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REVIEW ARTICLE

Biofertilizer microorganisms accompanying pathogenic attributes: a potential threat

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Abstract Application of biofertilizers containing living or dormant plant growth promoting bacterial cells is considered to be an ecofriendly alternative of chemical fertilizers for improved crop production. Biofertilizers opened myriad doors towards sustainable agriculture as they effectively reduce heavy use of chemical fertilizers and pesticides by keeping soils profuse in micro and macronutrients, regulating plant hormones and restraining infections caused by the pests present in soil without inflicting environmental damage. Generally, pathogenicity and biosafety testing of potential plant growth promoting bacteria (PGPB) are not performed, and the bacteria are reported to be beneficial solely on testing plant growth promoting characteristics. Unfortunately, some rhizosphere and endophytic PGPB are reported to be involved in various diseases. Such PGPB can also spread virulence and multidrug resistance genes carried by them through horizontal gene transfer to other bacteria in the environment. Therefore, deployment of such microbial populations in open fields could lead to disastrous side effects on human health and environment. Careless declaration of bacteria as PGPB is more pronounced in research publications. Here, we present a comprehensive report of declared PGPB which are reported to be pathogenic in other studies. This review also suggests the employment of some additional safety assessment protocols before reporting a bacteria as beneficial and product development.

Keywords Biofertilizers · PGPB · Rhizosphere · Endophytic · Pathogenicity

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Introduction

Development in agriculture for food production is one of the most considerable accomplishment of human history bringing green revolution that protect human from hunger. On the contrary, intensive agricultural practices like excessive soil inputs (fertilizers, pesticides and herbicides) negatively impacts environment (greenhouse gas emission, soil degradation and water contamination). Sustainability and human health mostly depend on the utilization of chemical fertilizers and pesticides (Funabashi 2018; Fanelli 2020). The excessive use of chemical fertilizers like nitrogen fertilizer do not remain available rather mix with ground water, which not only cause ground water pollution and eutrophication but also pollutes troposphere by NH_3 accumulation and stratosphere by N_2O, NO_x leading to ozone depletion which sequentially can have negative effect on agricultural yield and human health (Kanter and Searchinger 2018). It has long been a farmer's dream to improve the chemical composition and physical structure of the soil that provides proper nutrient and water availability to plants and help the plant roots to grow and maintain high crop yields under adverse environmental conditions. Soil scientists shed light upon conspicuous interactions that plants have with their microbiome (East 2013; Zhang et al. 2015; Imran et al. 2021). These plant

growth promoting bacteria (PGPB) open up strategies towards the sustainable agricultural practices. However, in addition to breeding and development of transgenic crop varieties, the administration of PGPB as bio-fertilizers containing living or dormant bacterial cells is additionally viewed to be an alternate strategy for improving the plant growth and development under adverse environmental conditions in an ecofriendly manner (Rozier et al. 2017; Itelima et al. 2018).

Biofertilizers are contemplated to have the ability for improving soil health, crop productivity, sustainability and refining the soil environment from biotic and abiotic stresses. Application of biofertilizers can effectively reduce the use of chemical fertilizers and pesticides, and maintain appropriate amounts of micro and macronutrients as well as plant hormones in the soil (Xu et al. 2014; Chen et al. 2017). These rhizosphere associated PGPB remediate soil contaminants and fix nitrogen in the plant roots (Gewin 2006). Biological strategies encompassing multifarious plant growth promoting rhizobacteria (PGPR) has gained considerable attention to remediate metal-contaminated arable land. Soil is a ubiquitous habitat of physiologically and taxonomically diverse microbiota. PGPR, among the whole soil microbiota, are predominantly present and colonize the soil micro-environment. These Phyto-beneficial bacteria are equipped with numerous plant growth promoting physiological traits, such as phytohormones production, 1-aminocyclopropane-1-carboxylate deaminase (ACCD) activity, phosphate solubilization, nitrogen fixation and siderophore production (Battini et al. 2017; Yasmeen et al. 2021).

In agricultural soils, regardless of high P content only minute quantity of P ($< 1\%$) is available for plant uptake, PGPB mobilizes both organic and inorganic forms of P and making it available for plants (Umesha et al. 2018). These plants associated microbes produce indole 3-acidic acid (IAA), which are involved in the signaling of plant microbe interaction, stimulate cell elongation, hinder the shedding and detachment of leaves, promote flowering and fruiting. IAA also provides support to growing seed in the soil to obtain maximum amount of nutrients and water (Kumar et al. 2018). Major obstacles in the way of improved agricultural yield primarily include abiotic stresses such as salinity, drought heavy metals and heat (Van Oosten et al. 2018). Bio-fertilizers are considered to be a promising solution capable of resolving these issues by controlling the levels of plant stress hormone i.e., ethylene, and breaking it down into α-ketobutyrate and ammonium by ACC deaminase produced by PGPB, which can be further utilized as C and N source (Tiwari et al. 2018). ACC deaminase producing PGPB also reduce the level of reactive oxygen species (ROS) in plants under stress conditions, enhances K^+ acquisition, uptake of water and photosynthesis (Safdarian et al. 2019; Yoolong et al. 2019). Biofertilizers have also been carefully considered for controlling plant diseases either acting as antagonists against plant pathogens or by producing metabolites, most importantly PGPB trigger plant defense mechanisms and boost plant's immunity against diseases (Tilman et al. 2002). Agricultural sustainability can be achieved using PGPB even in adversities and developing safe agricultural practices having minimal environmental influences. In this review, the current scenario of biofertilizers application is discussed along with the concerns regarding reported biofertilizers that can evolve as potential infection causing opportunist.

