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REVIEW ARTICLE

Disease management of tomato through PGPB: current trends and future perspective

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Abstract Tomato is the world's second most cultivated vegetable. During cultivation or post-harvest storage, it is susceptible to more than 200 diseases caused by an array of pathogenic fungi, nematodes, bacteria, and viruses. Although wide range of chemical pesticides are currently available to manage plant diseases, continuous application of pesticides not only affect the nutritional contents of tomato but also the texture or productivity of soil. In this context, plant growth promoting bacteria (PGPB) are one of the nature friendly, safe, and effective alternatives for the management of diseases and pathogens of tomato. Currently, numbers of microbes have been used as soil or plant inoculants in different plants including tomato as biocontrol. Besides disease inhibition, these inoculants also act as growth modulators. The present article describes the biocontrol potential of PGPB strains and mechanisms for the diseases management in tomato.

Keywords Biocontrol · Tomato · Plant growth promoting bacteria (PGPB) · Disease management

Introduction

Recently, it has been estimated that huge proportions of vegetable crops get deteriorated annually during growth or post-harvest storage, owing to the diseases caused by fungus, nematodes, bacteria, and viruses. This is one of the major limiting factors influencing the food production and human development over thousands of years (Dun-chun et al. 2016). From last 50 years, application of chemical pesticides has been the prevailing control measure for disease management in crop and vegetables production. The continuous exposure to chemical pesticides such as fungicides and weedicides adversely affect the productivity, texture of soil, nutritional content of vegetables, as well as the health of human being. Due to the hazards associated with chemically synthesized herbicides and pesticides, management of diseases via biological means is the novel emerging technology and gaining importance in better agricultural sustainability.

Tomato (*Solanum lycopersicum* L.) is the second most important vegetable crop next to potato in the world, with estimated production reaching as 170 million MT in 2014, where China accounts for 31% of the total, followed by USA, India, and Turkey as the major producers (http://www.fao.org/). Apart from being the important vegetable crop worldwide, tomato is also used as a model plant for genetical studies related to fruit quality, stress tolerance (biotic and abiotic), and other physiological traits. This is widely adapted to a variety of agro climate spanning from the tropics to temperate regions (Panthee and Chen 2010). Presently, the production and quality of tomato are known to be largely affected by the pathogens in the field or post-harvest processing (Walker 1971; Ramyabharathi et al. 2012). Disease development during field or/post-harvest storage and shipment without the effective inhibitor of microbial growth results in huge economic loss. Therefore, a critical need of sustainable approach for the plant disease management is necessary. In this context, soil or plant microbial inoculants of plant growth promoting bacteria (PGPB) seem to be promising approach for disease management in different crops and vegetables (Kumar et al. 2015a, c).

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Rhizosphere and plant growth promoting bacteria (PGPB) of tomato

Rhizosphere (interface between root and soil) is the most prominent zone for diversified plant–microbial interactions, determined by the root exudates that comprise array of chemical signals, carbon containing metabolites such as shedding of root cells, exudation, secretion, and the leakage of sugars, organic acids, and amino acids in soil matrix (Oku et al. 2012; Kumar et al. 2015b). While rhizospheric microbes mostly pose neutral effect on plants, even though some have positive or negative impact on the host development and health via complex interactions (Glick 2012). Some microorganisms are deleterious as they compete with plants for nutrients or cause disease (soil-borne plant pathogens), while others like mycorrhizal fungi and PGPB support their hosts by mobilizing nutrients, stimulating growth, increasing yield, or reducing biotic and abiotic stresses (Smith and Smith 2011).

Rhizobacteria inhabiting plant roots exert positive effects ranging from the direct ones like modulation of phytohormone levels, phosphate solubilization, ammonia production to the indirect effect like antibiotic, siderophore, and HCN production (Kumar et al. 2014, 2015a). Various species of bacteria like *Pseudomonas*, *Azospirillum*, *Azotobacter*, *Klebsiella*, *Enterobacter*, *Alcaligenes*, *Arthrobacter*, *Burkholderia*, *Bacillus,* and *Serratia* enhance plant growth and thus act as PGPB (Jasim et al. 2013; Kumar et al. 2014, 2015a, 2016a, b). In case of tomato, several plant growth promoting strains like *Pseudomonas fluorescens*, *Bacillus* sp., *Azotobacter*, *Serratia*, and *Micromonospora* (Pastor et al. 2012; Hammami et al. 2013; Babu et al. 2015; Martínez-Hidalgo et al. 2015) are involved in growth promotion as well as disease management.

