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Review Article

Biofertilizers: An Emerging Trend in Agricultural Sustainability

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ABSTRACT

Although biofertilizers have been used for an exceptionally long time, challenges still remain in using them to phase out chemical fertilizers. Chemical fertilizers generate environmental pollution and negatively impact beneficial organisms as well as human and animal wellbeing, causing a paradigm shift towards safer improved biofertilizers. Hence, improving the arsenal of microbial inoculants such as plant-growth-promoting rhizobacteria (PGPR) and plant growth-promoting fungi (PGPF), use of microbial consortia, use of uncommon inoculants such as extremophiles and microalgae, development of customized biofertilizers to suit the conditions of the fields and their geographical locations, identifying and popularizing other beneficial aspects of biofertilizers to use them as tools for bioremediation, improved plant physiology and degradation of pesticides have become the trends of biofertilizers. However, soil application of biofertilizers has limited success yet and to be explored. Because of the interactions of soil- introduced PGPR and PGPF can be excluded by the more resilient microbiome in soil. Therefore, different strategies have to be employed to facilitate complex interactions with soil, environment and phytomicrobiomes. New molecular technologies allow for using metagenomics, metatranscriptomics, metaproteomics and metabolomics to spur development. Phytomicrobiome engineering is also used in synthetic biology also may offer new trend. These will be key in developing the next generation of biofertilizers.

Keywords: microalgae, microbial consortia, mycorrhiza, Omics, PGPR, PGPF

1. INTRODUCTION

The conventional biofertilizers have been an eco-friendly alternative to much controversial chemical fertilizers for several decades [1,2]. Broadly biofertilizers are defined as substances, prepared from living microorganisms that colonize the rhizosphere or the interior of the plants and promote plant growth by increasing the availability of primary nutrients to the crops, when applied to soils, seeds or plant surfaces [1,2]. They are free-living microorganisms associated with root surfaces and root endophytic microorganisms that are able to colonize the intercellular or even intracellular spaces of plant tissues and increase the host plant growth [3,4]. However, the expansion of the biofertilizer industry has been hampered by several challenges that have not allowed them to develop into their full potential. With the conscience of the general public changing from a yield paramount intensive agriculture to ecofriendly, yet yield uncompromised agriculture, which is also termed sustainable agriculture, the focus has returned to the importance of biofertilizers [3]. With this wave of change, many trends have emerged in the development, use and application of biofertilizers. Plant growth promoting rhizobacteria (PGPR) and also fungi have been the biggest contributors to biofertilizers [4]. However, due to various challenges such as capturing the proper strains for culture, limited information of the interaction of microbes among each other and the hostplant, formulation, establishment, and persistence problems, their potential has not been fully realized. The rapidly improving technologies of molecular life sciences have offered tangible solutions to these challenges, providing a set of strategies such as increasing the pool of efficient PGPR and mycorrhiza, capturing other beneficial aspects, use of microbial consortia and getting more efficient responses from the plants. Additionally, the new technologies have also allowed the exploration of hitherto little known or unheard-of realms in the microbiota as biofertilizers, including microalgae and extremophiles [5]. The combination of advance omic techniques with biofertilizer could help to get more efficient technology in future.

2. PLANT GROWTH PROMOTING RHIZOBACTERIA (PGPR), A REVOLUTION AGAINST THE CLIMATE CHANGE

The adverse effects of climate change have severely affected the stresses on crops [6] since high quality agricultural lands have been affected by rising seas, erosion, salinization, and desertification. Hence, crops need to be maintained under favourable conditions in order to achieve most productive cultivation. Beneficial microbes associate with the holobiont plays a vital role [7]. When the environmental conditions are not in favourable, ability of PGPR to improve water and nutrient uptake has been utilized as a new trend in biofertilizers [8].

Microbes which assist with nutrient acquisition provide a spectrum of mechanisms such as, enhancing surface area accessible to plant roots, phosphorus solubilization nitrogen fixation, production of siderophore and HCN [9]. Rhizobial inoculants are the first ever commercialized microbial products and still used as nitrogen fertilizer in low productive lands [10]. However, development of commercialized free living nitrogen fixers such as *Azoarcus* sp., *Burkholderia* sp., *Gluconacetobacter diazotrophicus, Herbaspirillum* sp., *Azotobacter* sp., *Bacillus polymyxa*, and especially *Azospirillum* sp. has been advancement in agriculture which is a promising approach to reduce negative impact of climate changes on crop yield [11].

2.1 Signal Compound-Based Products

Effective signal compound has been isolated prior to product development. Purified PGPR broth cultures have been used to boost seed germination and early plant growth [12]. Thuricin 17 is one of the signal molecules produced by *Bacillus thuringiensis* NEB17 with potentialities to reduce the adverse effects on crops caused by abiotic stresses [13]. Furthermore, mitogen activated

protein kinase (MAPK), microRNA and histone deacetylases are important signal compounds of gene expression in plant immune responses, pathogen virulence and communications related to phytomicrobiome [12].

3. PLANT GROWTH PROMOTING FUNGI (PGPF)

PGPF are non-pathogenic saprophytes which have potential ability to ameliorate soil fertility, crop growth and induce, plant defense mechanisms [34,35]. Leaf and root endophytic ability of PGPF prevent the pathogenic infections and also facilitates uptake of nutrient via roots [35,36]. Similar to PGPR, PGPF also have potential of solubilizing phosphates, producing IAA, siderophores, cellulase, chitinase, etc., and influenced on improvement of plants vegetative and reproductive parameters [37,38]. PGPF can trigger induced systemic resistance (ISR) of plants against pathogens [38,39] by modifying the plant cell wall by the accumulation of lignin, callose and phenols. Further, PGPF inhibit the pathogen entry, multiplication [40] and activate plant enzymes related to defense against plant pathogens. *Aspergillus* sp., *Fusarium* sp., *Penicillium* sp., *Phoma* sp., *Piriformospora* sp., *Trichoderma* sp., and mycorrhizae are considered as the most important PGPF in crops [37-40].

3.1 Biofilms of PGPR for Possible Development of Microbial Consortia as Biofertilizers

Biofilms are a consortium of microbes that ensures the successful establishment on the environment. Biofilms are also a secretion from single microorganism that are involved in attachment of others. The ability of PGPR to associate as biofilms enhances the bacterial survival as well as the plant growth (Table 1) [41]. Additionally, biofilms of PGPR have the potentialities to suppress the growth of pathogens by secreting antimicrobial compound while colonizing the rhizosphere [42]. This approach can also be implemented by incorporating bacteria with fungi. Biofilms of *Pseudomonas*, *Bradyrhizobium* and *Penicillium* have potential ability to produce ammonia, IAA and siderophores, solubilize phosphate and have nitrogenase activity [42].

According to Wu et al. (2009), application of PGPR with PGPF increases the crop yield [43]. It was observed that the mixed culture of *Bacillus amyloliquefaciens* with *Trichoderma virens* improved the tomato and maize yield [44]. The combination of *Trichoderma* sp. with *Bradyrhizobium* sp. improved growth of soybean [42] and *Bacillus cereus*, *B. subtilis* and *Serratia* sp. reduced the *Meloidogyne incognito* pathogen attack in tomato while enhancing the nutrient quality [42].

3.1.1 Quorum sensing (QS)

Quorum sensing (QS) is a process of microbe cell-to-cell chemical communication that relies on releasing the chemical signaling molecules called auto-inducers [45]. The soil inhabiting microorganisms are capable of sensing and generating biomolecules having short and long chains including quorum sensing molecules, under various biotic and abiotic stresses, and symbiosis relationships [46]. Several plants are responded to bacterial QS with altered root growth and gene expression patterns and further induced resistance to plant pathogens, abiotic stresses and lead to improvement of the plant productivity and yield. For the instance, acyl-homoserine lactone (AHL), C6-HSL enhanced the seed germination, plant development and productivity in winter wheat (*Triticum aestivum* L.) and reduced the reliance on fungicides and fertilizers to control pathogens [46]. In legume-*Rhizobium* sp. symbiosis, *Rhizobium* sp. synthesize the AHL that triggers synthesis of exopolysaccharide, which is important for increasing of nodulation efficiency [45,46].