Bioaugmentation based applications

Bacterial formulations including consortium of different bacterial strains, and inocula from individual culture are used to promote plant growth and development, agriculture and environmental microbiology for biocontrol purposes. Various forms of bacterial inoculants including encapsulated gels, wettable powders, liquid suspensions and granules have been developed (Pandey and Maheshwari 2007; Manikandan et al. 2010). In context of biocontrol and plant growth promotion, naturally existing microbes take a long period for contributing their beneficial traits due to pathogen overload in soil. Since, to get visible effects on availability of optimal quantity of microbial inoculum, plant growth promotion and biological control of plant diseases with desired potential is required. Biological properties of desired organism and biofertilizers are gained by enhancing their number in the natural environment (selective favoring), and inoculating them as biofertilizers (exogenous supplementation) to get quicker and better results (Barros-Rodríguez et al. 2020).

A large body of literature endorses that the pathogenicity caused by microorganisms depend upon the incapability of animals or humans to elicit defensive response. The concentration of pathogenic organisms less than the lethal dose is able to cause infection in a healthy host (Rutherford and Bassler 2012). Several studies about the degradation pathway, consistency, mechanism of action, efficacy in the performance of plethora of PGPB have been performed, but little attention is given towards their impact on human health and environment. Deep screening of PGPB is required to identify bacteria that overlap with unsafe criteria with respect to animals and human health. The reality of some novel reports prompted the scientist/researchers to determine the possibility that plant growth promoting microbes needs to classify them accordingly to their potent biohazards (Martínez-Hidalgo et al. 2019). Microbial genetics suggests that the horizontal genes transfer is involved in the transition of beneficial

bacteria to opportunistic pathogens. So, it is important for microbiologists to determine the possible pathogenicity of PGPB, prior to their mass field applications and bioformulation scale-up.

Potential risks of inadequate tested microorganisms

The interest for the control of plant diseases has been increased in past few years due to the global requirement for eco-friendly approaches that would replace chemical fertilizers and pesticides (Fitzpatrick et al. 2018; Syed-Ab-Rahman et al. 2019). Biofertilizers are supplementary component to soil and crop management practices viz., crop rotation, organic adjustments, tillage maintenance, recycling of crop residue, soil fertility renovation and the biocontrol of pathogens and insect pests, which can significantly be useful in maintaining the sustainability of crop production (Yadav and Sarkar 2019). Rhizospheric niches in the soil also contain many pathogens, which can infect plants, animal and human. Several rhizosphere dwelling PGPB suggested as bio-fertilizers and bio-pesticides, may have the ability to colonize human tissues and organs leading to infections and disease development. Rhizosphere dwelling bacteria belonging to genus *Burkholderia, Enterobacter, Herbaspirillum, Ochrobactrum, Pseudomonas, Ralstonia, Staphylococcus, Stenotrophomonas, Bacillus, Serratia*, *Klebsiella* etc. are known to cause infections as they get involved in multiple interactions with their hosts i.e., plants and human (Berg et al. 2005; Vílchez et al. 2017).

PGPB exhibit phenotypic elasticity enabling pathogenic interactions with animals and humans

Infections can arise from bacteria inhabiting soil rhizosphere e.g., *Pseudomonas aeruginosa* and *Burkholderia cepacia* that commonly induce disease not only in immune compromised but also in healthy individuals (Hassan et al. 2015). Similarly, certain soil bacteria e.g., from genera *Stenotrophomonas* and *Enterobacter* which are involved in plant growth promotion, degradation of toxic substances and counteract against plant pathogens are also opportunistic pathogens having potential to infect human and cause serious diseases (Brown et al. 2012; Wall et al. 2015). Opportunistic bacteria that cause infections in human usually have the ability to survive in a variety of environmental conditions and niches, exhibiting exceptional phenotypic plasticity which enables them to modify phenotypic expression in response to changing environment. The rhizospheric environment is highly fluctuating which give rise to bacteria with enhanced fitness for rhizospheric competency and serves as evolving niche even for opportunists and pathogens (Dazzo et al. 2019). The factors that select the soil microbes to compete (for space and resources) within an environment outside host like rhizosphere also affect the evolution of pathogenicity and virulence; as many soil dwelling bacteria carry virulence factors (VF) which become growing opportunistic pathogens by making changes in gene expression, for example *P. aeruginosa* (Merikanto et al. 2014). VF displayed by opportunistic bacteria are pathogenic elements which are product of natural selection; not essential for bacterial viability rather their perpetuation imparts benefits by enhancing bacterial fitness. VF can be toxins, adhesins or secretory systems (Jameel et al. 2017). Large number of opportunistic bacteria found in association with rhizospheric interaction with plant roots can develop virulence properties in the course of extreme microbial competition. Genome analysis of *B. cepacia* strain F01, isolated from the agricultural field carry all virulence genes that are found in epidemic and clinical strains including *cblA,* flagella and lipase needed for attachment and invasion into lung epithelial cells.