Important diseases in tomato

Currently, more than 200 pests and diseases have been identified in tomato, causing losses in their production directly or indirectly (Nowicki et al. 2013). Diseases caused by fungi, nematodes, bacteria, and viruses are of the most severe concern in cereal crops and vegetables, which not only affect their nutritional contents, but also human health and overall economy. Some of the most important diseases in tomato caused by fungal pathogens are late blight, *Sclerotinia* rot, *Fusarium* wilt, *Fusarium* crown, and root rot. Late blight caused by the *Phytophthora infestans* is one of the most destructive diseases of tomato resulting in significant economic loss (20–70%) (Foolad et al. 2008; Nowicki et al. 2012, 2013). *Sclerotinia* rot, caused by *Sclerotinia sclerotiorum*, is another one of the important diseases affecting the tomato crop productivity. Wilt, crown, and root rot diseases in tomato caused by *Fusarium* species have been most intensively studied (Laurence et al. 2014; McGovern 2015). *Fusarium* wilt is common vascular disease caused by *Fusarium oxysporum*, resulting in extensive (10–80%) yield loss in many tomato producing countries (Kesavan and Chaudhary 1977). In root rot disease of tomato caused by *Fusarium* and *Phytoptora* sp., the plant foliage becomes yellow and wilts, eventually the plant dies. *Fusarium* crown root disease generally strikes the root system. At present, such pathogens are causing extensive loss to this important vegetable crop in the field and under green house conditions, and remain major limiting factors for tomato production. It is estimated that approximately 45% of the tomato yield has been reduced in India due to *Fusarium* sp. (Ramyabharathi et al. 2012).

Root-knot caused by the nematode *Meloidogyn*e sp. is the other most devastating and widespread disease in tomato (Hunt and Handoo 2009; Zhou et al. 2016). Nematode not only affects the crop yield directly but also makes the plants more susceptible to fungal and bacterial infections (Ashraf and Khan 2010). In China, it causes up to 30–50% yield reductions of tomato (Yang et al. 2011). This disease also severely reduces productivity of a variety of vegetables and crops worldwide. However, efficient control measures have yet been developed.

Bacterial leaf spot is common bacterial diseases of tomato caused by *Xanthomonas campestris*. It is highly destructive in both greenhouses as well as in field conditions, causing 10–50% yield loss (Kallo 1991). In India, tomato productivity loss has been estimated to range from 10 to 80% (Sharma and Sharma 2005), whereas annual production loss due to this disease is 10–20%, which may rise to 80% in some cases (Sharma and Sharma 2005; Reddy et al. 2012). *Ralstonia solanacearum* is the most important soil-borne plant pathogens that cause bacterial wilt in over 200 families of plants, including tomatoes and hampers their production (Huang et al. 2013). *Clavibacter michiganensis* infection systemically causes wilting and canker on the stem, while blister-like spots are developed in locally infected leaves causing substantial economic loss in tomato production worldwide. *C. michiganensis* virulence factor plays an important role during blister formation compared to wilting, and also causes local and systemic infection in tomato (Chalupowicz et al. 2016).

Viral disease of tomato includes tomato spotted wilt virus, one of the most important viral diseases which occasionally lead to plant death (Rossello et al. 1993). Tomato yellow leaf curl is another viral disease of cultivated tomato in the tropical and subtropical regions worldwide, and losses up to 100% are most frequent. In many regions, tomato yellow leaf curl is one of the limiting factors in tomato production. The causal agents are a group of Gemini virus species belonging to the genus Begomo virus, all of them named as tomato yellow leaf curl virus. Pepino mosaic virus is the rapidly emerging virus that has established itself as one of the most important viral diseases affecting tomato crops.

