of cell-free supernatants (CFSs) and CFSs metabolites of *Bacillus* spp. against fungal phytopathogens.

Bacillus Strain	Pathogen	Compound	Pt – Experiment	Ref
Bacillus amyloliquefaciens B94	*Rhizoctonia solani*	Iturin A2	C+F+E – V	[63]
Bacillus amyloliquefaciens BNM 122	*Rhizoctonia solani; Sclerotinia sclerotiorum*	Surfactin; iturin	C+E –V	[64]
Bacillus amyloliquefaciens ES-2	*Botrytis cinerea; Fusarium culmorum; Botryodiplodia theobromae; Magnaporthe grisea; Absidia corymbifera; Rhizopus arrhizus; Colletotrichum musae; Erysiphe graminis hordei; Endomycopsis*	Fengycin, surfactin	C+F+E – V	[65]
Bacillus amyloliquefaciens LBM 5006	*Aspergillus* spp.*; Fusarium* spp.*; Apiosordaria* sp.*; Bipolaris sorokiniana; Cercospora sojina; Diplodia* spp.*; Promopsis* spp.*; Rhizoctonia* spp.*; Verticillium albatrum*	Iturin, fengycin	C+F – V	[66]
Bacillus amyloliquefaciens LZN01	*Fusarium oxysporum f.* sp. *niveum*	Myriocin; sphingofungin E; sphingofungin F; 3-methyl-2-oxovaleric acid; gabapentin; sphingofungin C	C+F – V	[67]
Bacillus amyloliquefaciens PG12	*Botryosphaeria dothidea*	Iturin A	C+F+E – V	[68]
Bacillus amyloliquefaciens RC-2	*Colletotrichum dematium*	Iturin A2	C+F+DP – V	[45]
Bacillus amyloliquefaciens S76-3	*Fusarium graminearum*	Iturin A, plipastatin A	C+F+E – V	[69]
Bacillus endophyticus (KT379993); *Bacillus cereus* (KT379994)	*Fusarium solani*	Surfactin, fengycin	C+F – V	[70]
Bacillus licheniformis BC98	*Magnaporthe grisea*	-	C+E – V	[71]
Bacillus licheniformis N1	*Rhizoctonia solani; Botrytis cinerea; Colletotrichum* spp.*; Blumeria graminis*	Iturin A, Surfactin	C – V+G (*Solanum lycopersicum; Fragaria x ananassa; C. annuum; Hordeum vulgare*)	[50]
Bacillus megaterium; B. subtilis, B. subtilis ssp. *Subtilis.*	*Aspergillus niger; Aspergillus flavus*	-	C+F+DP – V	[72]
Bacillus pumilus	*Aspergillus; Penicillium; Fusarium*	Iturin A	C+F+E+DP – V	[73]
Bacillus pumilus MSUA3	*Rhizoctonia solani; Fusarium oxysporum*	Surfactin	C+F – V	[74]
Bacillus spp.	*Sclerotinia sclerotiorum;*	-	C+F+E – V	[75]
Bacillus sp. LCF1 (KP257289)	*Rhizoctonia sp; Sclerotium sp.*	Surfactin, iturin, fengycin	C – V	[76]
Bacillus sp. SJ-5	*Rhizoctonia solani; Fusarium oxysporum*	Jasmonic Acid	F+DP – V	[77]
Bacillus spp.	*Fusarium oxysporum f.* sp. *lycopersici*	Iturin A	F+E – V	[78]
Bacillus spp. (pxS1-1, CtpxS3-5, CtpxZ2, CtpxZ3)	*Colletotrichum acutatum*	Iturin, surfactin, fengycin	F – V	[79]
Bacillus subtilis AF 1	*Puccinia arachidis; Aspergillus niger*	β-1,4-N-acetylglucosaminidase (NAGase)	C+F – V	[80]
Bacillus subtilis (ATCC 6633, BBG100)	*Botrytis cinerea; Fusarium oxysporum*	Mycosubtilin, surfactin, subtilin, subtilosin, rhizocticins	C+E – V	[55]
Bacillus subtilis AU195 *Bacillus subtilis* B47	*Aspergillus flavus* *Bipolaris maydis*	Iturin Iturin A2	C+F – V C+E+DP – V	[81] [82]
Bacillus subtilis B-916	*Rhizoctonia solani; Magnaporthe grisease; Sclerotinia sclerotiorum; Alternaria oleracea; Alternaria brassicae; Botrytis cinerea*	Bacisubin	C – V	[83]
Bacillus subtilis B-FS01	*Fusarium moniliforme*	Fengycins A, fengycins B	C+F+E – V	[84]
Bacillus subtilis CL27; *Bacillus pumilus* CL45	*Alternaria brassicicola; Botrytis cinerea*	-	C+F – V+P (*Astilbe*)	[85]
Bacillus subtilis EA-CB0015	*Botrytis cinerea; Colletotrichum acutatum*	Iturin A, fengycin C	C+F+LPs – V	[86]
Bacillus subtilis ET-1	*Penicillium digitatum; Botrytis cinerea*	Iturin A	F+DP – V+R (*Citrus limon; Fragaria* × *ananassa*)	[87]
Bacillus subtilis FS94-14	*Ophiostoma ulmi; Verticillium dahliae; Ceratocystis fagacearum; Cryphonectria parasitica*	Iturin	E+F – V	[88]