3.2 Arbuscular Mycorrhizae and Their Role in Soil and Plant Rhizosphere

Most plant roots have symbiotic association with two broad groups of fungi, named as either endomycorrhizae or ectomycorrhizae. Approximately 95% of the plants in tropical forests in the world

Table 1. Effects of plant growth promoting rhizobacteria on plants.

PGPR	Mechanism of Action	Reference
Rhizobium leguminosarum	Growth promotion of canola and lettuce	[14]
Pseudomonas spp.	Early development of canola seedlings, growth promotion of pearl millet, growth stimulation of tomato, improvement of seed germination, seedling growth and yield of maize and banana	[15-20]
Azospirillum brasiliensis *A. irakense*	Growth promotion of wheat and maize plants	[21]
Azotobacter and *Azospirillum*	Enhance the growth and productivity of canola	[22,23]
Pseudomonas alcaligenes, Mycobacterium phlei and *Bacillus polymyx*a	Boost uptake of N, P and K by maize in low nutrient calcisol soil	[24]
Pseudomonas, Azotobacter and *Azospirillum*	Stimulation of growth and yield of chick pea	[25]
R. *leguminosarum* (Thal-8/SK8) and *Pseudomonas* strain 54RB	Improve the yield and phosphorus uptake in wheat, induced defense against sheath rot, sheath blight disease and leaf folder in rice, and bunchy top virus in banana, saline resistance in groundnut	[26-29]
Bacillus spp.	Biological control against tomato mottle virus, bacterial wilt disease in cucumber, blue mold disease of tobacco, downy mildew in pearl millet, blight of bell pepper	[30-33]

are arbuscular mycorrhizal [47]. Compared to the tree species in tropical and sub-tropical regions, the incidence of AMF has a reduced tendency to colonize with tree species in temperate region [48]. These mutualistic soil fungi usually promote plant growth [49,50]. Mycorrhizal fungi also influence in productivity and diversity of plants and soil characteristics [51]. Therefore, AMF can contribute to enhance plant and soil health in tropical ecosystems [52].

3.3 New Insights into Plant Mineral Nutrition in AMF Symbiosis

If a particular nutrient is deficient in soil solution, its uptake by plants is mainly depended on the root surface area. AMF have a greater potential to increase the effective root surface area through their external hyphae [53]. Further, AMF functioning to improve productivity of less fertile soils [54,55]. The external mycorrhizal hyphae are grown and form fungal and plant root network in rhizosphere and capable of absorbing nutrients far from soil and effectively uptake the nutrients [56]. Specially AMF hyphae can facilitate an adequate supply of phosphorus to be absorbed by plant roots [57]. The extraradical AMF hyphae are broadly analogous to extra root hairs which can exploit soil for nutrients [58]. Arbuscular mycorrhizal fungi facilitate nitrate absorption from soil and transfer it to host roots of different plants [59].

Mycelia of AMF may actively release nutrients from mineral particles facilitating to access pools of nutrients which are not readily available by the host plants [60]. The studies showed that AMF would have potential to produce organic acid anions that may act as chelating agents that can alter pH of soil which influences the rock

phosphate solubilization [61]. AMF therefore, have a major role in soil nutrient cycling and reduced the need for further external nutrient additions to soil [62]. Arbuscular mycorrhizal fungi reduce the soil nutrient leaching [63].

Arbuscular mycorrhizal fungi were improved plants potassium nutrition [64]. Micronutrients such as zinc and copper absorption by plants from soil also improved by AMF is important because these elements have a less mobility in many soils. Arbuscular mycorrhizal fungi may have a synergistic interaction with each other and host plants [64]. It was reported that the effects of AMF are higher when different AMF species are applied together as inoculums than the application of single AMF species [65]. Further, the application of native AMF consortia would be more productive due to synergistic interactions, in considering the plants growth and harvest yield [65,66]. Indigenous AMF in soil have been demonstrated to be performed better than commercial isolates, farmers are encouraged to produce their own AMF inoculum using native soils. Therefore, AMF biofertilization technology would be affordable for farmers, including those in developing countries [67].

3.4 Effect on Soil Aggregate Stability

AMF are very important in stable soil aggregate formation [68]. Labile carbon can be protected inside soil aggregates [69]. External hyphae of AMF, between 1 m - 20 m of AMF hyphae g^{-1} of soil, bind soil particles together and improve water stable soil aggregates formation [70]. It was hypothesized that AMF can make direct contribution to soil organic matter (SOM) [70]. Arbuscular mycorrhizal fungi form stable soil aggregates by binding soil particles together using glomalin, a glycoprotein produced by their hyphae [49]. In tropical soils glomalin was detected in concentrations of 60 mg cm^{-3} [71, 72]. Further, AMF also influence soil bacterial communities that can improve soil aggregation [73]. Further, a significant amount of soil carbon is derived by AMF influence the increase of soil organic matter content [71,73].

3.5 Interactions with Other Soil Organisms

In the rhizosphere, AMF synergistically interact with PGPR [74-77]. The high degree of specificity was observed in such interactions among plant, AMF and PGPR species involved [78]. Bacteria found to be occupied in specific AMF niches, i.e., spores, extraradical hyphae, intraradical hyphae [79]. Some bacteria promote AMF spore germination and hence, the root colonization will be increased [80]. Arbuscular mycorrhizal fungi effects on the activity of soil and plant associative microbes and stimulates root exudates, phytoalexins and phenolic compounds production [81]. It was reported that the soil inoculated with *Glomus mosseae* positively increased plant growth with the soil application of *Azospirillum* sp., *Azotobacter chroococcum* and *Pseudomonas* sp. [82]. Therefore, enhanced activity of such microorganisms in soil particularly *Pseudomonas* sp. provides access to organic sources of P present in the compost [79]. It was found that the co-inoculation of different types of beneficial microbial strains with AMF results better effects on both growth and yield of plants and microbial communities of soil, compared to the inoculation of single microbial inoculant [67]. The interaction between rhizobia and AMF might be possible due to the relatively high phosphorus demand for biological nitrogen fixation [83]. Colonization of feeder roots by AMF increased the resistance to soil pathogens which attack plants [84]. Soil actinomycetes are chitin decomposers and associated with AMF [85], producing both antagonistic [86] and positive effects [87].

3.5.1 Tripartite relationship among soil P solubilizers, N_2 fixers with arbuscular mycorrhizal fungi

Several studies revealed that the plant inoculated simultaneously with phosphate solubilizers and diazotrophic bacteria in the occurrence of AMF

increases the growth of legumes [88]. Phosphorus solubilizing microorganisms (PSM) increase plant growth by providing plant utilizable phosphates [89] and the diazotrophic bacteria increase soil nitrogen content [90, 91].

3.6 Control Plant Pathogens

Arbuscular mycorrhizal fungi have been observed in controlling many soilborne fungal pathogens and also *Alternaria solani* in tomato [92]. Arbuscular mycorrhizal fungi can also suppress plant-parasitic nematodes. However, even if the biocontrol role of AMF is well documented, they are yet to make an impact in actual field usage [92]. Further, AMF may stimulate colonization of roots by some biocontrol microorganisms, but yet to know the mechanisms of these interactions [93, 94]. The proposed mechanisms that explain this effect include mechanical barrier development against pathogen infections, pathogen suppressing, nutrient competition, siderophores production and stimulation of host defense mechanisms [95]. Root colonization by AMF involved in thickening of root exodermis and cortical cell walls which makes difficult in penetrating roots by pathogenic fungal hyphae [96].

3.7 Enhancement of Water Use Efficiency and Salinity Stress Tolerance

Evidence suggest that AMF increase the tolerance of the host plant against water stress [48, 97] and salt stress [98-100]. Auge (2004b) reported that AMF and plant root symbiosis increases leaf transpiration and stomatal conductance [101]. However, contribution of AMF symbiosis to drought tolerance is a complex phenomenon [101]. External hyphae of AMF can increase water absorption and hydraulic conductivity which improved plant water status, stomatal regulation and increased transpiration [102]. Further, this could enhance water use efficiency, higher nutrients absorption [98] and plant responses such as osmotic adjustment [100] and increase in antioxidant activity [103]. This leads to increase in CO_2 assimilation and photo-assimilate production, hence, improving plant growth and development in water deficit [104]. It has been reported that AMF influence salinity tolerance in host plants by producing higher biomass [105].

