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Review

Plant growth promoting bacteria in agriculture: Two sides of a coin

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ABSTRACT

Plant growth promoting bacteria (PGPB) provide multiple benefits in agriculture by enhancing crop productivity and nutrient content and suppressing the growth of pathogens. Development of beneficial plant-microbe interactions based on genomics, transcriptomics, proteomics and metabolomic data of both PGPB and host will lead to optimized microbial inoculants for enhancing crop yield and nutrient content. PGPB are promoted as a green technology which will reduce the use of chemical fertilizers thereby improving soil health. Although a significant increase in the use of PGPB in agriculture was observed in the last two decades, there is a dearth of long-term studies addressing the effects of PGPB on existing microbial community structure. It is likely that most or all PGPB are resistant to common antibiotics used to treat human diseases. Antibiotic resistance of PGPB may be due to the presence of antibiotic resistance genes and intrinsic resistance due to the presence of efflux pumps. The biological significance of resistance to antibiotics and metals and their relation to plant growth promoting activity, if any, is not known. The consequences of harboring antibiotic resistance may be negative if the trait is transferred to other soil or environmental bacteria. Strategies to develop PGPB strains with useful traits of plant growth promotion but without resistance to common antibiotics used by humans, would enhance agricultural productivity without the negative effects on the environment. Alternately, harboring antibiotic resistance may be positive if it is due to intrinsic resistance involving proteins which also have other functions. Antibiotic resistance of PGPB may be an essential trait if it is related to their plant growth promoting activity. Overall, there is a need to conduct large-scale screening of PGPB for antibiotic resistance and long-term studies to see the effect of the introduction of biofertilizers on native soil microbial community.

1. Introduction

Modern agriculture practices have sharply increased crop yields in the last 50 years, mainly resulting from the application of fertilizers, chemical pest control, irrigation, and development of hybrids. The intensive use of synthetic chemical fertilizers and pesticides in current agricultural practices created a range of environmental problems that include ground water contamination, soil quality degradation and biodiversity reduction (Tilman et al., 2001; Tilman et al., 2002; Diaz and Rosenberg, 2008). In addition, environmental factors such as drought, elevated temperature and CO_2 caused by the global climate change pose a growing threat to current agriculture (Ahuja et al., 2010). There is an increasing need for global crop production to meet the food, industrial processes and biofuel demands of our growing population, which will reach about 9 billion by 2050. Stimulated by the increasing demand, and the awareness of negative environmental and human health impact caused by current agriculture practices, worldwide agriculture is moving to a more sustainable and eco-friendly approach.

Soil microorganisms as a component of soil ecosystem play an important role in regulating soil fertility, nutrient cycling and maintaining plant diversity (Fitzsimons and Miller, 2010). Plant growth-promoting bacteria (PGPB) refer to free living bacteria in the soil and rhizobacteria that colonize root rhizosphere. The use of naturally occurring PGPB in sustainable agriculture has gained importance in the past decade due to their beneficial effects on soil and crop productivity. In addition to enhancing plant growth, PGPB help plants to cope with biotic and abiotic stresses.

PGPB tend to harbor genes for antibiotic and metal resistance. Antibiotic resistance can be an intrinsic property or it can be acquired. Intrinsic resistance can be attributed to the presence of specific characteristics such as the presence of multidrug efflux pumps, which are involved in performing metabolic processes in bacteria. This is supported by phylogenetic analysis of some genes involved in antibiotic resistance which suggest a long evolutionary history originating prior to the 'antibiotic era' (D'Costa et al., 2011; Van Goethem et al., 2018).

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Acquired antibiotic resistance can result from mutations in genes or the acquisition of resistance genes from other organisms by horizontal gene transfer. There is very little information on the biological significance of antibiotic resistance of PGPB.

2. Specificity of PGPB association with host plants: myth or reality

The major groups of PGPB belong Proteobacteria and Firmicutes (Jiang et al., 2008; Chen et al., 2010; Rojas-Tapias et al., 2012). In the phylum Firmicutes, *Bacillus* sp. are the predominant bacteria with plant growth promoting activity. In the phylum Proteobacteria, class Gammaproteobacteria includes the genera *Pseudomonas*, *Acinetobacter*, *Serratia*, *Pantoea*, *Psychrobacter*, *Enterobacter* and *Rahnella*. In addition, two free-living PGPB *Burkholderia* sp. and *Achromobacter xylosoxidans* belonging to Betaproteobacteria have been identified (Batista et al., 2018). The host plants associated with PGPB include those belonging to Fabaceae, Poaceae, Asteraceae, Brassicaceae, Asteraceae, Crassulaceae and Solanaceae families. Fabaceae (legume family) contains important agricultural plants such as soybean (*Glycine* max), pea (*Pisum sativum*) and alfalfa (*Medicago sativa*). In this family, the symbiotic relationship between nitrogen-fixing endophytic bacteria and leguminous plants has been well characterized (Oldroyd et al., 2011). Crop plants maize, sorghum and barley belonging to Poaceae family have been used for phytoremediation of metal contaminated soil due to their high biomass and potential use for biofuels (Vamerali et al., 2010). The PGPB associated with these plants are related to free-living *Pseudomonas* sp. and *Burkholderia* sp. as well as endophytic *Bacillus* sp. interacting with hyperaccumulator plants. *Brassica juncea* and *Brassica napus*.