Table 3. *Cont.*

Bacillus Strain	Pathogen	Compound	Pt – Experiment	Ref
Bacillus subtilis GA1	*Botrytis cinerea*	Fengycins, iturins, surfactins	C+DP – V	[89]
Bacillus subtilis HC8	*Fusarium oxisporum f.* sp. *radicis-lycopersici*	Iturins, fengycins, surfactin	F+E – V	[90]
Bacillus subtilis HussainT-AMU	*Rhizoctonia solani*	Surfactin	C+F+E – V+G+O (*Solanum tuberosum*)	[91]
Bacillus subtilis IH7	*Alternaria solani*	Bac IH7	C+E+DP – V	[56]
Bacillus subtilis KS03	*Gloeosporium gloeosporioides*	Iturin A	C+F+E – V	[92]
Bacillus subtilis NB22, UB24	*Alternaria mali; Cercospora kikuchii; Botrytis cinerea; Puccinia coronata; Rhizoctonia solani; Pyricularia oryzae; Cochliobolus miyabeanus*	Iturin	C+F+E – V+X+G (*Malus domestica; Cucumis sativus; Glycine max; Avena sativa)*	[53]
Bacillus subtilis SCB-1	*Saccharicola bicolor; Neodeightonia subglobosa; Cochliobolus hawaiiensis; Curvularia senegalensis; Curvularia lunata; Alternaria alternata;; Fusarium oxysporum; Fusarium verticillioides; Fusarium* sp.; *Phomopsis* sp.	Surfactin	C+F+E – V	[93]
Bacillus subtilis ssp.	*Fusarium oxysporum* f. sp. *radicis-lycopersici; Rosellinia necatrix*	Surfactin, fengycin, iturin A	C+E – V	[94]
Bacillus subtilis ssp. *subtilis*	*Setophoma terrestris*	-	C+F – V	[95]
Bacillus subtilis ssp. *subtilis* PGPMori7; *Bacillus amyloliquefaciens* PGPBacCA1	*Macrophomina phaseolina*	Iturin, surfactin, fengycin	C+F+E+DP – V	[96]
Bacillus subtilis UMAF6614, UMAF6619, UMAF6639, UMAF8561	*Podosphaera fusca*	Iturin, fengycin	C+F – V+X (*Cucumis melo*)	[97]
Bacillus vallismortis ZZ185	*Fusarium graminearum; Alternaria alternata; Rhizoctonia solani; Cryphonectria parasitica*	Bacillomycin D (n-C14, iso-C15)	C+F+E – V	[98]
Bacillus velezensis Y6, F7	*Ralstonia solanacearum; Fusarium oxysporum*	Surfactin, iturin, fengycin	C+F – V	[99]
Bucillus subitilis; Pseudomonas fluorescens	*Macrophomina phaseolina*	-	C+F – V	[100]
Bacillus mycoides (+ *Pichia guilermondii*)	*Botrytis cinerea*	-	C – V+R (*Fragaria* × *ananassa*)	[101]

PT, production technique utilized to obtain CFS/metabolites; C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes; V, in vitro antagonism; X, ex vivo antagonism; R, antagonism on fruit; P, in vitro growth; G, greenhouse/pot growth; O, open field growth.