3.8 Alleviation of Heavy Metal Toxicity by Arbuscular Mycorrhizal Fungi

Arbuscular mycorrhizal fungi can be thrived even in heavy metal contaminated soils [106]. Heavy metal polluted lands contain only autochthonous AMF strains which are tolerant to heavy metals and reduced population diversity and number [107]. AMF take up heavy metals through the fungal hyphae and can be transferred to the host plant roots [108]. Some plants can enhance the uptake and root-to-shoot transport of heavy metals, while in other cases AMF immobilize heavy metal within the soil [107]. However, published results revealed contradictory conclusions where heavy metals have shown positive, negative or neutral impacts on root AMF colonization in plants [109]. that the AMF colonization was reduced in maize (*Zea mays*) when the heavy metals, Zn, Cu, Ni, Cr, Pb and Cd were added to the soil. In contrast, root colonization and mycorrhizal spore numbers in metal polluted sites (Cd, Zn, Pb and Cu) were higher than that in the uncontaminated soils [110]. Some scientists suggest that AMF interact with micronutrients and heavy metals thereby restoring nutrient uptake by plants, which was earlier misbalanced by heavy metals [107]. Heavy metals are accumulated in the vesicles and hyphal walls, that could be acted as a biological barrier [111]. These heavy metals are bound to chitin, cellulose derivatives, and melanin which are the cell wall components of AMF [107]. Moreover, fungal vesicles are capable of storing toxic substances, providing a supportive detoxification mechanism contributing to enhanced tolerance to metals by mycorrhizal plants [112]. It was reported efficient P acquisition by AMF in plant roots facilitates the plant heavy metal tolerance [113]. AMF alleviate the Cd stress by modifying the plants polyamine

metabolism, thus stabilizing Cd in the plant root system [114]. However, heavy metal removal by arbuscular mycorrhizal plants is variable [115]. The contaminant element concentration of the substrate also influences efficiency of removal by arbuscular mycorrhizae. Further, AMF are associated with a majority of the plants polluted with heavy metals from industrial effluents and support them to survive in acidic soils [115].

Lead immobilization by AMF also appears to be caused by phosphate mineral dissolution and subsequent precipitation of pyromorphites [116]. Further, development of mycorrhizosphere by AMF inoculation has been reported to change the rhizosphere microbial diversity and alter overall rhizosphere microbial activity which may be responsible for the alleviation of toxicity of the heavy metal contaminated soil [117].

3.9 New Insights of Application of Biofertilizers

With the increasing global population, the demand for foods has been increased and farmers have encouraged to use synthetic fertilizers, pesticides and herbicides. In this adverse condition, biofertilizer can be used as a potential alternative. Now a days the use of biofertilizer is a new emerging field and has become an integral component in sustainable farming practices. These microbes are already being successfully used in few developing countries and are expected to grow with time.

Mycorrhizal technology mainly identifies the production and application of mycorrhizal fungal inoculum [118], directly addressing the decline in mycorrhizal abundance in agricultural fields [119]. The evaluation of crop growth and development by AMF inoculation in field conditions revealed that AMF has high potential to increase crop yields [120]. However, AMF inoculation in agricultural soils depends on the factors such as species compatibility, AMF niche availability and competing inherent fungi. These aspects need to be evaluated under local conditions for a more appropriate assessment of the viability of AMF to be used as biofertilizer [121].

3.9.1 Seed coating technology for biofertilizer application

Normally biofertilizers can be applied as liquid inoculants, directly to the soil or to the seed [67, 122]. There are some limitations in soil application as the inoculant has to be applied immediately, not easy to handle, decrease of microbial viability during storage and transportation, a high risk of contamination and a low survival of microbes in the soil. Due to these reasons, seed coating technique has been proposed as a promising tool for inoculation of different crop seeds with precise application of biofertilizers [123]. Seed coating technique has the potential to be a cost-competitive and time-saving approach for crop production, reducing application efforts and providing desirable characteristics to the seeds [123, 124].

4. TRENDS OF USING BIOFERTILIZERS AS MULTIFACETED SMART TOOLS

Fertilization increases the productivity in agricultural industries, and it has been the main strategy to improve the food supply for the continuously increasing world population. Despite the advantages of using chemical fertilizers in agriculture to improve the yield, it can simultaneously damage the environment and can cause potential harmful impacts on humans and animals [125]. Excessive nitrates and arsenic leaks into the groundwaters from chemical fertilizers can cause kidney issues and even the death of infants [126-131]. Eutrophication is considered one of the main deleterious effects of the abuse of chemical fertilizers [132, 133] Especially, the accumulation of nitrogen and phosphorus in ground and surface waters accelerates the growth of algae creating oxygen-free environments that would kill fish, make water unsuitable for the drinking or recreational activities [134]. Heavy metal accumulation in water and soil, toxic substances accumulation in fish and vegetables, deterioration of soil fertility, increased soil salinity, changing soil pH, etc. are considered as the other adverse

effects of using excessive amounts of chemical fertilizers [128, 135-138]. Higher usage of chemical fertilizers has shown even to contaminate the air that may contribute to the greenhouse effect [139]. Therefore, biofertilization is of great interest all around the world to provide for the growing demand in the food industry with minimum damage to the environment through sustained agricultural practices. Biofertilizers have shown many benefits compared to chemical fertilizers.

4.1 Biofertilizers to Enhance Plant Physiology

Photosynthetic organisms including plants provide the foundation for all the living on earth by producing sugars trapping carbon dioxide and light energy. There is evidence that the application of biofertilizers promotes the growth of the crop, fruit quality, and yield through increased photosynthesis by increasing chlorophyll and carotenoid like pigments, water use efficiency, improved oxidative status, etc. Application of biofertilizers with *Rhizobium* sp., *Pseudomonas* sp., and *Bacillus* sp. have increased the chlorophyll and carotenoid content of *Arachis hypogaea* L. plants increasing photosynthesis [140]. Inoculation of plant PGPR has significantly enhanced the growth, yield, and fruit quality of strawberry [141], runner beans [142] poplar seedlings [143]. Biofertilizers with *Rhizobium leguminosarum*, *Rhizobium* sp. IRBG 74, and *Bradyrhizobium* sp. IRBG 271 have increased the single-leaf photosynthetic rate of treated plants compared to untreated plants [144] while certain other *Rhizobium* strains have shown to increase the surface area of plant leaves leading to higher photosynthetic rate and water utilization efficiency [145]. In addition to apparent increments in plant photosynthetic pigments, biofertilizers have shown to affect the amino acid production as well. Positive effects of biofertilizers on plant protein content have been observed in groundnuts, maize plants, and amaranth for example [140, 146, 147]. It is interesting to find that the inoculation of biofertilizers containing mycorrhizal fungi, *Glomus fasciculatum* and *Glomus mosseae*, nitrogen fixer *Azotobacter chroococcum*, potassium solubilizer *Bacillus mucilaginosus*, and phosphorus solubilizer *Bacillus megaterium* has considerably increased the concentrations of phenolic compounds, phenolic acids, and flavonoids in addition to the chlorophyll content in spinach [148]. Crops are often affected by a variety of abiotic stresses, especially from higher salinity and drought [149-152]. The application of biofertilizers has increased the ability of plants to withstand these stress conditions. For example, inoculating oregano plants with arbuscular mycorrhizal fungi and/ or active yeast have increased the growth, yield, and water relations providing higher tolerance to drought [153]. Similarly, Abdel-Latef et al. have shown that adding biofertilizers containing *Azospirillum* or *Azotobacter* could lessen the harmful effects of higher salinity [154]. More research supports the ability of biofertilizers to improve stress tolerance of crops, for example, pepper [155], flax cultivars [156], wheat and cucumber [157].