It showed a close phylogenetic relationship with epidemic ET12 lineage compared to clinical strains and high resistance against multiple antibiotics (LiPuma 2010). Pathogenic factor pyocyanin, is a toxin produced by *P. aeruginosa* is driven by the presence of N-acetylglucosamine and peptidoglycan which are the major component of gram-positive bacteria; render advantage to *P. aeruginosa* in competitor rich environments like rhizosphere as it is a strong antimicrobial compound. Pyocyanin also damages human cells including the respiratory and cardiovascular cells leading to disease severity (Singh et al. 2017).

Rapid changes in structure and function of eco-system by modification of environment caused by human activities like agricultural land augmentation, deforestation, build-up of urbanization and expansion in human population especially in developing countries are consequently creating new possibilities for opportunistic generalist bacteria to develop or produce new ecological niches ultimately infecting new hosts (Udikovic-Kolic et al. 2014). Such irregular changes in environmental niches lead to genetic mutations in these bacteria that are shaped by variation in the environment and other interacting hosts. Bacteria that showed phenotypic heterogeneity in highly fluctuating environmental conditions can persist longer due to evolved survival mechanisms. Some of these phenotypic variations arise under environmental pressure in which cells sense signals from the environment and neighboring cells and generate response by making decisions in gene expression, thus acquiring a competent phenotype but there are also some molecular mechanisms independent of signals from

the environment (DebMandal et al. 2011). Bacterial opportunists and pathogens interact with various organisms like human, plants, fungi, annelids, insects, nematodes etc. in competent environments. This shared ecology applies evolutionary pressure due to which genes encoding VF are found to occur even in bacteria that were previously considered non-pathogenic.

Spread of antibiotic resistance genes

Another major concern is that soil microbes produce considerable concentrations of antibiotics to compete in soil environment and to restrict the growth of other organisms in their vicinity especially PGPB that are involved in biocontrol. Moreover, the majority of these soil inhabiting antibiotic producing organisms contained genes for self-defense (most of the time found on same gene cluster) that protects or confer resistance to antibiotics they produce. Bacteria e.g., *P. fluorescens* and *B. cepacia* demonstrate heterogeneous antibiotic resistance patterns having the ability to grow on streptomycin and penicillin by utilizing them as sole C and N sources (Walsh et al. 2011). The presence of the antimicrobial compounds produced by PGPB in soil exerts a selective pressure on neighboring microbes to evolve similar defense mechanisms. It leads to the rapid evolution and spread of antibiotic resistance in soil microbiome which is another added consternation in the incautious and excessive employment of PGPB "less tested for their biosafety profile" in open fields (Bonares et al. 2016).

One reason for the frequent existence of resistant bacteria in agricultural lands is the application of raw manure in fields, which contain antibiotic resistant bacteria as these manure sources (animals) are treated with huge quantities of antibiotics. The unnecessary use of antibiotics, alter the gut microbiome of farm animals that started to attain antibiotic resistance with the passage of time. Application of raw manure in the fields transfer these antibiotic resistant bacteria along with their "resistome" which raises chances of the spread of resistant genes among rhizospheric bacteria via horizontal gene transfer. Therefore, it is quite possible for potential PGPB isolated from a crop field or its rhizosphere to be a potential multi-drug resistant (MDR) strain. Deployment of such bacteria in bio-formulation even for field trial might spread this 'resistome' to human pathogens (Noyes et al. 2016; Checcucci et al. 2020). Also, environmental MDR bacteria can infect humans through contaminated agricultural products like vegetables and fruits (Zeng et al. 2018). The matter of antibiotic resistance becomes serious when isolated rhizospheric or endospheric microbes belong to a species commonly associated with opportunistic infections in humans. For example, *P. aeruginosa* and *P. putida*, are reported as potential candidates for bio-fertilizer and bioremediation in multiple studies, but contains plasmid mediated antibiotic resistant determinants. Another concern is that these antibiotic resistance genes in soil bacteria are going through continuous evolution through point mutations and horizontal gene transfer as studied in beta-lactamase genes polymorphism which can spread into environment and may lead to new epidemic or can eventually get transmitted to clinical strains. *P. putida* also found to harbor NDM-1 gene which encodes for an enzyme that confers resistance to bacteria against wide range of antibiotics even to carbapenem (Rosier et al. 2018). Application of bioinoculants or biofertilizers containing such PGPB can be a serious threat because these genes can proliferate and escalate into other soil bacteria. Such genes can spread through horizontal gene transfer to other bacteria in environment making them superbug; NDM-1 carrying gene plasmid harbored by *P. putida* can possess about 14 determinants to confer antibiotic resistance (Fatima and Anjum 2017). Therefore, it is particularly important to perform antibiotic susceptibility test on PGPB that are suggested as biofertilizer as the prevalence of such bacteria in an open environment could be a risk to human health and further enrichment of fields with such MDR-PGPB increases possibilities to enter the food chains.