B. amyloliquefaciens and *B. subtilis* are the most studied species. *B. amyloliquefaciens* strains were utilized to produce CFSs [66,67] and CFS metabolites [45,63–66,68,69,96] valid to inhibit in vitro growth of several fungal pathogens of both Ascomycota (e.g., *Fusarium* spp., *Colletotrichum* spp.) and Basidiomycota (e.g., *Rhizoctonia* spp.) phyla. The inhibition capacities of these CFSs and their metabolites were correlated with the presence of lipopeptides (e.g., iturins, fengycins, surfactins, and sphingofungins); however, no records about the in planta control are available in the literature. *B. subtilis* CFSs and metabolites obtained by *B. subtilis* strains have been assayed against several fungal pathogenic strains, in vitro, ex vivo, and in planta [53,55,56,80–90,92–97,100]. Noteworthy is the recent work of Hussain et al., in which the potentialities of metabolites of CFSs produced by *B. subtilis* HussainT-AMU were assessed in vitro and in planta, both in greenhouse and open field experiments [91]. Thanks to the presence of surfactin, the CFS of this strain was able to decrease *Rhizoctonia solani* infections by up to 71% and 50% under greenhouse and open field conditions, respectively.

CFSs [70,74,76,79,99] and CFS extracted metabolites [71–73,75,77,78,98] from other *Bacillus* species were reported to inhibit the in vitro growth of several fungal phytopathogens belonging mainly to *Aspergillus, Fusarium, Sclerotinia,* and *Rhizoctonia* genera. Interesting are the results obtained by Guetsky et al., who reported effective *B. cynerea* biocontrol on ex vivo strawberries by CFSs obtained from *Bacillus mycoides* and *Pichia guilermondii* [101]. Moreover, Kong et al. reported effective fungal inhibition by *B. licheniformis* N1 CFS and purified metabolites. In their work surfactin and iturin

A formulates at a concentration of 500 µg mL^{-1} were shown to control in planta disease caused by *R. solani*, *Botrytis cinerea*, *Colletotrichum* spp., and *Blumeria graminis* under greenhouse experiments [50].

In addition to *Bacillus* genus, other genera can be valid sources of CFSs and metabolites for the biocontrol of fungal phytopathogens. In Table 4 the details of studies of species belonging to these other genera are shown.

Table 4. Studies of biocontrol properties of cell-free supernatants (CFSs) and CFS metabolites of plant growth-promoting bacteria (PGPB) strains other than *Bacillus* spp. against fungal phytopathogens.