4.2 Biofertilizers as Tools of Bioremediation

Bioremediation is a process that uses microorganisms or plants to remove hazardous pollutants from ecosystems [158]. Heavy metals and toxic organic wastes that are released from different industries are of a focus of bioremediation for a healthy environment. The use of plants to remove or neutralize pollutants, phytoremediation, is a highly used bioremediation method, besides, to use microorganisms directly [159]. This method uses metal resistant plants to immobilize metals onto the root surface or accumulate into roots [160]. The addition of biofertilizers containing plant growth-promoting bacteria (PGPB), promotes plant growth by improving plant metal tolerance and uptake accelerating bioremediation [161, 162]. *Arthrocnemum macrostachyum* is considered a promising candidate for use in bioremediation of heavy metals because of its ability to uptake and accumulate heavy metals in soil and estuaries contaminated with heavy metals releasing from quarries [163]. Inoculation of *A. macrostachyum*

seeds with two bacterial consortia, one containing endophytes *Kushneria* sp.*, Micrococcus* sp.*, Bacillus* sp., and *Halomonas* sp., and another with rhizospheric bacteria *Vibrio* sp.*, Pseudoalteromonas* sp., and *Staphylococcus* sp., have shown to promote the seed germination in the presence of heavy metals (As, Cu, Pb, and Zn) by producing siderophores and solubilizing phosphates which is a very important macronutrient for plant growth [163]. Chen et al. Discussed the successful use of biofertilizers consist of PGPB to increase the efficiency of phytoremediation of pyrine and Ni by *Scirpus triqueter* in rhizospheric and non-rhizospheric soil [164]. Mercury based pesticides and fungicides are extensively used in agricultural fields to prevent fungal diseases [165, 166]. Rafique et al. have shown the potential use of mercury resistant and nitrogen-fixing bacteria that belongs to genera *Pseudomonas* sp.*, Cronobacter* sp.*,* and *Bacillus* sp. as biofertilizers to detoxify the mercury from the environment [167]. Similarly, the potential use of plant growth-promoting bacteria and rhizobacteria to ameliorate heavy metal toxicity has been shown many times with diverse microorganisms including *Achromobacter xylosoxidans*, *Bacillus* sp., *Pseudomonas* sp., *Psycrobacter* sp., *Rhizobium* sp., *Sinorhizobium* sp., *Xanthomonas* sp. [140]. These microorganisms reduce the production of stress hormone ethylene by the plants [168], produces siderophores with heavy metals [169], or remove the heavy metal toxicity by biosorption on to cells [170] and promote the growth of the plants improving the efficiency of photosynthesis.

4.3 Biofertilizers as Tools of Pesticide Degradation

Chemical fertilizers have been consistently used worldwide to control and prevent agricultural and household pests [171] but the same time this overuse has contributed to the contamination of water bodies, soil, and air causing harmful impacts to animals, humans, and to the environment. The fate of the pesticide collected in ecosystems is dependent on abiotic factors such as temperature, pH, moisture, and other biotic factors such as microbial community and plants [172]. Researchers have focused more on the microbial degradation of pesticides as it has been reported to be a primary mechanism of pesticide removal from the soil and water [173-175]. With the trend of using biofertilizers for sustainable farming, researchers have recognized using biofertilizers as a win-win situation for degrading pesticides while improving the productivity of the crops. Currently, many researchers have paid much attention to the bioremediation of pesticides using PGPR containing biofertilizers. *Azospirillum lipoferum, Paenibacillus polymyxa*, and other biofertilizer containing microbes have degraded the organophosphorus insecticides, chlorpyrifos, chlorpyrifos-methyl, cyanophos, and malathion in soil [176-180]. Recently, Hassen et al. have shown the possibility of using PGPR, *Pseudomonas rhizophila* S211, isolated from the pesticide-contaminated soil, as a biofertilizer to treat pesticides [181].

4.4 Biofertilizers as Agents of Pests and Disease Control

Plant pathogens and pests cause enormous losses in agriculture around the globe. It was reported that the yield losses associated with wheat (21.5%), rice (30%), potato (17.2%), maize (22.5%), and soybeans (21.4%) due to 137 pathogens and pests [182]. Over 4100 identified plant-parasitic nematodes have collectively contributed to approximately $80 – 118 billion-dollar worth damage to crops in a year [182].

The outspread use of antibiotics, more specifically their unrestricted and indiscriminate use in agriculture, the present antibiotic era is threatened by the emergence of high level of antibiotic and antimicrobial resistance (AMR) of important pathogens. A good number of human pathogens have developed resistant strains (MRSA, VRE, etc.) against commercial antibiotics causing challenging task presently to treat some life threatening diseases which were thought to be cured previously. Not only human pathogens, some

plant disease causing microbes have also developed resistance strains against important antibiotics like streptomycin and oxytetracycline. Antibiotics have been indispensable for crop protection in the United States for more than 50 years without reports of adverse effects on human health or persistent impacts on the environment [182]. These uses promote the selection of antibiotic resistance in bacterial populations. The resistant bacteria from agricultural environments may be transmitted to humans, in whom they cause disease that cannot be treated by conventional antibiotics.

Among different strategies to control and prevent nematode infections, biofertilizer application is of great interest. Application of biofertilizers, *Trichoderma viride* and *Pochonia chlamydosporia* with urea has increased the productivity of the red kidney beans (*Phaseolus vulgaris*) while controlling the root-knot disease caused by the nematode, *Meloidogyne incognita* [183]. The number of egg masses and the number of galls per root system have been reduced with the treatment of these biofertilizers [183]. Different strains of biofertilizers: *Azotobacter chroococcum*, *Bacillus polymyxa*, and *Pseudomonas fluorescens* alone or in combination with urea have reduced soil and root-associated parasitic nematodes while increasing the growth, yield, and chemical constituents of *Hibiscus sabdariffa* L *var. sabdariffa* plant [184]. Treating tomato plants with biofertilizers containing nitrogen-fixing *Paenibacillus polymyxa*, phosphate solubilizing *B. megaterium*, and potassium solubilizing *B. circulans* has reduced the population of *Meloidogyne incognita* nematodes [185]. Plant growth-promoting bacteria are also used in controlling nematode infections of plants. Biofertilizer contains plant growth-promoting bacteria has successfully used to control the *Meloidogyne incognita* infections of *Trichosanthes kirilowii* in the field [186]. In addition, cyanoacterial biofertilizers are also used in controlling nematodes. Inoculating soil with cyanobacteria, *Microcoleus vaginatus* has reduced *Meloidogyne incognita* infections in tomatoes [187]. In addition to controlling nematodes, there is evidence that biofertilizers can be used to control fungal diseases. For example, banana *Fusarium* wilt has been controlled through the application of biofertilizers [188].

5. Use of cyanobacteria and algae as biofertilizers

Algae are a large group of diverse microorganisms found in diversified ecosystems, able to photosynthesize utilizing sunlight as the main energy source. Therefore, algae are considered as one of the main primary producers of the organic compounds and act as a base in the food chain in the aquatic environment. They vary in size from single cells and one micrometer to larger seaweeds which can grow over fifty meters. As they are found in the diversified environments, they occur in almost every habitat type. Consequently, algae play a crucial function in agriculture sector where they are used as biofertilizers and soil stabilizers [189-191]. Modern-day crop cultivation is highly advanced and productive when compared to the beginning of commercial crop production in order to cater a rapidly increasing global population [189, 190, 192]. According to the World Health Organization, the global food production would increase by 50% in 2029. Subsequently, it is suggested that a green revolution with green technology is essential to achieve this. Thus, the use of algae as biofertilizers has become one of the current trends in modern agriculture [189, 190, 192].

Despite the argument of including cyanobacteria and algae in the same group, in the agricultural sector, they play a vital role similar to other algae including the microalgae and diatoms [189, 192-196]. The cyanobacteria could convert atmospheric nitrogen into ammonia, nitrites or nitrates, termed as nitrogen fixation. Diazotrophic cyanobacteria need sunlight as an energy source for the fixation of carbon and nitrogen [189, 192-196]. In addition, *Anabaena* spp. is widely used in rice fields as they are easy to apply and provide cheapest natural biofertilizer along with microalgae [189, 190, 194, 197- 201]. Further, algae are also used in crops like maize, wheat, cotton, mustard, potato, barley,

oats, tomato, radish, cotton, chili, lettuce and other types of vegetable crops [190, 195]. The recommended method of use of cyanobacteria is the application of cyanobacterial inoculation which enhances the growth of crops [195]. Countries like Japan, Thailand, China, Philippines, Bangladesh, and India have reported algal dominance in their paddy fields. Most of the *Anabaena*, *Nostoc*, and *Phormidium* are reported in higher abundance in the oxic part of the paddy fields whereas *Aulosira*, *Cylindrospermum*, *Fischerella*, *Lyngbya*, *Plectonema*, and *Stigonema* are reported in seldom [190]. However, among all of the cyanobacteria, only *Aulosira fertissima*, *Anabaena variabilis, Tolypothrix tenuis* and *Nostoc muscorum* have been considered as most effective to be used as biofertilizers [193, 202].