Many rhizospheric and endospheric PGPB species isolated from various crops, suggested as biofertilizers are reported to be involved in human infections. These infections arise mostly due to exposure to soil, water or farm products contaminated with such bacteria or are attained from health care units contaminated with environmental opportunists' strains in case of nosocomial infection (González et al. 2017). PGPB are extremely versatile because of their diverse ecological niches; when they inhabit rhizospheric soil, exhibit plant growth promoting features by intricating multiple strategies and get involved in plant favorable interactions by stimulating growth, inducing systemic resistance to plants by producing secondary metabolites associated with plant defense pathways. While contrarily, among those rhizosphere dwelling bacteria some species are human- and phytopathogen that employ various pathogenic approaches to stimulate host defense mechanism which involves synthesis of adhesin, toxins, pyocyanin and virulent factors thereby manifesting a pathogenic lifestyle by contaminating food and leading to food borne illnesses e.g., *B. cereus* (Pallen and Wren 2007; Rosier et al. 2018).

Evolution of pathogenic traits upon interaction with eukaryotic hosts

Non-pathogenic commensal bacteria can also evolve pathogenic traits under various conditions by patho-

adaptive mutations depending upon analogous set of strategies and molecular mechanisms they employ while interacting with their eukaryotic hosts. Various pathogenic bacteria produce VF targeted against non-mammalian hosts like plants, fungi, insects and nematodes, incidentally infect humans (Morens et al. 2004). The emergence of infections in a new host or a new infection in previously reported host is a well-known host dependent mechanism determined by multiple factors including changes in genetic makeup either by horizontal gene transfer, mutations, or recombination events. Anthropogenic agricultural activities develop new niches and new chance for infectious agents to evolve, adapt and spread to new niches ultimately to a new host (Sheppard et al. 2018). Competent environmental conditions giving rise to hypermutator bacterial strains are well studied in clinical strains (e.g., *B. cepacia* and *P. aeruginosa*) that are opportunist but the influence of environmental hypermutator strains have been disregarded and less understood. Defects in DNA mismatch repair mechanism (*mutS, mutL, mutH, uvrD*) are considered as major reason for the origination of hypermutation. Hypermutated bacterial populations are more likely to transfer and infect new hosts (Marvig et al. 2013). Favorable mutations enhance the competency on bacteria to survive are present in higher frequency in accessory genes, while in essential gene mutations are strictly regulated (Merikanto et al. 2017). Therefore, the occurrence of hypermutation in PGPB should also be considered important. Environmental opportunistic bacteria are mostly found to infect individuals with comorbidity and these bacteria are usually resistant to wide range of antibiotics. Also, such opportunistic pathogens (environmental strains) can grow independently of any host that make them difficult to control by routinely used antimicrobials as they are targeted towards obligate pathogens (Raphael and Riley 2017).

Arguments related to differences between environmental and clinical strains

Many can argue that environmental and clinical strains have genomic differences and using different strain of the same species in open field will not have any impact on human health or environment. An extensive study was conducted by Bevivino et al. (2002) on *B. cepacia* environmental and clinical strains associated with maize rhizosphere and cystic fibrosis (CF) patients. In this study they tried to evaluate likelihood of environment strain to cause human infection and a clinical strain to be a phytopathogen. Their findings surprisingly demonstrated greater percentage of environmental strains showed hemolytic activity, which is considered a virulence trait. These environmental strains also carry *esmR*, a genetic marker for evaluating bacterial transmissibility prevalently found in clinical strains considered epidemic strain marker. Also, clinical strains were able to macerate plant tissues and play role in plant pathogenesis. Similarly, Grosso-Becerra et al. (2014) studied genome variation between clinical and diverse group of environmental isolates of *P. aeruginosa* including twelve clinical isolates, two water dweller, two associated with plant and one from dolphin and found high genome conservation among them including genomic island associated with pathogenicity. Clinical and environmental strains produced VF like rhamnolipids, pyocyanin and elastase at varying concentration but their production was higher at body temperature i.e., 37 °C (Grosso-Becerra et al. 2014).

Environmental strains did not show antibiotic resistance in this study (Forghani et al. 2014). Similarly, Ngamwongsatit et al. (2008) isolated *B. cereus* from food and soil, and were tested for harboring enterotoxin producing genes. The prevalence of two enterotoxin genes *hblC* and *entFM* was considerably high among soil strains. These findings indicate that clinical and environmental strains of opportunistic pathogens may have functionally identical virulence characteristics. Therefore, the probabilities of possible human or mammalian infections increases and these concerns must be carefully considered.