PGPB Strain	Pathogen	Compound	Pt – Experiment	Ref
Alcaligenes faecalis BCCM ID 2374	*Fusarium oxysporum; Alteraria alternata*	Siderophores	C/C+DP – V	[102]
Chryseobacterium aquaticum	*Pestalotia theae; Rhizoctonia solani; Curvularia lunata*	-	C – V	[103]
Erwinia herbicola	*Puccinia recondita f.* sp. *Tritici*	Herbicolin A	C+F – V+G (*Triticum aestivum*)	[104]
Lactobacillus coryniformis ssp. *coryniformis*	*Mucor hiemalis; Fusarium poae; Fusarium graminearum; Fusarium culmorum; Fusarium sporotrichioides*	-	C+F – V	[105]
Lactobacillus plantarum	*Colletotrichum capsici*	-	C+F – V+P (*Capsicum annuum*)	[106]
Paenibacillus sp. B2	*Fusarium solani; Fusarium acuminatum*	Polymyxin B	C+DP –V	[61]
Pseudomonas aeruginosa RZS3; *Alcaligenes* sp. STC1	*F. oxysporum; Alternaria alternata; Cercospora arachichola;*	Siderophores	C – V	[58]
Pseudomonas batumici EB132; *Pseudomonas trivialis* EB133; *Pseudomonas grimontii* EB150; *Burkholderia stabilis* (EB159, EB193)	*Alternaria panax; Botrytis cinerea; Cylindrocarpon destructans; Rhizoctonia solani*	-	C+F – V	[107]
Pseudomonas chlororaphis PCL1391	*Fusarium oxysporum f.* sp. *radicis-lycopersici*	Phenazines	C+E – V	[108]
Pseudomonas fluorescens	*Macrophomina phaseolina*	-	C+F – V	[100]
Pseudomonas fluorescens PCL1606	*F. oxysporum f.* sp. *radicis-lycopersici*	2-hexyl 5-propyl resorcinol	C+E+DP – V	[109]
Pseudomonas sp. AB2	*Rhizoctonia solani, Botrytis cinerea, Fusarium oxysporum*	N-Butylbenzenesulphonamide	C+E+DP – V	[110]
Pseudomonas spp.	*Aspergillus niger; Aspergillus flavus*	-	C+F+DP – V	[72]
Serratia sp. ZoB14	*Sclerotium rolfsii; Colletotricum acutatum; Fusarium oxysporum; Rhizoctonia solani*	-	C+DP – V	[111]
Streptomyces goshikiensis	*F. oxysporum* sp. *niveum*	-	C+E – V	[112]
Streptomyces pactum Act12; *Streptomyces rochei* D74	*Sclerotium rolfsii; Fusarium oxysporum*	-	F – V	[113]
Streptomyces roseoflavus US80	*Fusarium* sp.; *Verticillium dahliae*	irumamycin; X-14952B, 17-hydroxy-venturicidin A	C+E+DP – V	[114,115]
Streptomyces sp. 3–10	*Amphobotrys ricini; Alternaria alternata; Aspergillus flavus; Aspergillus niger; Aspergillus parasiticus; Bipolaris maydis; Botrytis cinerea; Colletotrichum siamense; Curvularia lunata; Drechslera graminea; Fusarium oxysporum; Monilia fructigena; Pestalotia theae; Sclerotinia minor; Sclerotinia sclerotiorum; Rhizoctonia solani; Sclerotium rolfsii*	Reveromycin A, B	C+E – V+X (*Fragaria* × *ananassa*)	[116]

Table 4. *Cont.*

PGPB Strain	Pathogen	Compound	Pt – Experiment	Ref
Streptomyces sp. MR14	*Fusarium moniliforme*	-	C/E – V+G (*Solanum lycopersicum*)	[117]
Streptomyces sp. RP1A-12	*Sclerotium rolfsii*	-	C+E – V+G (*Arachis hypogaea*)	[118]
Streptomyces spp.	*Botrytis cinerea; F. oxysporum f.* sp. *ciceri; Fusarium andiyazi; Fusarium proliferatum; Macrophomina phaseolina; Rhizoctonia bataticola;*	-	C+F – V	[119]
Xenorhabdus nematophila mutant	*Botrytis cinerea; Rhizoctonia solani; Exserohilum turcicum; Physalospora piricola; Curvularia lunata; Gaeumannomyces graminis; Fusarium graminearum*	-	F – V	[120]
Xenorhabdus nematophila TB	*Botrytis cinerea*; Alternaria solani; Bipolaria maydis; Bipolaris sorokiniana; Dothiorella gregaria; Exserohilum turcicum; Physalospora piricola; Rhizoctonia cerealis; Sclerotinia sclerotiorum*	-	C+F – V *C+F+E – P (*Solanum lycopersicum*)	[121]
Xenorhabdus nematophila YL001	*Alternaria brassicae; Alternaria solani; Botrys cinerea; Clomerela cinyulate; Curvularia lunata; Exserohilum turcicum; Magnaporthe grisea; Physalospora piricola; Sclerotinia sclerotiorum; Verticillium dahliae*	Xenocoumacin 1, 2	C+F – V	[122]
Xenorhabdus spp.C19A1:D25	*Fusicladium carpophilum; Fusicladium effusum; Monilinia fructicola; Glomerella cingulata; Armillaria tabescens*	-	C+F – V	[123]

PT, production technique utilized to obtain CFS/metabolites; C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes; V, in vitro antagonism; X, ex vivo antagonism; P, in vitro growth; G, greenhouse/pot growth.