Microbial communities associated with plants and soil have been shown to display some specificity for each plant species which can be attributed to secondary metabolites released by root exudates. Understanding PGPB genetic diversity will expand the knowledge base regarding beneficial plant-microbe interactions and can be useful in the formulation of new inoculants and improving cropping systems for the most profitable application. Phylogenetic analysis based on 16S rDNA amplification followed by restriction analysis of samples from cold deserts of Himalayas identified 82 species belonging to four phyla: Actinobacteria (19%), Bacteroidetes (3%), Firmicutes (41%) and Proteobacteria (37%) (Yadav et al., 2015). Actinobacteria, Bacteroidetes and Firmicutes are gram positive while Proteobacteria are gram-negative. Another study identified a small but significant α-diversity (within sample) and β-diversity (between samples) in the rhizosphere of 27 maize inbred lines tested across four different field locations in the US which are likely to be associated with host genetics (Peiffer et al., 2013). Proteobacteria were found to be the dominant group in maize as well as other plants such as *Arabidopsis* and rice are considered to be r-selected bacteria with higher growth rates compared to the non-rhizospheric soil which is enriched with k-selected bacteria (Lundberg et al., 2012; Edwards et al., 2015). In addition to similar patterns shown by rice and maize with reference to the influence of host genetics on soil bacterial composition and the dominance of proteobacteria, methanogens were identified in rhizosphere, rhizoplane and endosphere of rice which are associated with methane emissions in rice fields. Root microbiome composition varied among thirty angiosperm species (Fitzpatrick et al., 2018). The existing data shows that there is some commonality of bacteria associated with different plants and also there are specific bacteria associated with specific plant species.

3. Mechanisms for multitasking by PGPB

PGPB promote plant growth usually by two mechanisms: direct or indirect way (Fig. 1). Direct mechanisms include facilitating resource acquisition and modulating plant hormone levels. On the other hand, indirect mechanisms include the inhibition of various pathogens which hamper the growth and development of plants thereby acting as a biocontrol agent (Glick, 1995; Vurukonda et al., 2018). PGPB promote plant growth by improving the uptake of macronutrients (nitrogen, potassium, calcium, magnesium, phosphorus and sulfur) and micronutrients (chlorine, iron, boron, manganese, zinc, copper, molybdenum and nickel). Soil pH decrease occurs via production of organic acids or stimulation of proton pump ATPase which improves solubilization of these nutrients (Mantelin and Touraine, 2004). Atmospheric N-fixing bacteria such as *Rhizobium* and *Bradyrhizobium* can establish symbiosis forming nodules on roots of leguminous plants such as soybean, pea, peanut, and alfalfa, which convert nitrogen into ammonia which is used as a source of nitrogen (Murray, 2011). However, this process is mostly limited to legume crops. Free-living bacteria such as *Azospirillum*, *Azoarcus*, *Azotobacter*, *Bacillus polymyxa*, *Burkholderia*, *Gluconoacetobacter* and *Herbaspirillum* have the ability to fix nitrogen. These PGPB can fertilize several agronomically important crops such as wheat, sorghum, maize, rice and sugarcane (Pérez-Montaño et al., 2014). In the soil, a large amount of insoluble phosphorus is present which cannot be absorbed by plants thereby limiting their growth. PGPB convert the phosphorus into a soluble form which can be utilized by plants. Most of the phosphate taken up by a cell is in the form of HPO_4^{2-} or PO_4^{-}. Phosphate solubilizing bacteria such as *Azospirillum*, *Bacillus*, *Burkholderia*, *Erwinia*, *Pseudomonas*, *Rhizobium* and *Serratia* which convert insoluble phosphates into soluble form through the process of acidification, chelation, exchange reactions and production of gluconic acid (Richardson et al., 2009; Pérez-Montaño et al., 2014). Many PGPB carry out a dual role of plant growth promotion as well as a biocontrol agent. The trait of plant growth promotion can be employed for multitasking of increasing crop productivity and growing plants in marginal soil for producing biofuel.