The point about differences among environmental and clinical strains is valid to some extent as they have genomic differences, but at the end we should catechize ourselves that how often did we performed pathogenicity tests on these "PGPB" before field application or screened them in laboratory for carrying virulence genes or factors or antibiotic resistance genes (Islam et al. 2016). There is no such report in any publication that mentions complete safety assessment of these PGPB or bio-fertilizers in laboratory or before trial and application. If this improvident practice continues, in worst cases, someday this would lead us to the inception of an epidemic or at least it's going to target vast majority of malnourished or immunocompromised individuals (Hequette-Ruz et al. 2018; Rojas-Solís et al. 2018). Some bacterial species exhibiting both plant growth promoting as well as pathogenic characteristics are listed in the Table 1.

Right steps towards the use and applications of PGPR

The practice of developing and implementing biofertilizers should employ some safety protocols in order to evaluate the detrimental effects. In the race of publishing research and creating products, some plant beneficial bacteria that are involved in serious human infections are being declared

Table 1 List of bacterial species exhibiting plant growth promoting as well as pathogenic characteristics

Species	Plant growth promoting characteristics	References	Pathogenic characteristics	References
Alcaligenes faecalis	Enhance IAA production Increase inorganic phosphate solubilization	Ray et al. (2016), Jung et al. (2018)	Cause peritonitis Endophthalmitis	Kahveci et al. (2011), Carmeli et al. (2016)
Arthrobacter agilis	Help in uptake of Fe under saline conditions Produce volatile compounds that help to inhibit the fungal pathogens like *B. cinerea* and *P. cinnamomic*	Velazquez-Becerra et al. (2013)	Produce compounds that inhabit the growth of beneficial fungi *Tricoderma virens* and *T. atroviride*	Velazquez-Becerra et al. (2013)
Azospirillum brasilense	Increase root and shoot weight Increase root length IAA production	Liu et al. (2016)	Cause skin wounds in humans	Qin et al. (2014)
Azospirillum lipoferum	Increase root and shoot weight Increase root length Nitrogen fixation IAA production Enhance root biomass	Stets et al. (2015)	Discovered in human wounds Cause skin wounds in humans	Berg et al. (2013)
Bacillus cereus	Nitrogen fixation Auxin Production Phosphate solubilization Nodulation Biocontrol ACC deaminase production Protects tomato from bacterial wilt and nematode Induces drought tolerance Siderophore production Biomass enhancement in *Arabidopsis thaliana* Increase plant growth Induce resistance against pathogens	Niu et al. (2011), Kumar et al. (2015), Zhou et al. (2015), Chun-Hao et al. (2017), Parvin et al. (2018)	*B. cereus* infections are quite infrequently reported in human. Infects new borne babies and patients undergoing chemotherapy, surgery, or dialysis Wounds and skin infection, infections in operated bones and joints Bacteremia Diarrhea Hemorrhagic shock Bleeding from the lower digestive tract Produce hemolysins Produce phospholipases Produce proteases	Article (2009), Bottone (2010), Veysseyre et al. (2015), Shrivastava et al. (2016)
Burkholderia contaminans	Phosphate solubilization IAA production Zinc solubilization ACC deaminase production Ammonia production	Tagele et al. (2018)	Associated with hospital outbreak Skin infections Wounds infections UTI Infections in cystic fibrosis patients and septicemia	Martin et al. (2011), Coutinho et al. (2015)

Table 1 continued

Species	Plant growth promoting characteristics	References	Pathogenic characteristics	References
Burkholderia cepacia	IAA production Phosphate solubilization Ammonia production Growth promotion of oil palm Production of antibiotic pyrrolnitrin Control fungal infections in red pepper Catalase Chitinase Pectinase Improve plant agronomic parameter	Jung et al. (2018), Parvin et al. (2018), Yagmur and Gunes (2021)	Bloodstream infection in NICU Sepsis Bacteremia Chronic granulomatous disease Outbreak in cancer wards Bloodstream infections related to catheter High grade fever with chills and pneumonia Osteomyelitis in patients having renal disease Rarely, septic arthritis Genitourinary infection Cause soft rot in onions Pathogen for patients having cystic fibrosis	Govan and Deretic (1996), Kim et al. (2016), Shrivastava et al. (2016)
Enterobacter aerogenes	IAA production ACC deaminase production Phosphate solubilization Confer Cd tolerance to plants HCN production Protease activity Siderophore production Improves plant health	Liu et al. (2016, 2018), Pramanik et al. (2018)	Infection at surgical sites Infections in individuals undergoing surgery, chemo, and radiotherapy Respiratory tract infections Sepsis Bacteremia	Clina et al. (2017), Shen et al. (2017)
Paenibacillus spp.	Increase plant height Enhance panicle weight	Phi et al. (2010), Fournier et al. (2015)	Cause bacteremia in patients having permcath for hemodialysis Joint infection	Ouyang et al. (2008), Rieg et al. (2010), Braz et al. (2019)
Pseudomonas stutzeri	Nitrogen fixation (suggested as possible substitute for N fertilizer) Root colonization IAA production ACC deaminase production Rice growth promotion even in saline environments and in the presence of heavy metals Degradation of soil contaminants like phenol and other organic pollutants Catalase + ve Oxidase + ve Biocontrol	Hossain (2016), Pham et al. (2017), Rojas-solís et al. (2018)	Infections are rare and mostly observed in immune compromised and malnourished individuals Caused mostly by exposure to soil, water and from health care units Bacteremia Endocarditis Arthritis Meningitis Skin infections Peritonitis Pneumonia Wound infections Respiratory tracts infections	Loyse et al. (2006), Charpentier (2018), Halabi et al. (2018)