5.1 Importance of Algae in Agriculture

The requirement of main nutrients such as N, P and K sources play a crucial role in crop production. Therefore, there is a trend to supply N fertilizers with biofertilizers to enhance soil fertility and facilitate the plant growth [189-191, 194, 203, 204, 225]. In the aquatic environments, N and P are the limiting nutrients and algae are well adapted to scavenge for the resources by the structural changes, storage and increase resource utilization. In addition to these physiological and biochemical adaptations, they could excrete the substances to enhance nutrient availability of the environment. Moreover, algae are beneficial in the agricultural sector in different ways (Figure 1) [189-191, 195- 197, 199, 203-210, 225].

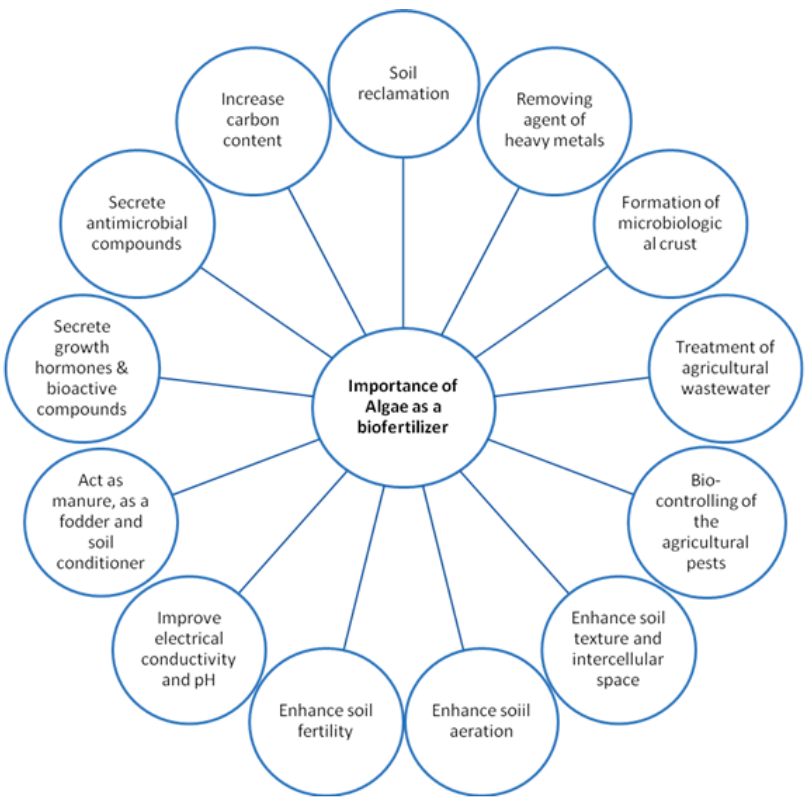

Figure 1. Importance of algal biofertilizers.

5.2 Source of Algal Biofertilizer and Natural Compounds

Algae residues can be obtained from the wastewater treatment system, anaerobic digestion of biofuel (biomethane) production, aquaculture wastewater and brewery effluent that can be used in agricultural fields as a replacement to chemical fertilizers or as a method of recycling [189, 196, 197, 205, 206, 211-218]. However, large brown, red algae and green algae are used as sources rich in potassium but less in nitrogen and phosphorus whereas other algae including microalgae provide nitrogen, phosphorus, potassium, carbon, calcium, amino acids, vitamins, cytokinin, auxins and gibberellins. Moreover, vitamins, auxin, cytokinin and jasmonic acid secreted by algae are used as biological stimulants in agricultural crops. Most of the produced hormones are intracellular hormones and some algae secrete hormones that can be released to growth media and surroundings [189, 190, 197, 205, 219, 220, 221, 192, 196, 198, 204, 207, 208, and 222]. Moreover, cyanobacterial hormone extracts are liable for the promoting of germination and growth of rice seedlings [191]. However, only few researches have been conducted and according to Guo et al. [191], it was due to algae and cyanobacteria secreted hormones. In general, they have been used in combination with algae, bacteria, fungi, ploughed as processed seaweed meal or as concentrated liquid fertilizers [189, 190, 193, 219]. Concentrated liquid fertilizers are the widest used formulation that acts as a rich source of trace elements and cytokines like growth regulatory substances, gibberellins, abscisic acid (ABA) and indole-3-acetic acid (IAA) [189, 193, 198, 207, 211, 221, 223]. In addition, liquid fertilizers from the marine algae extract products are applied as a granular powder or soil drench and foliar spray as a soil conditioning and manure [193, 221, 223, 224,].

5.3 Soil Fertility and Quality

As chemical fertilizers have been used long term along with usage of heavy equipment, they have led to changes in the soil structure, soil parameters, imbalance of nutrient compositions and decrease of nutrients in the field. These are the main reasons for the depletion of nutrients and increase of soil erosion due to the difficulties of water balancing and nutrient mobilizations [190, 191, 195]. Presence of algae in the soil, reduces the soil erosion by producing soil crust with exopolysaccharides which prevent leaching of nutrients, especially nitrogen, regulating the water flow through the soil [189-191]. Further, algae promote mineralization and solubilization of both macro and micronutrients in soil [191, 192, 204, 205, 209, 223, 225], producing soil polysaccharides, dehydrogenase, urease, organic acids. Humic acids produced by *Anabaena variabilis* and *Westiellopsis prolifica*, that can solubilize P in complex molecules such as hydroxyapatite, triphosphate and rock phosphates [190, 191, 209, 226]. They also produce siderophores that act as chelating substances for ferric ions ($Fe^{+}3$) copper (Cu) and other trace elements such as manganese (Mn), molybdenum (Mo), cobalt (Co), nickle (Ni), boron (B) and zinc (Zn) [190, 191, 193, 209, 210]. Moreover, one of the main benefits of algae as biofertilizers is that they can directly provide and increase the organic carbon content of the agricultural field by providing exopolysaccharides. Increase of soil nitrogen can be achieved by the use of cyanobacteria inoculated biofertilizers as directly and in biofilm form, which can fix atmospheric nitrogen [191, 209, 212]. Studies have revealed that inoculated fertilizers with the cyanobacteria can replace 25-50% of the nitrogen in chemical fertilizers. Further, the use of algae as biofertilizers revealed these combinations provide higher yield in the crops [191- 193, 196, 198, 204, 207, 209, 227].

5.4 Disease and Pest Control

Algae can produce antimicrobial substances including hydrolase, carbamidocyclophane A, peptide toxins, ambigol A, benzoic acid, majusculonic acid, and nematicides that increase disease-resistance

of crops against pathogenic microorganisms like bacteria, fungi, nematodes and other microbial groups (Table 2). Some cyanobacteria could secrete insecticidal compounds such as benzoic, chlorinated compounds and majusculamide compounds produced by *Calothrix* sp., *Scytonema* sp. and *Anabaena laxa* respectively. Furthermore, algal biofertilizers improve the root microbial systems and interactions and promote the growth of the crops. In addition, algae generate some bioactive compounds like polyphenols, tocopherols, cyanotoxins, herbicides, as well as antimicrobial pigments acting against soilborne pathogens [191, 109, 204, 207, 210, 221, 223]. Beside the secretion of hormones, cyanobacteria could regulate plant defense mechanism by activation of pathways such as antioxidant and pathogenic mechanisms by using the substances like β-1, 3 endoglucanase, catalase, peroxidase, polyphenol oxidase, chitinase and phenylalanine ammonia lyase. Further, both microalgae and cyanobacteria in combination improve the crop immunity by directly and indirectly and achieving a balance between biotic and abiotic stresses [191].