PGPB as biocontrol agent in tomato

Some pest management researchers have focused their efforts on developing alternatives to synthetic chemicals for controlling pests and diseases. Among these alternatives to as biological control or biocontrol are referred. The term biocontrol is used not only to control diseases in plants but also disease management practiced during the fruits storage. Plant growth promoting bacteria (PGPB) as biocontrol agents (BCA) have certain advantages over the conventional chemical control methods, because the former are ecofriendly, non-toxic, naturally occurring microorganisms, and their application is sustainable not only for the environment but also to the human health. Another advantage of PGPB as biocontrol agent is the mode of action against the pathogens or the diseases, which also helps in the enhancement of crop growth and yield. The important mechanisms involved in the antagonism by BCA, are the production of antibiotics, cell wall degrading enzymes, bio-surfactants and volatiles, and also induction of systemic resistance (ISR) in plants (Pérez-Montano et al. 2014; Kumar et al. 2015c). PGPBs are also involved in competition for space, nutrients, and stimulation of the plant's defense capacity (Van der Ent et al. 2008).

Studies on the control of pathogens by rhizobacteria usually focus on pathogenic microorganisms, but they are equally effective against weeds and insects (Flores-Fargas and O'Hara 2006; Siddiqui et al. 2005; Kumar et al. 2015c). The effective control of soil-borne diseases using PGPB has been reported by many authors (Whipps 2001; Lucy et al. 2004; Berg and Smalla 2009). Recently, a large number of bacterial strains have been isolated and identified for their development as biocontrol agents against tomato diseases. Punja et al. (2016) used *Bacillus subtilis* strain under greenhouse conditions to control the post-harvest fruit infection. *B. subtilis* strains were also utilized by Kilani-Feki et al. (2016) for the suppression of *Botrytis cinerea*, the causative agent of tomato fruit rot. Gowtham et al. (2016) utilized ten rhizobacterial strains to manage the *Fusarium* wilt in tomato, and found that two different strains *Bacillus amyloliquefaciens* and *Ochrobacttrum intermedium* significantly inhibited the incidence of wilt and also enhanced the vigor index of seedlings. Abdallah et al. (2016) inoculated seven different endophytic strains isolated from the native *Nicotiana glauca* plants, and found 94–88% significant reductions in yellowing and wilt symptom, and 95–97.5% in vascular browning. Hammami et al. (2013) screened the effectiveness of *Pseudomonas fluorescens* strains against different diseases such as damping-off, root rot, stem canker, and leaf blight of tomato. Khan et al. (2012) utilized *Paenibacillus lentimorbus* strains for controlling early blight disease by *Alternaria solani* in tomato.

Goudjal et al. (2014) utilized endophytic actinomycetes for the biocontrol of *Rhizoctonia solani* causing damping-off in tomato. These strains significantly inhibited the pathogen growth, and enhanced the growth parameters of tomato. In recent years, the biocontrol of plant diseases, particularly using the antibiotic metabolites of actinomycetes, has emerged as an alternative to chemical control agents (Huang et al. 2011). The role of actinomycetes in biocontrol of soil-borne plant pathogen has been demonstrated against *Fusarium* spp. (Gopalakrishnan et al.2011), *Phytophthora* spp. (Shahidi Bonjar et al. 2006) and *Pythium* spp. (Hamdali et al. 2008).

Some of the fungal strains have also been used as biocontrol for pathogens and diseases in tomato. Kriaa et al. (2015) isolated glucose oxidase producing *Aspergillus tubingensis*, which inhibited growth and spore production in *Fusarium solani*. *Trichoderma* isolates have also been reported as the potential biocontrol for some fungal pathogens in tomato. You et al. (2016) reported *Trichoderma*-mediated growth inhibition of *Botrytis cinerea,* and their application in soils promoted growth of tomato. Some of the important strains of PGPB and their biocontrol potential against the pathogens are described in Table 1.

Mechanisms of biocontrol by PGPB

Disease controls through BCA (biocontrols) commonly rely on competition for nutrients and space at the infection site, production of metabolites, and manipulation of bacterial signaling molecules (Kloepper 1993; Wu et al. 2009). In all such cases, pathogens are antagonized by the presence and activities of other organisms they encounter (Fig. 1). The primary mechanism of pathogen suppression via nutrient competition involves the secretion of compounds like siderophores that efficiently sequester iron and deprive the pathogen from this important element (Raaijmakers et al. 2002). Some bacteria inhibit pathogen's growth by secretion of metabolites that include antibiotics, toxins, surface active compounds (biosurfactant), and cell wall degrading enzymes (Whipps 2001; Compant et al. 2005; Haas and Defago 2005; Kumar et al. 2015c), whereas their specific metabolites also trigger the induction of systemic resistance (Van Loon et al. 1998). It is obvious that several mechanisms of action work simultaneously in