Table 1 continued

Species	Plant growth promoting characteristics	References	Pathogenic characteristics	References
Pseudomonas aeruginosa	Phosphate solubilization IAA production Ammonia production Zinc solubilization Provide induce systemic resistance to plants through secondary-metabolite production Bio control	Yasmin (2017)	*P. aeruginosa* is a human and phytopathogen that employ various approaches to surpass host defense mechanism by synthesizing adhesin, toxins, pyocyanin and virulent factors Chronic lung infections UTI Abdominal tract infections Usually show resistance towards carbapenem (by making carbapenemase) which are used as a last line of defense to treat bacterial infections	Carmeli et al. (2016), Nicholas et al. (2018)
Pseudomonas putida	IAA production ACC deaminase production Phosphate solubilization Helps plant to cope with drought stress Alleviates salt stress	Almaghrabi et al. (2013)	Bloodstream infections Post-surgical infections Pneumonia Gastroenteritis as a sole disease	Fiore et al. (2019)
Pseudomonas fluorescens	Produce antibiotics Help in biocontrol Enhance growth mechanism in plants Regulate diseases	David et al. (2018)	Resistance against antibiotics in bacteria Resistant bacteria harm the plant by producing acids and depleting organic matter in the soil	Keswani et al. (2019)
Serratia marcescens	IAA production Phosphate solubilization Biocontrol of phytopathogenic fungi Induced Systemic Resistance Heavy metal stress alleviation Increase yield	Dhar Purkayastha et al. (2018), Jeong et al. (2015)	Outbreak of sepsis in patients undergone surgery Outbreaks in neonatal units Osteomyelitis	Samuelsson et al. (2014)
Streptomyces spp.	Increase grain yield Increase dry matter Increase root length Increase stover yield	Dimkpa et al. (2008)	Cause pulmonary infection in patient with sarcoidosis	Riviere et al. (2012), Dubern et al. (2015), Russo (2015)

as biofertilizers (Kumar et al. 2015; Hequette-Ruz et al. 2018). The deployment of such microbial populations in open fields could lead to unfortunate side effects on human health especially the farmers working in fields and final consumer (Chun-Hao et al. 2017). It is highly important to figure out basic additional lab protocols and diagnostic tests in research as new prevention strategy against health and environmental concerns (Fig. 1).

Phenotypic methods are generally not considered satisfactory for identifying bacteria even at genus level (Kuroki et al. 2009; Zhou et al. 2016). Therefore, all studies reporting PGPB depends on molecular identification by sequencing of 16S rRNA gene as it is highly conserved region in bacteria consisting of nine hypervariable regions which can usually distinguish between species. The extent of conservation of 16S rRNA gene varies among different genera, since some studies propose the use of Gram's staining, cell morphology and chemotaxonomy along with 16S rRNA gene sequence homology (Veysseyre et al. 2015). We suggest phylogenetic identification of bacterial strains at earlier stages, before exposing bacteria to the open-air or field experiments. Bacteria that are well known

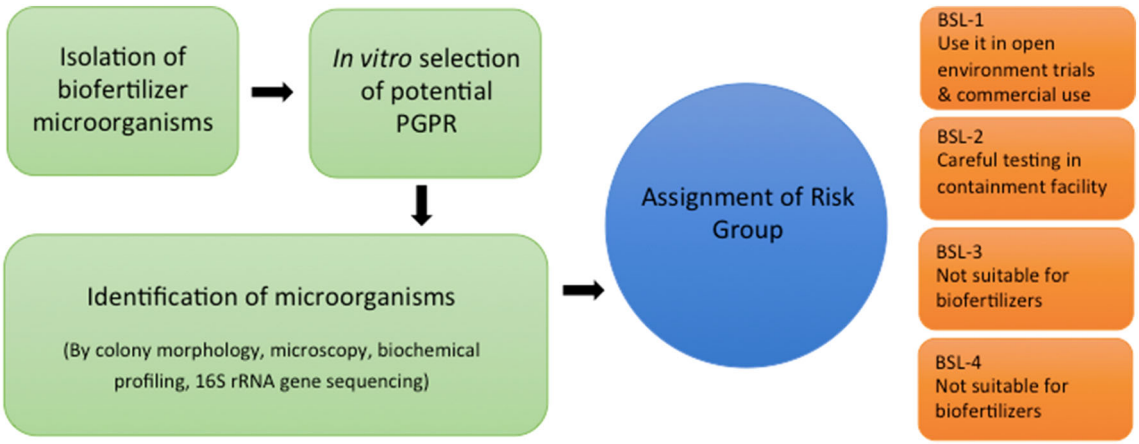

Fig. 1 Steps for PGPR based formulation development

for human opportunist infections should not be proceeded further to overcome the hazards (Tagele et al. 2018).