Although the use of algae as a biofertilizer is a modern agricultural trend, only a few studies have been conducted regarding their applications such as immunity importance, disease analysis, the function of antibiotics and metabolites, cost-benefit analysis and toxins with their direct and indirect effects to prevent toxicity for non-target organisms [191]. The current market potential of algal biofertilizers is enormous; however, the most important fact is the economic feasibility of using algae as a biofertilizer with a low cost of production. Moreover, fewer studies have been conducted focusing on the socioeconomic impacts and the challenges that associate with commercialization level of production of the algal biofertilizers [191, 209]. Further, to increase the quality and productivity, modern molecular methods like genomics and proteomics would provide strategic tools that can increase the effectiveness of use algae as a biofertilizer. Therefore, conducting this kind of studies about the algal biofertilizers would be a trend in the future [191, 192].

6. USE OF OMICS TOOLS IN THE DEVELOPMENT OF EFFICIENT BIOFERTILIZERS

The plethora of emerging omics technologies such as next generation sequencing platforms, microarrays and other chip-based technologies and high through put profiling technologies have revolutionized the field of agriculture allowing the possibility of a quantum leap of conventional biofertilizers into more precise, efficient and dependable alternatives to chemical fertilizers. The novel omics technologies have concurred some of the conventional challenges such as identification of mixed and unculturable strains, differentiating genetic variants, deducing complex pathways and comprehension of signaling processes in inter species interactions. While it is quite encouraging that the studies on genes (genomics), mRNA (transcriptomics), proteins and protein interactions (proteomics) and metabolites (metabolomics) have improved our understanding of the phenomena involved in responsive biofertilizers, the new challenge would be the integration of data inside and between the domains. These become even more challenging when the biochemical data are limited. Tools of omics can intervene at several stages of the production of biofertilizers these include; identification and selection of strains of the plant microbiome using metagenomics and metaproteomics, investigating the respective biochemical pathways [196], improving the strains for more efficient performance [230-232] and genetic engineering of plants for better response [202, 233].

6.1 Genomic Tools in the Identification and Strain Selection for Biofertilizers

The techniques important in identifying potential microbial cultures and consortia are next generation (NG) sequence strategies such as whole genome sequencing, RNA sequencing and metagenomics. Whole genome sequencing and

Table 2. Algal biofertilizers against disease and pest control.

Properties of excretory compound	Pathogens	Cyanobacteria and algae used in biofertilizers	Reference
Antifungal activity	*Alternaria alternata, Rhizopus stolonifera, Rhizoctonia solani, Rhizoctonia* spp., *Botrytis cinerea, Pythium debaryanum, Pythium* spp., *Phytophthora capsici, Fusarium moniliforme, F. oxysporum* fsp. *lycopersici, Fusarium* spp.	*Oscillatoria* spp.	[191, 209]
		Nostoc spp.	[191, 209]
		Anabaena spp.	[228,191,209]
		Calothrix spp.	[228, 192]
		Nostoc muscorum	[228]
		Nodularia spp.	[191, 209]
		Calothrix	[191]
		Anabaena variabilis RPAN59	[191, 228]
		A. oscillarioides RPAN69	[191,228]
	Candida albicans,	*Nodularia harveyana*	[191, 209]
		Nostoc insulare	[191, 209]
	Armillaria sp., *Fusarium oxysporum* f.sp. *melonis Rhizoctonia solani, Penicillium expansum, Phytophthora cambivora, P. cinnamomi, Rosellinia* sp., *Sclerotinia sclerotiorum, Verticillium alboatrum*	*Nostoc* strain ATCC 53789	[191, 209]
	Botrytis cinerea, Erysiphe polygoni	*Chlorococcum humicolum*	[192]
Antibacterial activity	*Staphylococcus aureus, Bacillus cereus*	*Nodularia harveyana*	[191, 209]
		Nostoc insulare	[191, 209]
	Staphylococcus aureus, Bacillus subtilis, Micrococcus flavus,	*Oscillatoria redekei* HUB 051	[209]
Nematocidal activity	*Meloidogyne incognita*	*Oscillatoria chlorina*	[191]
		Anabaena oryzae	[191]
		Nostoc calcicola	[191]
		Spirulina sp.	[191]
		Microcoleus vaginatus	[191,209, 229]
	Meloidogyne triticoryzae	*Aulosira fertilissima*	[191, 209]
	Meloidogyne arenaria	*Oscillatoria chlorina*	[209]
		Chlorella vulgaris	[206]
	Caenorhabditis elegans	*Nostoc* strain ATCC 53789	[191, 209]
Insecticidal activity	*Helicoverpa armigera, Sylepta derogata*	*Scytonema* sp.,	[191]
		Nostoc strain ATCC 53789	[191, 209]

RNA sequencing help to understand responsible genes and gene networks including regulatory elements. While metagenomics provides a platform where massive amount of sequencing could be produced parallelly [234]. However, in-depth understanding that could be provided by some unique genes may play a necessary part in culture selection for efficient biofertilizer regimes. Hence, it is evident that some genomic strategies allow identifying the whole playing field and the others allow the selection of best players for successful biofertilizers.

6.1.1 Use of metagenomics to identify potential microbes for biofertilizer applications

With its ability of recovering genetic materials directly from samples [235], metagenomics has become the standard tool for the identification of all organisms involved in a specific activity, sample or a habitat. Hence it could be considered as the primary strategy for identifying all potential microbes in habitats that could expand the arsenal of hitherto known contributors to the biofertilizer industry. A typical workflow of a metagenomic program would start from experimental design and continues to meta data (Figure 2). Hence, it follows a multidisciplinary approach combining biology, omics and statistical analysis. The robustness of the approach helps to use samples from sources outside the rhizosphere including marine environments [236] and extreme niches [237].

6.1.1.1 Identifying rhizosphere microbes as inoculants for biofertilizers using metagenomics

Development of inoculant strains starts with the capture and identification of single strains or consortia (co-cultivated or co-inoculated microbial cultures). However, the success of these inoculants in commercially viable biofertilizers depends on their traits. These traits can be broadly categorized into five stages; capture and refinement, production, establishment, function, and downstream impacts [238] ranging from their growth on media to persistence in the environment including the ability to compete with other organisms. While it is important to have information on the functional traits, establishment which is more ecological, should also be considered simultaneously. Although ideal strains should possess both characters, such combinations may be rare. Hence, culture-based capture methods may not ideally pick up strains that are good at establishment and persistence.

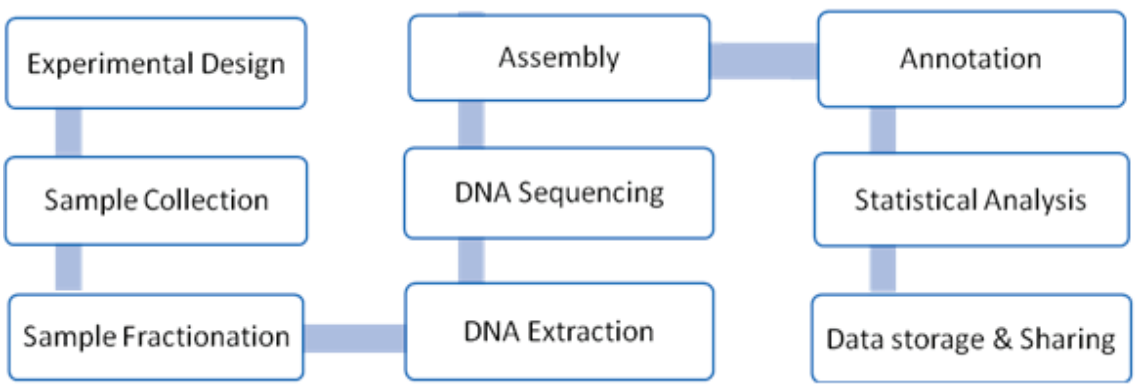

Figure 2. Workflow diagram of a typical metagenomic project according to Thomas et al. [271].

Moreover, many unculturable strains may possess ecological characters that make them superior in the environment. In order to have integrated information (both functional and ecological), there aren't a better option than metagenomics which capture both culturable and unculturable microbes giving a broader sweep of the potential inoculants. Metagenomic approaches of studying microbiomes could be categorized into sequenced based metagenomics and functional metagenomics. While the outputs of functional genomics contribute to strain selection, strain improvement and improving plant response to microbes in the field of agriculture, the sequence-based metagenomics help to capture total strains in the rhizosphere.