Table 1 Biocontrol potential of PGPB against tomato diseases

Sr. no.	Disease	Disease causing organism	Antagonistic organisms	References
1	Bacterial speck	*Pseudomonas syringae* pv. *tomato*	*Pseudomonas* sp., *Bacillus amyloliquefaciens/methylotrophicus* and *Pseudomonas veronii*	Romero et al. (2016)
2	Bacterial spot	*Xanthomonas campestris*	*Bacillus subtilis*	Abbasi and Weselowski (2015)
3	Bacterial wilt and canker	*Clavibacter michiganenensis*	*Pseudomonas putida*	Aksoy et al. (2017)
4	Bacterial wilt	*Sclerotinia sclerotiorumm* *Fusarium solani* *Alternaria alternata*	*Pseudomonas fluorescens*	Hammami et al. (2013)
5	Bacterial wilt	*Ralstonia solanacearum*	PGPR	Huang et al. (2013)
6	Bacterial wilt	*Ralstonia solanacearum*	Lactic acid bacterium	Konappa et al. (2016)
7	Bacterial wilt	*Ralstonia solanacearum*	*Ralstonia pickettii* QL-A6	Wei et al. (2013)
8	Bacterial wilt	*Ralstonia solanacearum*	Endophytic bacteria	Nawangsih et al. (2011)
9	Crown and stem rot	*Rhizoctonia solani* and *Sclerotium rolfsii*	*Burkholderia cepacia* T1A-2B and *Pseudomonas sp.* T4B-2A	De Curtis et al. (2010)
10	Damping-off	*Pythium aphanidermatum* and *Pythium ultimum*	*P. corrugata*, *P. fluorescens*, *P. marginalis*, *P. putida*, *P. syringae*,*P. viridiflava*	Gravel et al. (2005)
11	Early blight	*Alternaria solani*	*Pseudomonas, Bacillus, Azotobacter, Seeatia*	Babu et al. (2015)
12	Early blight	*Alternaria solani*	*Paenibcillus lentimorbus*	Khan et al. (2012)
13	*Fusarium* crown and root rot of tomato	*Fusarium oxysporum* f.sp. *radicis-lycopersici*	*Bacillus megaterium* c96 and *Burkholderia cepacia* c91	Omar et al. (2006)
14.	*Fusarium* wilt	*Fusarium oxysporum* f. sp. *lycopersici*	*Alcaligenes faecalis* S18 and *Bacillus cereus* S42	Abdallah et al. (2016)
15.	*Fusarium* wilt	*Fusarium oxysporum*	*Bacillus pumilis*	Benhamou et al. (1998)
16.	*Fusarium* wilt	*Fusarium oxysporum*	*Bacillus amyloliquefaciens*	Gowtham et al. (2016)
17.	*Fusarium* wilt	*Fusarium oxysporum*	*Bacillus amyloliquefaciens*	Loganathan et al. (2014)
18.	*Fusarium* wilt	*Fusarium oxysporum*	*Bacillus subtilis*, *P. fluorescens*	Sundaramoorthy and Balabaskar (2013)
19	*Fusarium* wilt	*Fusarium oxysporum*	*P. putida*	Srinivasan et al. (2009)
20	Root rot	*Fusarium solani*	*Aspergillus tubingensis*	Kriaa et al. (2015)
21	Grey mould or fruit rot disease	*Botrytis cinerea*	*Bacillus subtilis V26*	Kilani-Feki et al. (2016)
22	Grey mould or fruit rot disease	*Botrytis cinerea*	*Trichoderma harzianum*	Elad et al. (1993)
23	Grey mould or fruit rot disease	*Botrytis cinerea*	*Streptomyces sp.*	Li et al. (2011)
24	Grey mould or fruit rot disease	*Botrytis cinerea*	*Candida oleophila*	Lima et al. (1997)
25	Grey mould or fruit rot disease	*Botrytis cinerea*	*Paenibacillus polymyxa*	Helbig (2001)
26	Tomato Rot disease	*Rhizoctonia solani*	*Bacillus subtilis* B99-2	Ma et al. (2015)