4. Does PGPB introduction affect soil microbial community structure in a positive or negative way?

Both abiotic and biotic stress negatively affects the survival and fitness of plants. Plants modulate stress responsive genes to maintain homeostasis in stressed conditions (Shaik and Ramakrishna, 2014) which is enhanced by PGPB resulting in better crop yield and soil fertility (Jha and Singh, 2017). Hyperaccumulating and/or high biomass plants have the ability to mitigate heavy metal contamination in soil (Pidatala et al., 2016; Pidatala et al., 2017). This capability can be further enhanced by PGPB especially *Pseudomonas* sp. and *Bacillus* sp. which enhance plant biomass through nutrient acquisition in marginal and heavy metal contaminated soil (Li et al., 2014; Dhawi et al., 2015; Dhawi et al., 2016; Ma et al., 2017). Drought stress was shown to enhance Actinobacteria in the microbiome of sorghum root (Xu et al., 2018). Many PGPB strains act as potential biocontrol agents against multiple plant diseases (Liu et al., 2017). *Streptomyces* sp. modulate defense related metabolism in tomato infected with *Pectobacterium* (Dias et al., 2017). A recent study reported that *Streptomyces* or other PGPB could be used for the production of secondary metabolites which can be employed for crop nutrition and protection as a replacement for chemical fertilizers and pesticides (Rey and Dumas, 2017). Most of our current knowledge is limited to microbial community structure with very little information about their function. It is a challenging task to decipher which microbial groups are functionally active: a riddle that can be solved with metatranscriptomics of soil microbes. The functional microbial communities will vary according to geographical locations, environmental conditions, soil quality, plant genotype and developmental stage. How do genetically modified (GM) plants alter soil microorganisms? A rice insertional mutant of calcium/calmodulin-dependent protein kinase gene, which is an ortholog of the gene involved in symbiosis in legumes, altered rhizospheric microorganisms (Ikeda et al., 2011). A similar analysis is needed to examine the effect of GM plants with altered genes not related to known plant-microbe interactions. Transgenic plants alter rhizospheric microbial community structure and metabolic function but their effect on soil microbial community is transient (Dunfield and Germida, 2003). Introduction of active

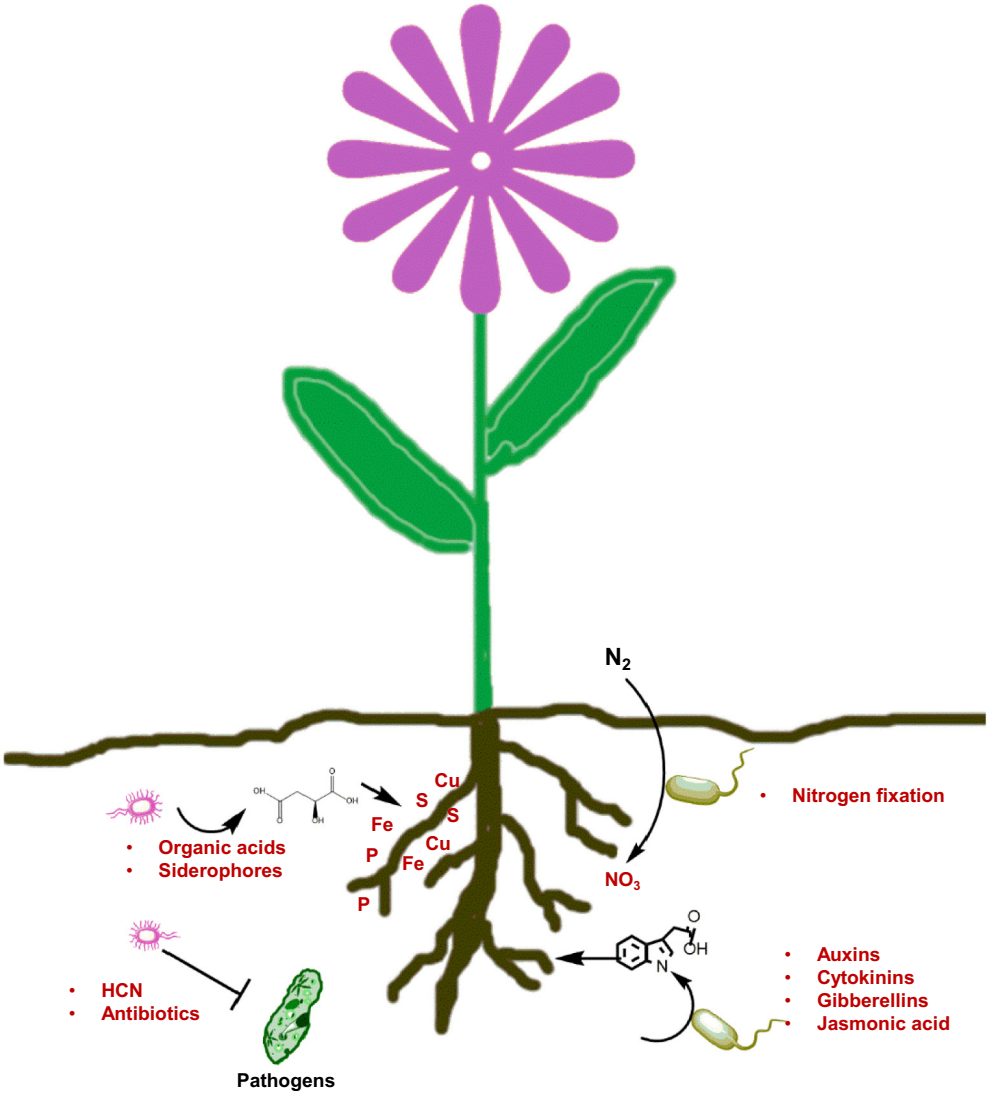

Fig. 1. Mechanisms used by plant growth promoting bacteria (PGPB) to enhance interactions in the rhizosphere for higher grain yield and nutrient content. PGPB produce plant hormones, siderophores and organic acids and solubilize phosphate. They produce hydrogen cyanide and antibiotics to control pathogens.