Caenorhabditis elegans, a free-living soil dwelling nematode usually feeds on bacteria and is considered to be the most standardized non-mammalian model organism to study host-microbiome interactions, infections and virulence of opportunistic human pathogens having many advantages including simple life cycle and ease of maintaining in lab (Mahenthiralingam et al. 2008; Martin et al. 2011). Moreover, various mutants of *C. elegans* can be generated with compromised immune system which provides a deeper understanding of the virulence potential of tested opportunist in individuals with comorbidities. Inducing infection in *C. elegans* is relatively effortless by simply growing the worm on agar plates in labs on growth mediums routinely used to grow nematodes (NGM) where they are provided with non-pathogenic *E. coli* lawn as food source. For virulence assay *E. coli* are replaced or supplemented with freshly grown bacteria or fungi, virulence needs to be tested with equal numbers of worms on each plate followed by incubation at 37 °*C* for 24 h (Coutinho et al. 2015; Biswas et al. 2017). Every 24 h live or dead nematodes are counted manually under microscope. Pathogenicity assays should be performed in three or six replicates along with non-pathogenic *E. coli* as control group. *C. elegans* should also be examined for intestinal colonization and infection symptoms under dissecting microscope. If tested bacteria demonstrate high mortality rate it should not be considered safe or considered for further safety assessment through mice models (Tiwari and Singh 2017). For pathogens demonstrating low virulence; fecundity assay is also considered important as an indication of lost host fitness in addition to reduced life span and mortality rate. Various modified versions of pathogenicity assay in *C. elegans* can be tested by utilizing immune compromised mutants with the aim to enhance assay sensitivity but basic experimental framework remains the same.

The objective of incorporating antimicrobial susceptibility test is to identify the antibiotic resistance in soil-environment strains to ensure their biosafety profile. The most simple, inexpensive method to verify drug resistant phenotype is disk diffusion method interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines (Shen et al. 2017; Liu et al. 2019). In this test, usually a filter paper disk containing known concentration of desired antibiotic is placed on an agar plate (Mueller–Hinton Agar) already spread with tested bacteria along with a control and incubated for at least 20–24 h (Qin et al. 2014; Furlan et al. 2019). The diameter of inhibition zones are compared to latest CLSI values and ultimately strains are categorized into three levels: susceptible, intermediate, or resistant (Rossi-Tamisier et al. 2015). CLSI provided guidelines are available for each bacterial species and against which type of antibiotics (e.g., extended-spectrum β lactamase, Carbapenems etc.) specific species should be tested along with concentrations. Some modified versions of this test gradient diffusion assay are based on the principle of concentration gradient on agar plate which provides quantitative measurement. It uses long thin strips saturated with dried antimicrobial drug on its lower side and concentration gradient scale printed on upper side. The test employs same procedure where readings are recorded at intersection of bacterial growth on scale but additionally it gives minimum inhibitory concentration (MIC) values. That deduces minimum concentration of antibiotic required to inhibit bacterial growth. Lower MIC values are indication of less antibiotic resistance (Feistel et al. 2019).

Hemolytic activity refers to the lysis and destruction of red blood cells caused by bacterial strains and considered to be an attribute of pathogenic bacteria. Hemolytic tests recognize potential toxicity of bacteria towards eukaryotic cells. Hemolytic activity is assayed on nutrient agar

medium amended with 5% (v/v) sheep blood incubated at body temperature i.e., 37 °C. Plates are inoculated with bacteria needed to be investigated and incubated for 48 h. Appearance of clear zones around the bacterial colony is an indication of positive implication of virulence (Amini & Namvar 2019).

Polyphasic approach of microbial taxonomy and advancement in bacterial identification

The eukaryotic concept of interbreeding in same species is impossible due to asexual mode of reproduction in prokaryotes. Previous studied reported that important variations in biochemical and physiological present between bacterial delineation due to huge genetic variability (Achtman and Wagner 2008; Ritchie et al. 2017). Thus, various previously classified bacteria were reconsidered for classification. However, polyphasic approach is used to classify bacteria, wherein data is included from genotypic, phenotypic (physiological, morphological and biochemical) and chemotaxonomic aspects (Rosselló-Mora and Amann 2001; Coenye et al. 2005). Assessments of phenotypic traits are quite time-consuming and intensive, as well as comprehensive knowledge of bacterial metabolism and physiology is required (Feistel et al. 2019). However, apart from in silico studies for taxonomic delineation of bacteria, it is quite compulsory to compare the morphology and physiology under same growth condition and media of closely related organisms for taxonomic purposes.

In this context, several commercial platforms and kits such as phenotypic microarray by Biolog, API, Vitek and BioMerieus are available to study the bacterial phenetics using little efforts and time (Váradi et al. 2017). Although, these kits mostly provide protocol and media primarily suited for fast growing organisms but sometimes fail for rare genera and slow growing microorganism that have not still been reported extensively. Therefore, utilization of these kits becomes an issue in some cases (Dubern et al. 2015).