Table 1 continued

Sr. no.	Disease	Disease causing organism	Antagonistic organisms	References
27	Grey mould or fruit rot disease	*Botrytis cinerea*	*Micromonospora*	Martínez-Hidalgo et al. (2015)
28	Grey mould or fruit rot disease	*Botrytis cinerea*	*Bacillus amyloliquefaciens*	Mari et al. (1996)
29	Grey mould or fruit rot disease	*Botrytis cinerea*	*Bacillus subtilis*	Hang et al. (2005)
30	Grey mould or fruit rot disease	*Botrytis cinerea*	*Pseudomonas rhodesiae, Pseudomonas* sp., *Exiguobacterium* sp., *Bacillus amyloliquefaciens/ methylotrophicus, Pseudomonas veronii, Pseudomonas* sp. and *Pantoea eucalypti*	Romero et al. (2016)
31	Grey mould or fruit rot disease	*Botrytis cinerea*	*Trichoderma*	You et al. (2016)
32	Post –harvest diseases	*Penicillium* and *Rhizopus*	*Bacillus subtilis*	Punja et al. (2016)
33	Root-knot disease	*Meloidogyne incognita*	*Bacillus methylotrophicus* strain R2-2 and *Lysobacter antibioticus* strain 13-6	Zhou et al. (2016)
34	Stem cankar	*Alternaria alternata*	*P. fluorescens*	Pastor et al. (2012)
35	Tomato bacterial wilt	*Ralstonia solanacearum*	*Streptomyces virginiae* Y30 and E36	Tan et al. (2011)
36	Vascular wilt and crown root rot	*Fusarium oxysporum* f. sp. *lycopersici* and *F. oxysporum* f. sp. *radicis-lycopersici*	*Pseudomonas fluorescens* Pf-5 and SB65, *P. corrugata* SB40 and *Burkholderia Cepacia*	Larkin and Fravel (1998)

many BCA. Some of the general mechanisms regarding biocontrol of tomatoes diseases are briefly discussed below.

Production/synthesis of antimicrobial metabolites

Antibiosis is an attractive and a highly effective mode of action as witnessed by BCA in disease suppression, especially in the soil-borne infections in a number of crops (Handelsman and Stab 1996). In general, BCA produce antimicrobial metabolites, the low-molecular weight diverse group of organic compounds, which are deleterious for the growth and metabolic activities of other microorganisms (Fravel 1988; Raaijmakers et al. 2002). In the past decades, a large number of microorganisms, especially the bacterial genera, have been used for the production of metabolic products. Some of the metabolites produced by bacterial BCA have broad spectrum activity and act against various groups of microorganisms (Raaijmakers et al. 2002). Some species of *Bacillus* and *Pseudomonas* produce a large number of antimicrobial products which act against pathogenic fungi, nematodes, bacteria, helminths, etc. (Thomashow and Weller 1995; Raaijmakers et al. 2002; Almaghrabi et al. 2013).

Secondary metabolite such as pyrrolnitrin (3-chloro-4-(20-nitro-30-chlorophenyl) pyrrole), produced by different bacterial strains like *Pseudomonas* (Ligon et al. 2000), *Serratia* sp. (Kalbe et al. 1996), and *B. cepecia* (Burkhead et al. 1994), effectively acts against different pathogens. Another metabolite 2,4-diacetylpholoroglucinol (DAPG) produced by *Pseudomonas fluorescens* CHA0 has been greatly utilized for the suppression of root-knot in tomato (Siddiqui and Shaukat 2003). Phenazine produced by *Pseudomonas* sp. effectively acts against pathogen *Fusarium oxysporum* in tomato (Chin-A-Woeng et al. 1998). Production of antimicrobial metabolite is modulated by exogenous and endogenous factors, addition of fertilizers, carbon sources, and minerals (Shanahan et al. 1992; Duffy and Defago 1999). The addition of glucose enhanced production of DAPG in *Pseudomonas* strains, whereas the supplementation of phosphate fertilizer repressed the process (Duffy and Defago 1999).