PGPB alter resident microbial community structure which is dependent on their interactions with the indigenous microbial community. They may have a synergistic effect or antagonistic effect. All these alterations had temporary, spatially limited and transient effects on the resident microbial population (Castro-Sowinski et al., 2007; Qiao et al., 2017). A field study on assessment of GM cotton on soil microbial community shows that there is no significant difference in conventional and GM cotton GK-12 actinobacterial population (Zhang et al., 2017). A similar study on maize shows that GM maize does not influence the colonization of endophytic *Bacillus subtilis* strain nether in plant nor in bulk soil (Sun et al., 2017). Transgenic *Brassica* sp harboring synthetic antifungal resistance (NiC) genes does not affect the rhizospheric microbial community structure and soil microbial enzymatic activity compared to non-transgenic plant (Khan et al., 2017). Persistence of GM plant residues can be hazardous to non-targeted beneficial soil microbial community. Additional studies involving different plants and soils are needed to address the impact of GM plants on non-targeted organisms.

5. Antibiotic resistance of PGPB: Hidden secret with huge impact

Several bacterial strains isolated from soil such as *Pseudomonas* and *Bacillus* sp. are frequently used as inoculants in field and greenhouse conditions for plant growth promotion. However, these bacterial species have Antibiotic Resistance Genes (ARGs) (Wellington et al., 2013; Kang et al., 2017). Overuse of antibiotics in animal husbandry and in pharma industry causes the spread of ARG in soil and environment (Riber et al., 2014). Soil microbiome was found to have cassettes of ARGs belonging to five classes of antibiotics and was proposed to serve as a reservoir for exchange with ARGs of clinical isolates (Forsberg et al., 2012). Organic fertilizers amended with pig manure were implicated in the spread of tetracycline resistance gene in cucumber rhizospheric soil (Kang et al., 2016). The number of ARGs in soil bacteria was found to increase in soil with relatively higher levels of nitrogen fertilizer (Forsberg et al., 2014). These resistance genes are often present on broad host range plasmids, transposable elements and integrons (Heuer et al., 2011; Gillings, 2017). Many known PGPB contain more than one chromosomal and plasmid-borne ARGs based on genome sequencing data (Fig. 2; Kang et al., 2017). ARGs are more prevalent in Proteobacteria than Bacteroidetes. Soil amendments with Proteobacteria may have potential risk because they can transfer ARGs to other bacteria and possibly to plants. Plasmids in some soil bacteria contain *bac* gene which confers resistance to bacitracin produced by *Bacilli*. This gene is acquired by horizontal gene transfer and is required for the survival of bacteria due to the presence of *Bacilli* species in most

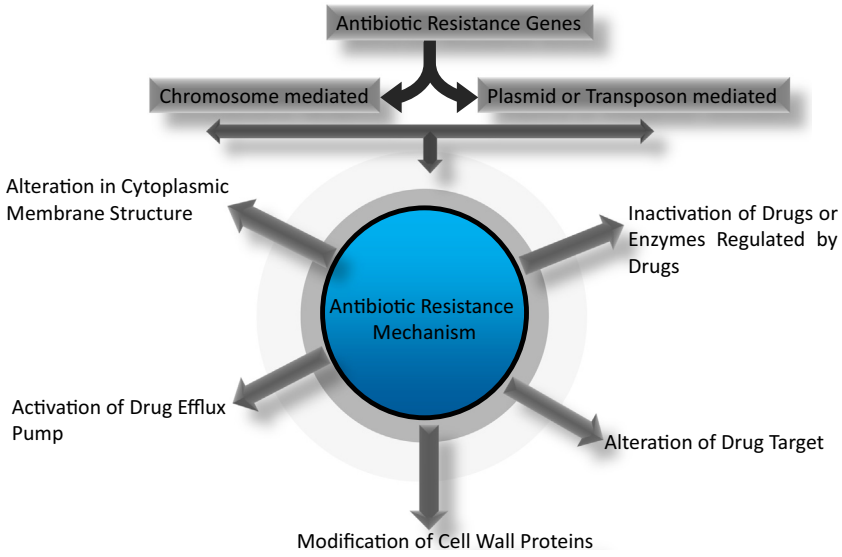

Fig. 2. Mode of action of antibiotic resistance genes (ARGs) of plant growth promoting bacteria (PGPB). ARGs are present on either plasmids or chromosomes. Antibiotic resistance in some cases is the result of the presence of multifunctional proteins which are involved in other functions such as efflux transporters for metals and other molecules.

soils. Hence the risk of development of antibiotic resistance in plants and animals is a major concern in deploying PGPB in agriculture. There are some studies which indicate that heavy metal contaminated soil co-select the microbes which are resistant to multiple antibiotics (Li and Ramakrishna, 2011). Cross-resistance and co-resistance are the two mechanisms involved in co-selection of antibiotic resistance in microbes.

Various groups reporting the significance of PGPB on plant growth and as a biocontrol agent, widely ignore the potential risk of ARGs associated with these microbes. There is an urgent need to consider negative aspects associated with these beneficial microbes before inadvertently introducing them in the field (Kang et al., 2017). Employment of specific methods to exploit the beneficial attributes associated with PGPB includes using microbes with very few ARGs and optimization of metabolite production in PGPB for plant promotion. Although genome editing tools like CRISPR/Cas9 can be employed to avoid antibiotic resistance and allelopathy gene from bacterial strains, there are concerns over the deployment of GM bacterial strains in the environment. This concern can be overcome by the removal of the plasmid carrying genes responsible for antibiotic resistance provided that the plant growth promoting activity of the PGPB is not compromised. An alternative approach would be the development of bio-formulation with bioactive compounds from PGPB. However, this approach has the disadvantage of not producing bacterial compounds on a continuous basis.