One of the first studies available in the literature reports the *Erwinia herbicola* CFS in planta biocontrol capability against *Puccinia recondita* f. sp. *tritici* in a *Triticum aestivum* greenhouse experiment, thanks to the presence of herbicolin A [104]. However, no other reports can be found on this species. In the recent literature, there are many studies of the in vitro biocontrol potential of *Pseudomonas* spp. CFSs [58,107] and CFS metabolites [72,100], thanks to the presence of siderophores, phenazines, and 2-hexyl 5-propyl resorcinol N-Butylbenzenesulphonamide [108–110]. The in vitro inhibition of fungal pathogens has also been demonstrated for the CFSs and metabolites of other species of *Alcaligenes* [58,102], *Chryseobacterium* [103], and *Paenibacillus* [61] genera.

Actinomycetes are also a source of formulates for the management of fungal plant diseases. However, only a few studies have evaluated CFSs or metabolites obtainable by these microorganisms [124] and dealing exclusively with the *Streptomyces* genus [112–116,119]. Noteworthy are the studies of Kaur et al. and Jacob et al., who reported good in planta biocontrol capabilities of CFS on *Fusarium moniliforme* on *S. lycopersicum* [117] and *Sclerotium rolfsii* on *Arachis hypogaea* [118], respectively. LABs are capable of producing several bioactive metabolites that effectively counteracted several plant diseases [32,105]. El-Mabrok et al., for example, reported *L. plantarum* CFS' effective inhibition of *Colletotrichum capsici*, both in vitro and during a *Capsicum annum* seed germination experiment under sterile conditions [106]. Several works report the capability of CFSs of *Xenorhabdus* spp. to inhibit some fungal phytopathogens in vitro [120,122,123]. For this genus, relevant is the study of Fang et al.,

who reported that the extracted metabolites from *X. nematophila* TB CFS can inhibit *B. cinerea* under in vitro *S. lycopersicum* cultivation [121].

4.3. Oomycete Phytopathogens

Oomycetes are endemic phytopathogens responsible for destructive outcomes in several crop plants. There are only a few anti-oomycete compounds for the control of their diseases. These pathogens are spreading severely and developing resistant strains [125]. In Table 5, details of the studies concerning the application of CFSs and their metabolites against oomycetes phytopathogens are summarized.

Table 5. Studies of biocontrol properties of cell-free supernatants (CFSs) and CFSs metabolites of plant growth-promoting bacteria (PGPB) against oomycetes phytopathogens.