Production of cell wall degrading enzymes

Production and secretion of cell wall degrading enzymes are the major mechanisms used by BCA to control soil-borne pathogens (Kobayashi et al. 2002; Kumar et al. 2015c). These enzymes affect the structural integrity of target pathogens cell wall (Budi et al. 2000). Cell wall degrading enzymes secreted by biocontrol strains used β-1, 3-glucanase, chitinase, cellulase, and protease that exert direct

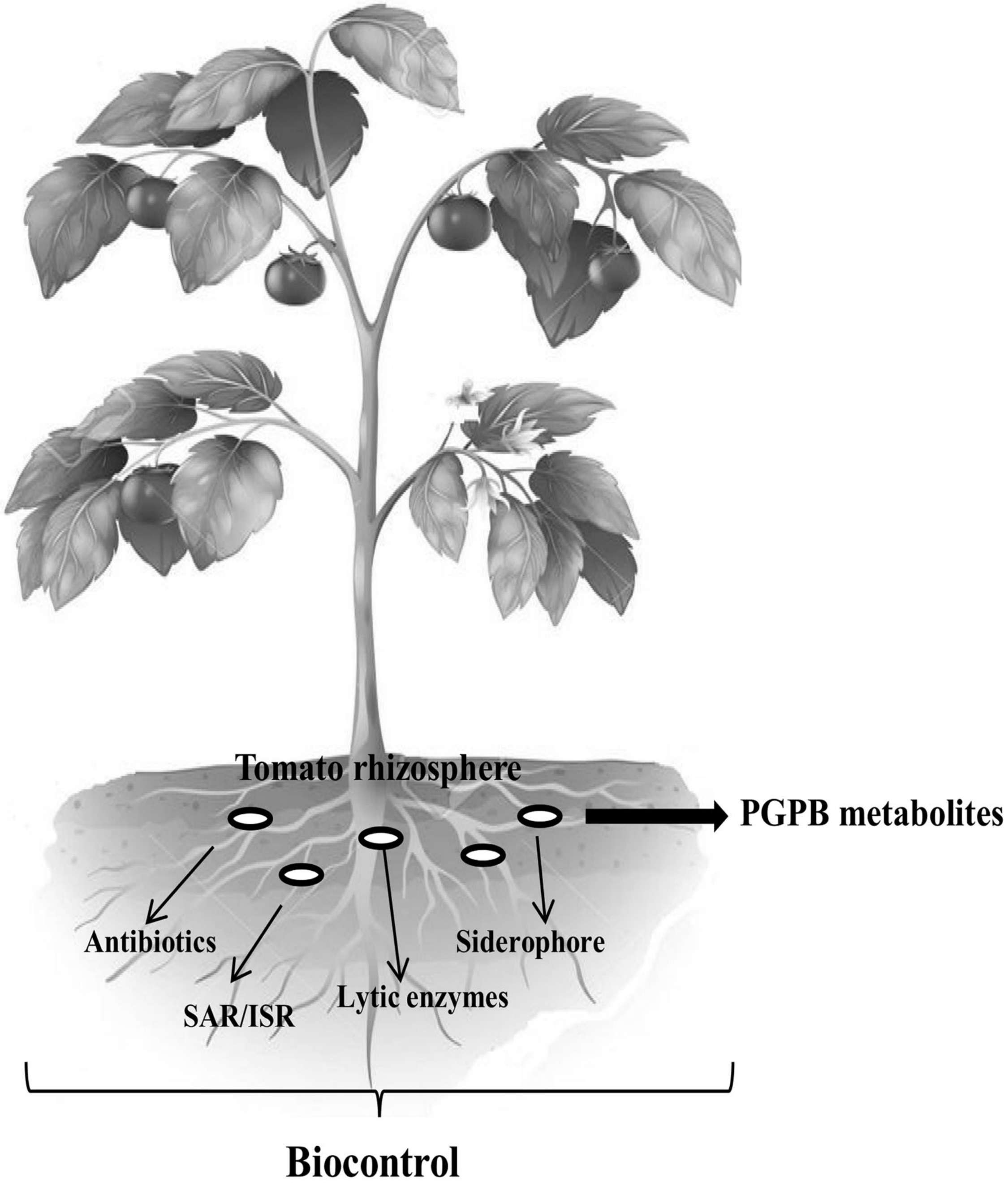

Fig. 1 Overview of plant growth promoting bacteria in disease management of tomato