6.1.1.2 Sequence based metagenomics in the capture of potential strains for biofertilizers

Basic output of the sequence-based metagenomics is the identification of microbial taxa in the rhizosphere samples to the genus or species level. Due to the advancements in metagenomics, many parallel techniques have been developed under sequence-based metagenomics. Fundamentally these techniques could be categorized into either targeted gene sequencing or whole genome sequencing (WGS). The predominant target gene sequence based metagenomic tool for bacteria is the 16S rDNA due to the highly conserved nature of the sequences [239]. For fungi it is the internal transcribed spacer (ITS) sequences. Although, there is the possibility of using 18S rDNA, for fungi, ITS regions have become the norm in taxonomic studies due to the variability of the conserved regions.

6.1.1.3 16SDNA sequences and ITS regions in deducing rhizosphere taxonomic groups

The capture of taxonomic groups at the genomic level and species level of a rhizosphere sample, these targeted sequence-based metagenomic methods offer a more ideal solution than WGS based methods due to the complex nature of the data generated in WGS methods. Several hypervariable regions of the 16S rRNA sequences (V1-V9) have been used in phylogenetic work [240]. However, subsequently it has shown that V4, V5, V6 and V6-V7 are the best for metagenomic analysis [241]. Several 16S rRNA next generation sequencing platforms are available such as Illumina MiSeq, Ion Torrent PGM and Roche 454 pyrosequencing. A comparative study on metagenomics has shown that all three platforms perform equally well, while having some unique strengths. For instance, Illumina MiSeq provides better depth and breadth in sequencing, Roche 454 provides longer reads and Ion Torrent PGM provides the best speed of sequencing [242, 243].

Even in a 16S RNA metagenomic study for rhizosphere microbes, it is possible to end up with many reads. In order to convert the hemorrhage of data into meaningful outcomes, several software is required. The type of software used depends on the metagenomic platform used. For instance, Illumina reads is used for short sequence reads and PacBio reads is used for lengthy sequence reads [244]. The initial raw data generated need to be further trimmed and filtered to remove, primer and barcode sequences, ambiguous bases and chimeric sequences. The filtered reads are then used to generate operational taxonomic units or OTUs. However, even at this stage, it is necessary to remove singleton OTUs which are clusters with single reads. A rhizosphere metagenomic study conducted with Illumina MiSeq platform has identified 36 taxa at phylum level with 1.3 million reads having at least 80% similarity [245]. Assigning taxa after a metagenomic analysis is conducted using bioinformatic software and a reference data base. A metagenomic study conducted on soil microbial population and enzyme activities using MiSeq platform, used MiSeq Reporter for preliminary data analysis with Qiime for assigning taxa at the species level based on Greengene database for bacteria and UNITE for fungi [246]. With the advancement in software development for analysis of metagenomic data,

the concept of better coordinated pipelines (workflows) has come into fray. Pipelines have been designed for various stages of the analysis such as amplicon pipelines for SSU LSU and ITS, metagenomics and metatranscriptomic raw reads pipeline for taxonomic and functional analysis and assembly pipeline providing pathway and system annotations for assembled contigs [247]. Instead of single pipelines, the idea of hosting multiple analysis pipelines is fast becoming the norm and hubs like MGnify (formerly known as EBI metagenomics) (*Home < MGnify < EMBL-EBI*, n.d.) offer a free service that makes integrated omics analysis a reality.

6.1.1.4 Use of targeted metagenomics to screen potential strains from other habitats

While it is optimistic to think that cultures identified from other environments including the extreme niches could be successfully developed into biofertilizers, the fact that they may play a role in strain improvement either through recombinant technology or the information necessary for gene editing, cannot be ruled out. Moreover, customized biofertilizers for different geographic areas and temperature regimes may become a trend in the future and soils without ideal conditions for cultivation may become the norm rather than the exception. Under these circumstances soil reclamation could be the first step of microbial inoculant intervention. Such inoculants may frequently be used more as strains supporting bioremediation rather than biofertilizers in enriched or contaminated soils. For instance, a rhizosphere metagenomic study conducted in oil-contaminated soil has revealed the significant presence of hydrocarbon degrading phyla [245].

6.1.2 Metagenomics of the extremophiles a prospective source of biofertilizer

Hyperthermophiles, thermophiles, psychrophiles and halophiles make up majority of the extremophilic microbes. Traditionally research on extremophiles have been fully dependent on culture-based techniques. However, with the advent of metagenomics, this realm of research has seen an unprecedented level of expansion. A metagenomic study on western deserts of Himalaya has identified many psychrophilic microbes with plant growth promoting (PGP) capabilities, including phosphate solubilization, ACC deaminase activity, production of molecules such as IAA, gibberellins and production of siderophores, optimally at the psychotropic regime [248]. A metagenomic study conducted on sediments of hypersaline Siberian soda lakes resulted the identification of microbes belonging to 45 phyla including 5 new species belonging to Candidate Phyla Radiation (CPR) and novel dominant lineages in previously identified functional groups in C, N and S cycling bacteria. Moreover, it is interesting to note that in this study the most represented group belonged to bacteria [249]. Acidophiles and acid tolerant microbes are another source of microbes that could fast become beneficial as biofertilizers especially when some cultivable land, such as rice fields have already become acidic. Cultures isolated from peat swamp forests of Southern Thailand have shown a number of PGP traits such production of IAA, ALA, siderophores, phosphate solubilization and nitrogen fixation at below 5 pH range [250], showcasing the importance of this group in future biofertilizer strategies in acidic fields.

6.1.3 Whole genome sequencing (WGS) strategy for selection of strains

The technique used in WGS metagenomic research is termed whole genome shotgun sequencing. In addition to Illumina MiSeq, Ion Torrent PGM and Roche 454, MinION of the Oxford Nanopore Technologies has become an increasingly dependable technique for WGS. It offers several unique features such as rapid real-time bacterial metagenomics, longer scaffolds for WGS and subtyping [251]. Studies have identified about 97% sequence alignment accuracy using MinION which is constantly turning out updated versions [252].

WGS has several advantages over amplicon-based sequencing strategies such as 16S rRNA in metagenomics, these include the ability detect all microbe groups (bacteria, fungi and microalgae) simultaneously, the ability to assign taxa at the species or strain level and functional annotation of sequences. Hence, WGS offers an ideal starting tool for selecting microbial inoculants for biofertilizer development. However, WGS also suffers some disadvantages when compared with amplicon-based sequencing, these include possible requirement of reference genomes, variability of sequence abundance based on the extraction and sequencing protocols and inability to capture genomes in low frequency in complex communities [253]. Based on the data of the WGS further tools are necessary for predicting the number of genes in the genomes and assigning functions to annotated genomes. For instance, a shotgun multiplexing WGS based on 454-sequencing platform conducted on cultures isolated from soil samples rhizospheres of coconut, cocoa and arecanut used Glimmer-MD gene prediction and annotation tool and Gene Ontology (GO), SEED classification and KEGG pathway for functional analysis of the annotated genomes [254].

A shotgun WGS study conducted with rice field microbial isolates of *Rodopseudomonas palustris* (PS3 and YSC3) using Illumina MiSeq and PacBio SMRT sequencing platforms clearly indicated that both isolates contained PGP associated gene clusters including phosphate solubilizing genes, IAA synthesis genes, ACC deaminase and ALA biosynthesis genes. However, the study also provided insights into probable presence of some homologous IAA genes as several well-known IAA synthesis genes were missing from both the isolates [255]. WGS data sets are increasingly made available in opensource servers for comparison and further analysis, providing standardized protocols and regulation for open access data. National Ecological Observatory Network (NEON), USA has hosted publicly accessible soil metagenomics data on MG-RAST (Metagenomics Rapid Annotation using Subsystem Technology) portal comprising 66,454 available metagenomes [166].