Modern anthropogenic activity contributes resistance to multiple antibiotics in soil bacteria. These bacterial strains contain genes which confer resistance to tetracycline, penicillin, carbapenem, cephalosporin, beta-lactam, aminoglycoside, and chloramphenicol which are naturally produced by soil microbes. There are various mechanisms involved in antibiotic resistance which include interference with cell wall synthesis (e.g., β-lactams and glycopeptides), cell membrane inhibitors (polymyxins and daptomycin), protein synthesis inhibitors (tetracyclines, chloramphenicol, aminoglycosides) and nucleic acid synthesis inhibitors (fluoroquinolones and rifampicin) (Hall and Mah, 2017). One bacterial species often found in soil samples is *P. aeruginosa*, which is an opportunistic pathogen resistant to multiple antibiotics encoded via genes located on chromosomal and plasmid DNA. Antibiotic resistance through genetic mutation is well documented in laboratory and clinical studies. Upregulation of β-lactamases including AmpC as well as efflux pumps, alteration in membrane proteins and chemical modification of antimicrobial agents (aminoglycosides) confer antibiotic resistance in *P. aeruginosa* (Lister et al., 2009; Poole, 2011). It is not clear if the antibiotic resistance in PGPB originated due to exposure to antibiotics or due to the production of antibiotics by PGPB. There is some evidence to indicate that development of resistance to some antibiotics predates anthropogenic activity based on the presence of ARGs in Antarctic soil samples (Perron et al., 2015; Van Goethem et al., 2018). Some microbes have also acquired resistance against semisynthetic antibiotics like amikacin suggesting that input of new antibiotics lead to high levels of resistance in microbes. Soil microbes produce antibiotics which limit the growth of other microbes in the soil employing intrinsic resistance mechanism which is considered to be a desirable trait for beneficial rhizobia population for their growth and survival (Naamala et al., 2016). Soil and clinical bacteria have the ability to withstand antibiotics via intrinsic and acquired resistance. In contrast to acquired resistance, intrinsic resistance is independent of previous antibiotic exposure and is not caused by horizontal gene transfer. There are many genes in bacteria which are responsible for intrinsic resistance to different classes of antibiotics, including β-lactams, fluoroquinolones and aminoglycosides. Intrinsic resistance in bacteria is basically the consequence of changes in cell envelope permeability and activity of efflux pumps. Intrinsic resistance is common in environmental microbes which have the ability to resist the action of antibiotics as a result of the vertical transfer of genes coding for the required structural and functional attributes. It is a naturally occurring phenomenon present in many bacteria especially Gram-negative bacteria. Intrinsic resistomes of *Acinetobacter baylyi* (Gomez and Neyfakh, 2006), *P. aeruginosa* (Fajardo et al., 2008; Alvarez-Ortega et al., 2011), *E. coli* (Liu et al., 2010) and *Staphylococcus aureus* (Blake and O'Neill, 2012) were identified by gene inactivation and transposon mutagenesis. Mutagenesis studies identified genes with mutations that lead to increased susceptibility to ß-lactams, inactivation of efflux pump and proteins involved in peptidoglycan biosynthesis/modification. Some of the intrinsic resistance causing proteins are species specific (Cox and Wright, 2013). Moreover, mutations in some genes showed resistance to one class of antibiotic but susceptibility to another class of antibiotic (Olivares et al., 2013). Intrinsic resistance uses global regulators as observed in *P. aeruginosa*, where a post-transcriptional repressor protein, catabolite repression control (Crc) regulates susceptibility to antibiotics by modulating expression of transporters and lipopolysaccharide (LPS) composition. *E. coli* with inactive AcrAB efflux pump have increased resistance to macrolides. Another example of intrinsic resistance is daptomycin resistance in Gram-negative bacteria which have low anionic phospholipids in the cytoplasm which reduce calcium-mediated insertion of daptomycin at the target site in the membrane. Many Gram-negative bacteria are intrinsically resistant to antibiotics because they are not able to cross the outer membrane. For example, vancomycin which

targets D-Ala-D-Ala peptides involved in peptidoglycan crosslinking is effective only in Gram-positive but not in Gram-negative microbes (Blair et al., 2015). Bacterial lipocalins (Blc) are highly conserved proteins in bacteria which lead to antibiotic resistance by sequestering antibiotics in extracellular space (El-Halfawy et al., 2017). Heterologous expression of lipocalin genes from diverse bacteria was functional in *Burkholderia cenocepacia*. Recent reports show that regulatory small RNAs, GlmY and GlmZ are involved in intrinsic resistance in Enterobacteriaceae such as *E. coli* and *Salmonella* where they regulate glucosamine-6-phosphate synthase involved in the synthesis of bacterial cell envelope (Khan et al., 2016). In addition to the common players described above, some cryptic genes which confer resistance to antibiotics only when their expression levels are increased under specific conditions have been described in *Salmonella* and *Acinetobacter* (Gang and Jie, 2016; Koskiniemi et al., 2011). Most of these bacteria do not have plant growth promoting activity. It is possible that PGPB may have similar or different genes for intrinsic resistance. Knowledge of genes and other regulatory factors involved in intrinsic resistance in PGPB can be used for their optimal utilization and understanding their biological relevance.