PGPB Strain	Pathogen	Compound	Pt – Experiment	Ref
Bacillus subtilis NB22, UB24	*Phytophtora infestans*	Iturin	C+F+E – V+X+G (*Solanum lycopersicum*)	[53]
Bacillus subtilis M4	*Phytium ultimum*	Fengycin, iturin, surfactin	C+E+DP – G (*Phaseolus vulgaris*)	[126]
Bacillus subtilis	*Plasmopara viticola*	Fengycin, Surfactin	C+F – X (*Vitis vinifera*)	[127]
Bacillus subtilis CU12	*Pythium sulcatum*	Fengycin	C+DP – V	[128]
Bacillus subtilis mutant	*Phytium aphanidermatum*	Mycosubtilin	C+F – V	[55]
Bacillus sp. LCF1 (KP257289)	*Phytophthora sp.*	Surfactin, iturin, fengycin	C – V	[76]
Bacillus licheniformis N1	*Phytophtora infestans*	Iturin A, Surfactin	C – V+G (*Solanum lycopersicum*)	[50]
Bacillus toyonensis EB70; *Paenibacillus terrae* EB72	*Pythium* sp.; *Phytophthora cactorum*	-	C+F – V	[107]
Bacillus vallismortis ZZ185	*Phytophthora capsici*	Bacillomycin D	F+E – V	[98]
Lactobacillus plantarum IMAU10014	*Phytophthora drechsleri*	3-phenyllactic acid; Benzeneacetic acid, 2-propenyl ester	C+F+DP – V	[129]
Photorhabdus spp.	*Phytophthora* sp.	-	C – V+G (*Carica papaya*)	[130]
Pseudomonas fluorescens SS101	*Phytophtora infestans*	Massetolide A	C+DP – G (*Solanum lycopersicum*)	[131]
Pseudomonas aeruginosa	*Pythium myriotylum*	phenazine 1-carboxylic acid	C+DP – V	[132]
Pseudomonas sp. AB2	*Pythium ultimum*, *Phytophthora capsici*	N-Butylbenzenesulphonamide	C+E+DP – V	[110]
Serratia sp. ZoB14	*Pythium myriotylum*; *Phytophthora infestan*	-	C+DP – V	[111]
Streptomyces similaensis	*Phytophthora* sp. D4	β-glucanase extracts	C+DP – V	[133]
Streptomyces sp.TN258	*Pythium ultimum*	-	C+F – V+G (*Solanum tuberosum*)	[134]
Streptomyces sp. 3–10	*Pythium aphanidermatum*; *Pythium ultimum*	Reveromycin A, B	C+E – V+G (*Fragaria* × *ananassa*)	[116]
Xenorhabdus nematophila	*Phytophthora infestans*	SID	C+E – V	[135]
Xenorhabdus nematophila TB	*Phytophthora capsici*	-	C+F+E – V+P (*Capsicum annuum*)	[121]
Xenorhabdus nematophila	*Phytophthora capsici*	Xenocoumacin 1, 2	C+F – V	[122]
Xenorhabdus nematophilus var. pekingensis	*Phytophthora infestans*	Xenocoumacin 1	C+DP – V+X+G (*Solanum tuberosum*)	[136]
Xenorhabdus nematophila mutant	*Phytophthora capsici*	-	F – V	[120]

PT, production technique utilized to obtain CFS/metabolites; C, centrifugation; F, Filtration; E, solvent extraction; DP, several downstream processes; V, in vitro antagonism; X, ex vivo antagonism; P, in vitro growth; G, greenhouse/pot growth. SID, racemic 3-indoleethyl(3′-methyl-2′-oxo)pentanamide.

Only a limited number of works are present in the literature, mostly addressing the biocontrol of *Phytophthora* spp. and *Pythium* spp. Members of these fungal-like genera have been widely studied throughout the world due to the serious losses they cause [137]. *Phytophtora* spp. effective biocontrol has

been obtained on: (i) *S. lycopersicum* by CFS metabolites of *B. subtilis* NB22 and UB24 [53], *B. licheniformis* N1 CFS [50], and *Pseudomonas fluorescens* SS101 CFS metabolites [131]; (ii) *Carica papaya* by CFS of *Photorhabdus* spp. [130]; (iii) *C. annuum* by *X. nematophila* TB CFS metabolites [121]; (iv) *Solanum tuberosum* by *X. nematophilus var. pekingensis* CFS metabolites [136]. *Pythium* spp. biocontrol has been obtained on: (i) *Phaseolus vulgaris* by *B. subtilis* M4 CFS metabolites [126]; (ii) *S. tuberosum* by *Streptomyces* sp. TN258 CFS [134]; (iii) *Fragaria* × *ananassa* by *Streptomyces sp.* 3–10 CFS metabolites [116]. Beyond *Phytophthora* spp. and *Pythium* spp., the control of *Plasmopara viticola* infection on ex vivo *Vitis vinifera* leaves has been obtained by *B. subtilis* CFS application [127].

Biocontrol of bacterial, oomycetes, and fungal pathogens can also be achieved by bacterial BFs, bacteriocins, and hydrolytic enzymes. Several formulations of these molecules have great potential for use in agriculture. Mode of action and inhibition effectiveness have been extensively reviewed for BFs [35–37], bacteriocins [38,39], and hydrolytic enzymes [138].

5. CFSs and Metabolites - Limitations and Advantages

Data on the use of CFS in agriculture are extremely limited and their application in agriculture has been completely ignored in recent decades. No published studies have investigated formulation and shelf life of CFSs; thus, the limitations are mainly related to the downstream processes for their production. According to Doran et al. [9] downstream processes can often be technically challenging due to:

- Metabolites' lability: these compounds are sensitive to temperature, high salt concentrations, and addition of chemicals (i.e., solvents, strong acids and bases).
- the complexity of the broth mixture.
- contamination susceptibility.