The chemotaxonomy method basically deals with the chemical composition of organism, such as sufficient variability of fatty acid methyl ester profiles, ribosomal protein profiling, polyamines, polar lipid profiles, and quinones are currently used for chemotaxonomic purposes of bacteria. Profiling of ribosomal proteins with matrix assisted laser desorption time of flight/mass spectrometry (MALDI-TOF/MS) is relatively a rapid and low cost strategy for the identification of microbial strains. It is equally applicable for fungi, bacteria, anaerobes and archaea as well as MALDI-TOF/MS is better as compared to chemotaxonomic methods because it provides detection, rapid authentication and strain level information (Fig. 2).

Other than chemotypic identification, bacterial classification can also be based on genotyping and genetic content

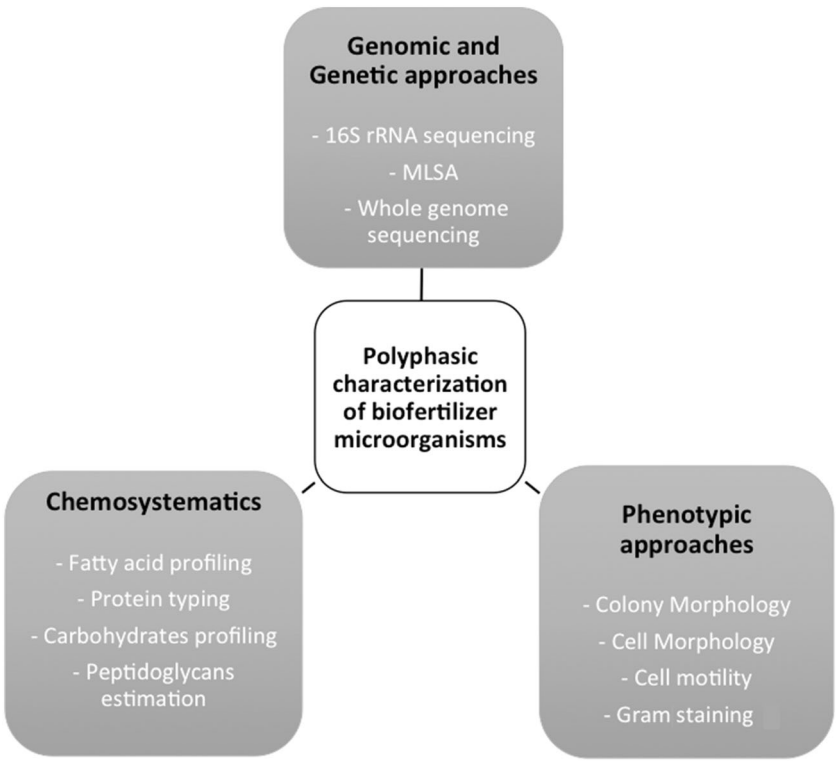

Fig. 2 Polyphasic approach for characterization of PGPR at species and strain level

of microbial cells. Genotyping based methods are classified into three categories i.e., hybridization based methods, fingerprinting or DNA band pattern-based method and sequence-based methods (Hussain 2011). Fingerprinting based methods includes amplified fragment length polymorphism (AFLP), pulse field gel electrophoresis (PFGE), ribotyping, and randomly amplified polymorphic DNA (RAPD). While sequence-based methods include housekeeping genes, small subunit ribosomal rRNA, multilocus sequence analysis (MLSA), multi-locus sequence typing (MLST) and whole genome sequencing. While, 16S RNA based sequencing and MLST methods provide resolution at genus level, while MLST and fingerprinting based-methods provide resolution at strain level. However, whole genome sequence has rapidly replaced these methods for bacterial species delineation. The selection of identification methods depends upon several factors such as time, cost, efficiency, resolution and reproducibility. In this regards, whole genome sequencing become inexpensive, easy, and plausible future of bacterial taxonomy.

Conclusion

Due to the adverse effects of excessive applications of chemical fertilizers and pesticides, extensive research, has been executed in the development of microbial formulation for biodegradation of agricultural pollutants, biological control of plant diseases and PGP traits across the world. Several novel groups of fungi and bacteria with efficient biocontrol and PGP potentials have been discovered but little attention has been given to their biosafety assessment. In our opinion, impetuous and incautious agricultural practices in the domain of bio-fertilizers may compromise the integrity of our environment and public health in future, which could be our next great challenge. So, we must design new strategies to reduce and eliminate the negative impact of our agricultural models and current proposals to protect the biological integrity of our planet. We must aim to incorporate some additional scientific protocols in utilization of bio-fertilizer research to assure their biosafety. Scientific community should develop unanimity that large scale and open field use of such plant beneficial bacteria which pose serious health threat to human would be an unwise and imprudent action. It may be costly and laborious for successful biofertilizer candidates to carry out some additional safety assessment lab test before field trials and commercial production but human health and environment worth it.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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