6. Systems biology approach with omics technologies to uncover inner workings of PGPB

Multiple advanced 'omics' technologies have enabled us to gain insights into the structure and function of plant-associated microbes. Advancements in 'omics' platforms allow us to explore the complex metabolic and regulatory network in plant-PGPB interactions, leading to the selection of efficient bacterial strains with improved traits like nutrient uptake and tolerance to biotic and abiotic stress. Omics approaches will address the whole complement of DNA, RNA, proteins and metabolites of the soil microbiome influencing plant growth and stress tolerance (Fig. 3). The importance of functional microbiome in plant fitness and disease protection cannot be understated. Microbiomes influence fundamental plant traits that are beneficial or detrimental to plant growth. They regulate various genetic pathways involved in recognition of host-specific factors. As the plant is not able to move, it is dependent on microorganisms in the immediate environmental surroundings. Multiple factors such as temperature, pH and exudates from bacteria and plants shape the microbiome (Lakshmanan et al., 2014). Integration of multiple omics data employing bioinformatics and statistical tools and in silico models can link potential PGPB with enhanced plant health. Statistical methods enable the association of a specific group of bacteria with a treatment group (Rebollar et al., 2016). Indicator species analysis and Kolmogorov-Smirnov Measure can identify bacteria belonging to an operational taxonomic unit (OTU) associated with a specific treatment. Co-occurrence networks can identify the association of specific group of bacteria with biological or metabolic pathways. Omics approaches can play an important role in rhizosphere engineering for the manipulation of the microbiome to optimize plant function and improve soil health. Engineering the rhizospheric bacteria by utilizing known signaling networks and players involved in the interaction between the host plant and microorganisms would lead to minimal or no ecological and environmental impacts (Baltrus, 2017; Quiza et al., 2015). Massive genomic sequencing of host plants and associated microbes can identify novel mechanisms involved in their interactions. Several plant species and pathogens have been completely sequenced, assembled, and annotated. *Pseudomonas* and *Xanthomonas* are the two bacterial pathogens which have contributed significantly to the field of plant-pathogen interactions (Quirino et al., 2010). In general, proteins that are related to amino acid metabolism, immune system, RNA binding proteins chaperonins and glycolysis were the most responsive proteins in bacterial inoculated plants (Banaei-Asl et al., 2015; Dhawi et al., 2017).

Proteomic analysis of fungi associated with barley grains identified secreted proteins which are involved in cell wall degradation and carbohydrate metabolism (Sultan et al., 2017). Extracellular proteome map of PGPB *Bacillus amyloliquefaciens* FZB 42, identified proteins involved in plant innate immunity which play a crucial role in establishing beneficial plant-microbe interactions (Kierul et al., 2015).