6.1.4 Use of integrated omics approach in selecting strains for biofertilizers

Although targeted sequence metagenomics capture data on the potential microbes that could be used as inoculants for biofertilizers, the approach cannot go beyond the simple identification of the taxa involved. The true potential can only be investigated via the techniques of whole genome sequencing, transcriptomics, proteomics and metabolomics. While all these techniques could individually offer insights into the potential arsenal for selection of strains, it has become customary to use an integrated omics approach due to the ability of cross referencing between the technologies and the better prediction capabilities.

6.2 Transcriptomics, Proteomics and Metabolomics in Selection of Strains

Although WGS can provide valuable information about the genome composition, gene clusters and function of genes involved, through gene prediction, annotation and function analysis tools, further analysis at transcriptomic, proteomic and metabolic levels is necessary not only to confirm the predictions but also to understand expression levels, regulatory networks and the metabolic profiles. Although relevant gene clusters could be identified by WGS, some microbial strains have not shown the expected PGP phenotypes. For instance, research on two closely related plant associated *Rhodopseudomonas palustris* strains (PS 3 and YSC 3) has shown that only one strain was capable of PGP even with very similar PGP gene clusters identified in both genomes [255]. This proves the presence of the genes do not guarantee the functional output of the genes. Besides gene expression for PGP microbes very much depends on the interaction maintained with the relevant plant through chemical exudates released to the rhizosphere.

6.2.1 Shotgun metatranscriptomics approach

With the advent of different platforms in RNA sequencing, metatranscriptomic approaches have become a vital strategy to expand the basic information provided by metagenomics. Metatranscriptomics allow to study functional ecology rather than the annotated ecology of the genomics. Thus, providing insights into how the expressions change over a period with respect to changing environmental factors and interactions with other organisms. Hence, together with metaproteomic and metabolic profiling, meatranscriptomic studies could help establishment and persistence of microbial strains and consortia used as biofertilizers.

Transcriptomics are based on two strategies the RNA-Seq [256] and genome tilling arrays [257]. While RNA-Seq allows direct sequencing of the whole transcriptome, genome tilling arrays include hybridizing cDNA of both strands to the array. Although both the techniques depend on referencing genomes, updated versions of RNA-Seq have been applied to investigate novel genomes. When applied to prokaryotic transcriptomics, RNA-Seq requires an alternative mechanism of priming due to lack of polyA mRNA. These include random hexamer priming, oligo dT priming and priming with specific RNA probes ligated to Mrna [258]. A number of metatranscriptomics studies have been conducted with rhizosphere samples to identify functional microbes [259]. For instance, a rhizosphere metatranscriptomic analysis conducted using RNA-Seq on the effect of glyphosate indicated that genes in the carbohydrate metabolism, protein metabolism and respiration were upregulated compared to the control samples [260]. Another study focusing on metagenomic and metatranscriptomic analysis of soil metagenomes clearly identified that although some strains are dominant in metagenomic analysis, functionally they may not be active [261].

6.2.2 Metaproteomics and metabolite profiling approach

Metaproteomics, which is the investigation of microbial proteins by mass spectrometry (MS) [262] could be of two basic types, the intact protein MS/MS or top down and shotgun or "bottoms up" tandem MS/MS working with peptides. While top down technologies are good at providing post-translational modifications [263], shotgun methods provide the better proteome depth [264]. A typical shotgun metaproteomic workflow involves sample preparation, MS analysis and proteome informatics [265]. Developments in metaproteomics have allowed inference into food sources and metabolic pathways of microbes which can be used effectively to select efficient cultures for development of inoculants for biofertilizers. A study conducted with one such approach which used direct protein stable isotope fingerprints (SIF) to measure stable C isotope ratios ($\delta^{13}C$) of microbes in communities was able to infer food sources of microbes and metabolic pathways of C assimilation [266]. The workflow used in a metaproteomic study can have a direct impact on the outcomes. A seawater metaproteomic study that compared gel-based and gel free protein fractionation methods with four different protein data bases clearly showed that number of proteins, taxonomic structures and function of the proteins varied with the type of workflow used [267]. Based on this evidence ideally the experimental workflows need to be diverse to get a better metaproteomic analysis.

Metabolomics deals with the use of metabolites produced by the cells which could be isolated from the cells, tissues and the environments to infer the microbial processes. Metabolomics involve metabolic profiling or metabolic fingerprinting. Many techniques can be used in metabolomics including nuclear magnetic resonance (NMR), time of flight mass spectrometry (ToF-MS),

Fourier-transform infrared spectrometry (FT-IR), GC-MS, HPLC and ultra-high-performance liquid chromatography (UPLC). While elucidating the metabolite profile helps recognize various PGP functional molecules such as growth factors and hormones, antibiotics, siderophores and many more, identifying these metabolites has also helped spawn a new trend in using metabolites in formulation with bioinoculants giving rise to more efficient biofertilizers [268, 269].

6.3 Commercially Available Biofertilizer

Although several studies have been proven the potential of biofertilizer in sustainable farming, there are limited adoption in farmer field. For instance, in Asian countries, use of microbial agents in crop farming has limited only to 2.5% of the total chemical usage. Such constrains on biofertilizer mainly due to the poor awareness on available products and their application. In addition, lack of durable products with low- cost substrates and packages, changing of performance according to the crop and agro-climatic conditions, and no plenty of information on human, animal and plant safety [269, 272]. However, beneficial microorganisms have been formulated with different solid, liquid or semi-solid substrates and available commercially as biofertilizer inoculants (Table 3). Formulation is important because the introduced microbe has to compete and survive with the well-established existing microorganisms, hence the substrate used provides a better microenvironment until adapting to the new environment [272].

Table 3. Some commercially available biofertilizer formulations in India and Philippines.

Biofertilizer	Commercial name	Target crops	Observed benefits
Rhizobium sp.	Jai Vijai Bio-gold	Soybean and groundnut like legumes	Enhances 10-35% yield, adds 50-200 kg N/ha
Azotobacter sp.	JIBANU-SARA	Wheat, rice and vegetables like non-legumes	Enhances 10-15% yield, adds 20-25 kg N/ha
Azospirillum sp.	GROTOP	Rice, maize, sugarcane, barley, sorghum, oats and millet like non-legumes	Enhances 10-20% yield
Blue-green algae	Skipper Khad	Rice	Adds 20-30 kg N/ha
Phosphate-solubilizing bacteria (PSB)	Phospho Shakthi	For all crops- soil application	Enhances 5-30% yield
mycorrhizal-based inoculant	Brown Magic	Orchid	Induces early flowering, more suckers and longer spikes
Trichoderma spp.	Biocon		Enhances absorption of mineral nutrients and can replace the fertilizer requirement of plants by up to 50 %
Enterobacter spp.	Nutrio	Eggplant and sugarcane	Improves the yield with corresponding 50% reduction on the use of inorganic fertilizer

Modified from [269, 272].

7. Conclusions

Crop production has been dependent on soil fertilization since earlier times. Although chemical fertilizers are known to increase the crop production, considering the long-term consequences, heavy usage of chemical fertilizers are obviously not sustainable at all. Therefore, use of biofertilizers provides a promising solution for world to fertilize soil with a minimal damage, but with many significant benefits. Microbial consortia including both bacteria and fungi are capable of enhancing the growth and crop yield and also protect crops from pathogen attacks thus, can be introduced as an efficient biofertilizers. Arbuscular mycorrhizal fungi also play an important role in enhancing the soil quality and plant health in tropical ecosystems. However, various challenges such as limited knowledge about soil microbial interactions, problems in isolation, formulation, establishment and persistence have been masking the true potential of biofertilizers.

With the new advancements and cutting-edge technologies of molecular life sciences which have been emerging during past few decades, it is possible to make more precise efficient and dependable alternatives to chemical fertilizers. Omics technologies will be useful in identification and selection of suitable genes and strains of plant microbiome, Strain improvement through recombinant technology, customizing biofertilizers for different geographical areas and give insights about certain microbes which can be used as inoculants in biofertilizers and their requirements based on their environment. The above technologies can be used to fill the gaps between the current knowledge on microorganisms used as inoculum, readdress their drawbacks which leads to identifying the new trends of developing more reliable biofertilizer and ultimately develop more sustainable, eco-friendly and effective biofertilizers as the best alternative to chemical fertilizers. Phytomicrobiome engineering is also used in synthetic biology also may offer new trend. These will be key in developing the next generation of biofertilizers.

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