These factors limit the operation units that can be applied, lowering the purity and stability of final products. Concerning the use of CFSs as fertilizers, other possible limitations are similar to those found for other biofertilizers, namely [139]:

- lower nutrient content that may be inadequate for maximum crop growth.
- slower nutrient release rate.
- highly variable nutrient composition.

On the other hand, CFSs have more advantages than synthetic fertilizers that can overcome these negative aspects [139]:

- a more balanced nutrient supply.
- soil biological and fertility status enhancement.
- soil structure improvement.

These advantages sustain crop production whilst safeguarding agroecosystem health.

Concerning bacteriocins, purified metabolites, hydrolytic enzymes, and BFs, currently large-scale application and production are limited mostly due to the high cost of production [31,140,141].

6. Perspectives

Our literature survey underlined that studies of CFSs and their metabolites should be encouraged. This resource from bacteria is in our opinion very interesting both from the scientific and commercial point of view. The metabolites present in CFS-based formulations have demonstrated effectiveness against a certain number of species. The biocontrol potential against fungi, bacteria and actinomycetes has also been demonstrated. The biostimulant market is in constant increase, with an annual growth rate of 10.4% in 2016–2021. Thus, the formulation of new products by biostimulant producers could be a valid financial investment in such a lucrative market. However, the formulation of new products ready to be

commercialized would require new scientific and industrial scale-up studies. This request would challenge the scientific world as a not yet fully explored field. New studies should deal with the: (i) identification of PGPB species with interesting metabolite profile; (ii) selection of procedures to obtain cost-effective formulation; (iii) chemical characterization of formulates; (iv) modes of action; (v) effectiveness studies under different environmental conditions; (vi) studies on formulation stabilities (vii) product registration and commercialization. Even if this process is long and challenging, we think that these formulations could be one of the new tools useful for sustainable agriculture, equal to the biostimulants present on the market. Our literature survey shows that *Bacillus* is the most promising genus for the isolation of CFSs and/or their metabolites. Moreover, several *Bacillus* strains are already commercialized in biostimulant/biocontrol products. Thus, the scale-up procedures for reaching the formulation stage should also be less challenging. The collaboration of different field specialists (i.e., academics, industrial and commercial fields, farmers) should be activated to explore the CFS field and obtain new biostimulant products. We believe that the formulation of natural products for agriculture is not only important at the scientific and economic level but also for our planet. To cope with an increasingly global food demand, agriculture is maximizing production by excessive use of chemicals. The development of new fields of study and the publication of scientific reports can lead to the awareness of farmers and companies engaged in food production.

7. Conclusions

From the data reported, it is evident that the literature contains only a few reports useful for the creation of valid scientific evidence to support the development of CFS formulations. The majority of the reports deal with environmental controlled biostimulant and in vitro microbial biocontrol experiments. Among the 109 articles selected and examined, the *Bacillus* genus seems to be the most promising due to the numerous articles that support its biostimulant and biocontrol potentialities. Several CFSs and CFS metabolites of *Bacillus* strains demonstrated activity against a broad spectrum of bacterial, fungal, and oomycete pathogens, under different cultivation conditions. The present review underlined that research on this topic needs to be encouraged; evidence so far obtained has demonstrated that PGPB could be a valid source of secondary metabolites useful in sustainable agriculture. For the production of CFS-based formulations useful for agriculture, new PGPB strains/metabolites should be studied and obtained. Moreover, through advanced biotechnologies, standardized formulations and shelf life investigations should be carried out. To introduce these formulations in agriculture, future studies of CFSs should include effectiveness tests with trials in greenhouse and field experiments. The present review creates the first literature summary of CFSs and their metabolites as plant growth-promoting bacteria. Data organization provided details of their use as biostimulant and microbial biocontrol agents in agriculture. This review can also be used as a starting point for drawing up new reviews regarding the use of CFSs and their metabolites. These formulations can be exploited for other purposes in agriculture (e.g., biocontrol of nematodes, insects, protozoa).

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