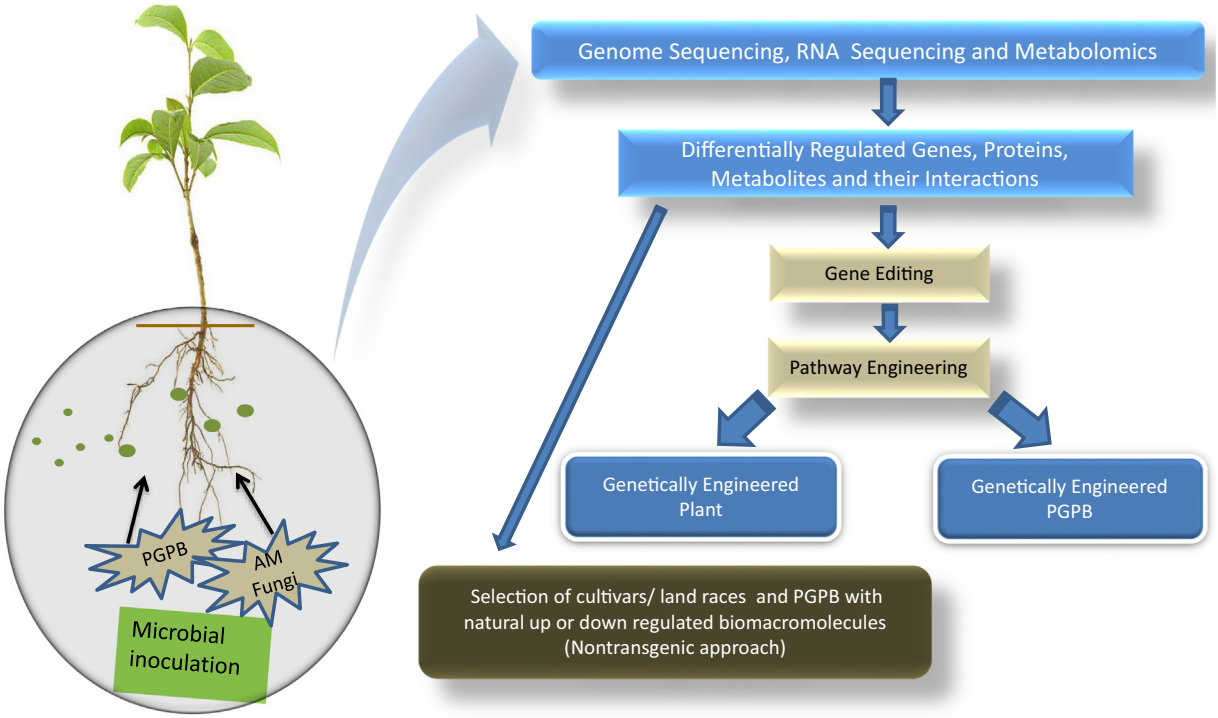

Fig. 3. Interaction between plant and rhizospheric microbiome differentially regulate genes, proteins and metabolites. Omics technologies can be employed to identify these changes in order to optimize plant growth. Gene editing and pathway engineering can be used to modulate genes for enhanced interactions between plant roots and soil microbiome.

Several plant cell wall hydrolyzing enzymes, i.e. arabinose, glucomannanase and xylanase are released by PGPB especially during stationary growth phase in response to plant root exudates. Acetolactate synthase involved in the synthesis of acetoin involved in plant growth and protection against pathogens was upregulated. A recent study showed that inoculation of *Paenibacillus polymyxa* E681 could improve the plant health by activating antioxidant, defense related proteins, hormones and phytoalexins (Kwon et al., 2016). Beneficial microbial consortia consisting of *Trichoderma harzianum*, *Bacillus subtilis* and *Pseudomonas aeruginosa* enhanced antioxidants and led to differential expression of defense related proteins such as transketolase, alcohol dehydrogenase and V-type proton ATPase E in pea (Jain et al., 2014; Jain et al., 2015). Two upregulated pea proteins, Clp and FtsH have a role in regulating protein stability and quality. The gene corresponding to Clp protein was also found to be responsible for copper resistance in PGPB belonging to *Pseudomonas* species (Li et al., 2012).

Cucumber plant inoculated with the PGPB *Paenibacillus polymyxa* NSY50 mitigated the injury caused by *Fusarium oxysporum* f. sp. *cucumerinum* (FOC) infection by upregulation of carbohydrate and amino acid metabolism (Li et al., 2014). Combined (NSY50 + FOC) treatment led to the accumulation of antioxidant protein flavin oxidoreductase (YqiG) as well as modulation of carbohydrate metabolism thereby enhancing plant growth (Du et al., 2016). NSY50 application reduced FOC abundance thereby decreasing pathogen colonization in the cucumber rhizosphere and enhanced beneficial microbes (Shi et al., 2017). Involvement of jasmonic acid signaling and upregulation of proteins common to both biotic and abiotic stress were observed in resistant cucumber plants (Zhang et al., 2016).

Specific plant genotypes support the growth of microbes that can enhance their own fitness. New tools now allow us to re-engineer the rhizosphere through inoculation with microbes that can form a connection with native microbiome which might have been lost due to excessive use of fertilizers and domestication (Wallenstein, 2017). *Bacillus amyloliquefaciens* strain produces surfactin which acts as a signaling molecule for interactions with other microorganisms and regulates carbon metabolism and fatty acid biosynthesis (Zhi et al., 2017). Significant genomic differences between plant-associated and non-plant-associated *B. amyloliquefaciens* and *B. subtilis* strains from different niches were identified where plant associated microbes mainly regulate intermediary and secondary metabolite biosynthesis and antibiotic synthesis. Plant root exudates primarily consist of organic compounds which lead to the enrichment of rhizospheric microbiome (Van der Heijden and Schlaeppi, 2015). All of this information can be used for the improvement of microbial communities. Comparative proteomic studies can be useful in understanding the mechanisms of biotic and abiotic stress tolerance in PGPB inoculated plants.

Metagenomics and metatranscriptomics provide insights into common microbial functions based on individual microbial population existing in a microbial community. Systems-wide omics paired with computational approaches could be a potential approach to monitor the interactions among strains at the molecular level (Müller et al., 2016). Studies show that the same agricultural field despite the same cropping history, crop genotypes and management practices, has different crop productivity which is associated with soil microbiome composition. Machine learning approaches can be used to predict productivity based on microbiome composition (Chang et al., 2017). A higher proportion of *Rhizobiales* order, *Bradyrhizobiaceae* family and *Bradyrhizobium* genus were present in high productivity areas while *Steptophyta* and *Planctomycetes* were present in low productivity areas.

Metabolomics provides a comprehensive understanding of biological pathways involved in a given experimental condition and provides clues about gene to metabolite relationship. Rhizospheric metabolomics can be used to investigate the exudation from plants and microbes. For example, actinobacteria especially *Streptomyces* sp. can act against nematodes because of their ability to produce nematicidal compounds. AVICTA, a commercially available product which is used against a wide variety of plant parasitic nematodes was purified from *Streptomyces avermitilis* (Kaur et al., 2016). Further, the soil microbe, *Streptomyces hydrogenans* strain produces compounds which act as a potential nematicidal agent against *Meloidogyne incognita* and fungal phytopathogens.