inhibitory effect on the hyphal growth of fungal pathogens, and chitinase and β-1, 3-glucanase lyse chitin, insoluble linear polymer of α-1, 4-*N*-acetylglucosamine of cell wall of pathogens (Labuschagne et al. 2010). Some of the biocontrol strains like *P. aeruginosa*, and *P. fluorescens* possess chitinolytic activities that degrade the chitin in the cell wall (Nelson and Sorenson 1999). Someya et al. (2000) reported chitinolytic and antifungal activities of the potent biocontrol strain of *S. marcescens* B2 that effectively acted against the soil-borne pathogens *R. solani* and *F. oxysporum*.

Induced resistance (IR)

Induced resistance (IR) is defined as an enhancement of plant's defensive capacity against a broad spectrum of pests and pathogens (Ramamoorthy et al. 2001). The elevated resistance is due to an inducing agent like the pathogen or upon exposure to biotic or abiotic stimuli. There are two major types of IR which includes induced systemic resistance (ISR) and systemic acquired resistance (SAR) (Kumar et al. 2015c). Plants acquire enhanced level of resistance to pathogens upon exposure to biotic stimuli provided by many PGPB, which are activated by certain molecules to as elicitors. Elicitors are generally cell wall polysaccharides, salicylic acid, cyclic lipopeptides, signal molecules like *N*-acyl-homoserine-lactones (AHLs), phytohormones, ethylene, and jasmonic acid (Van loon 2007; Van der Ent et al. 2009; Pérez-Montano et al. 2014). Induced systemic resistance in tomato against *Botrytis cinerea* involves jasmonic acid signaling as observed during biochar amendments (Mehari et al. 2015). The siderophore, pyocyanin, and pyochelin produced by *Pseudomonas* species are reported to induce resistance in tomato plants against tobacco mosaic virus (Choudhary et al. 2007). In another study, it was observed that root inoculation of tomato plants with *Micromonospora* strains effectively reduced leaf infection by the fungal pathogen *Botrytis cinerea*. The *Micromonospora* induced defense mechanism upon exposure to pathogen attack has been validated by gene expression studies. Tomato plants treated with PGPR *Micromonospora* sp. responded in terms of strong and quick induction of jasmonate-regulated defense pathway upon exposure to pathogen (Martínez-Hidalgo et al. 2015).

Future prospective

Food security for the ever increasing human population can be achieved by sustainable management of natural resources. Various studies reported a significant role of PGPB in agricultural management. However, knowledge gap is still underlying plant–microbe interactions under different stress conditions particularly the biotic ones. Knowledge of rhizosphere ecology governing the distribution of pathogens and antagonists may open the door for enhancing biocontrol effectiveness against phytopathogens. Future research demands intensive rhizo-engineering based on favorable identification and partitioning of the novel biomolecules, which might create the unique setting for interactions between plants and microbes. Alternatively, exploration and application of multi strain microbial inoculants over the single strain could be the effective means for disease suppression. In addition, genetic modifications for enhancing the biocontrol efficacy can also be an emerging research field for future disease managements. For instance, the transformation of strains with increased levels of antimicrobials and growth enhancing metabolites can be the better options (Walsh et al. 2001). Temperature-dependent activity can be enhanced by the addition of ice-nucleating PGPB. Furthermore, role of non-symbiotic endophytic PGPB in disease management and growth promotion is very limited. The microbial, biochemical, and molecular study using cutting edge tool may provide in-depth knowledge for better understanding of interactions between the plants and interacting microorganism. For example, root colonization of *Pseudomonas fluorescens* PICF7, an olive root endophyte triggered expression of genes potentially coding for olive lipoxygenase (LOX-2), phenylalanine ammonia lyase (PAL), acetone cyanohydrin lyase (ACL) in not only the targeted organ (root) but also showed broad pattern of plant defense in terms of tissues (Cabanas et al. 2014). To sum up, future challenge is to improve the efficacy and durability of biocontrol under field conditions. If this is resolved, the efficacy of biocontrol could feasibly be improved through implications of the expertise to develop improved screening protocols, formulations, and application procedures, as well as the innovative integrated disease management practices.

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Compliance with ethical standards

Conflict of interest None of authors have conflict of interest.

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