Metabolomics with the help of other omics technologies in tandem such as transcriptomics and proteomics has provided many tools for predicting gene function and regulatory networks (Urano et al., 2010). Metabolic profiling of tomato plants subjected to a natural pesticide, azadirachtin modulated biochemical pathways similar to that observed with *Bacillus subtilis* treatment (Pretali et al., 2016). Non-targeted metabolomics would be most useful because it can identify new compounds without any bias for a specific class of compounds as in targeted metabolomics. Overall, proteomics and metabolomics can be used to screen effective PGPB strains that could be used in crop management and commercialization of bioformulations (Lorito et al., 2010).

Data from transcriptomics, proteomics and metabolomics can be used to construct gene networks and analyze protein-protein and protein-metabolite interactions. These studies will identify biologically relevant interactions of unique proteins expressed during plant-microbe interactions which can be used for improving plant nutrient uptake and yield. A similar approach using next-generation technologies (Crofts et al., 2017) can uncover the functional significance of antibiotic resistance of PGPB and its relevance to plant growth promoting activity. Interactome studies facilitate systems biology approach by unraveling novel interactions involving proteins and biological pathways which can be exploited not only for crop improvement but also unravel the inner workings of PGPB with reference to their interactions with soil bacteria and host plant in different environmental conditions.

7. Role of PGPB in agriculture: promise versus bottlenecks

There is an increasing demand for microbial inoculants due to increasing cost of agrochemicals and demand for green technologies in society. In the global market, approximately 12% increase per year has been reported for biostimulants (Calvo et al., 2014). Large-scale commercial production has been achieved with some PGPB like *Burkholderia*, *Pseudomonas*, *Rhizobium*, *Azospirillum*, *Azotobacter*, *Bacillus* and *Serratia* sp. (Parray et al., 2016). However, the use of microbial inoculants for agricultural practices is governed by varying policies in different countries (Bashan et al., 2014). The main bottlenecks are shelf-life, reliability and consistency of microbial inoculants under field conditions. Gram-negative bacteria have shorter shelf-life compared to spore-forming gram-positive bacteria. Super-inoculants which contain all the desired characters were proposed (Schoebitz et al., 2013). However, some of the PGPB have been reported to be opportunistic human pathogens such as *Burkholderia cepacia* and *Pseudomonas aeruginosa* (Kumar et al., 2013; Li et al., 2013), which pose ecological and human risks that should be addressed properly before their production at the commercial level. Improvements are needed to develop more efficient PGPB consortia, new carriers based on nanoparticles and the optimization of application devices. Another issue of concern is that plants harbor various human pathogens and it has been reported that many of them have beneficial plant growth promoting effects which improve plant health (Berg et al., 2005; Allerberger and Sessitsch, 2009; Compant et al., 2010). Further investigation is required which addresses the concern of potentially pathogenic bacteria in sustainable agriculture. Plant rhizosphere is optimized in such a way that beneficial microbes colonize easily than pathogenic microbes (Egamberdieva et al., 2008). Reassessment of the bio-safety of PGPB products is under process in USA, European and other countries. Climate change can alter the plant-microbe interaction by modifying the rhizosphere biology, resource availability and biogeochemical cycling (Abhilash et al., 2016). The full potential of PGPB will be realized once the shortcomings with reference to long-term effects on soil microbial communities, acceptance by farmers, economic viability and government

regulations are addressed.

8. Conclusion

PGPB enhance plant growth and yield by regulating biomacromolecules and interactions among them. The presence of antibiotic resistance in PGPB and their negative aspects (if any) need to be addressed based on long-term studies. The biological significance of the presence of antibiotic resistance in PGPB and their relation to plant growth promotion needs to be investigated. An integrated systems biology approach is best suited to study plant-PGPB and PGPB-soil microbe interactions and optimize them using transgenic and non-transgenic approaches. The complex interactions among plants, soil and microbes in relation to micronutrient dynamics represent a unique opportunity for improving soil fertility. A microbial formulation is an environmental friendly option compared to chemical fertilizers. There is a strong market for microbial inoculants worldwide. Soil microbial population can be managed either by the development of microbial inoculants or the manipulation of existing natural microbiome. There is a need and potential for identifying new PGPB from extreme environment and exotic locations which multiple benefits: higher crop productivity, pathogen control and soil remediation. Advances in high throughput technologies for the identification of microbes, their characterization and production will lead to efficient utilization of PGPB. The future of PGPB is dependent on its acceptance as a green technology which provides superior economic and environmental benefits compared to chemical fertilizers. There is a window of opportunity for PGPB to be the main players of the next green revolution, which is one side of the coin. The other side of the coin reflects possible negative impacts due to antibiotic resistance and the lack of long term studies (lasting for several years) on the effect of PGPB on soil microbial community structure. This aspect of PGPB is ignored by the scientific community at large with the available knowledge equivalent to that of the tip of an ice berg. The above concerns can be addressed by conducting field trials over multiple years and employing omics technologies followed by analysis of targeted biomacromolecules (genes, proteins and metabolites) to understand changes in both plants and PGPB.

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Conflict of interest

All the authors declare that they have no conflict of interest.

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