Molecular Insight Into Key Eco-Physiological Process in Bioremediating and Plant-Growth-Promoting Bacteria

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Over the past few decades, the massive increase in anthropogenic activity and industrialization processes has increased new pollutants in the environment. The effects of such toxic components (heavy metals, pesticides, etc.) in our ecosystem vary significantly and are of significant public health and economic concern. Because of this, environmental consciousness is increasing amongst consumers and industrialists, and legal constraints on emissions are becoming progressively stricter; for the ultimate aim is to achieve cost-effective emission control. Fortunately, certain taxonomically and phylogenetically diverse microorganisms (e.g., sulfur oxidizing/reducing bacteria) are endowed with the capability to remediate such undesired components from diverse habitats and have diverse plant-growth-promoting abilities (auxin and siderophore production, phosphate solubilization, etc.). However, the quirk of fate for pollutant and plant-growth-promoting microbiome research is that, even with an early start, genetic knowledge on these systems is still considered to be in its infancy due to the unavailability of in-depth functional genomics and population dynamics data from various ecosystems. This knowledge gap can be breached if we have adequate information concerning their genetic make-up, so that we can use them in a targeted manner or with considerable operational flexibility in the agricultural sector. Amended understanding regarding the genetic basis of potential microbes involved in such processes has led to the establishment of novel or advanced bioremediation technologies (such as the detoxification efficiency of heavy metals), which will further our understanding of the genomic/genetic landscape in these potential organisms. Our review aimed to unravel the hidden genomic basis and eco-physiological properties of such potent bacteria and their interaction with plants from various ecosystems.

Keywords: plant growth promotion, heavy metal resistance, meta-omics approaches, molecular mechanism, eco-physiological properties
INTRODUCTION

Delineating the genetic landscape of pollutant-degrading microorganisms and their use in eliminating environmental pollutants has always been preferred over physicochemical treatment strategies. Nevertheless, use of a microbe-assisted bioremediation process started a century ago when it’s in the late 1960’s it was used to remove contaminated oil mixed with water (Pieper and Reineke, 2000). Later, this new treatment approach emerged as one of the most promising methods for bioremediation in various areas for petroleum hydrocarbon degradation as well as in other contaminated habitats (Antizar-Ladislao, 2010). Among the major environmental pollutants, heavy metals and organic compounds, such as mineral oil hydrocarbons, polyaromatic and halogenated hydrocarbons, and benzene derivatives, severely affected the terrestrial as well as aquatic ecosystem or niches (Dvorák et al., 2017).

However, among the existing environmental pollutants or contaminants, heavy metals achieved momentous attention due to their deadly long-term consequences on our society. In general, the toxic class of heavy metals includes Hg, Cr, Pb, Zn, Cu, Ni, Cd, As, Co, and Sn, which are released from the fertilizer and pesticide industry, sewage sludge, energy and fuel production, mining, combustion of fossil fuels, electroplating, photography, and electric appliance manufacturing. Notably, their long-persistent or recalcitrant chemical nature eventually has a hazardous impact on plant and human health (see Table 1 for detailed information) as well as on other living organisms; this simultaneously damages our eco-friendly framework and the ecological dynamics of their native beneficial microbial community (Ahemad, 2019). In the context of the present scenario, it has become imperative for us to concentrate on our efforts toward creating novel bio-based and cost-effective sustainable remediation technology. Opportunely, certain taxonomically and phylogenetically diverse microorganisms (e.g., sulfur oxidizing/reducing bacteria) are endowed with the metabolic potential to remediate such undesired components from various habitats, along with having diverse plant-growth-promoting abilities (phytahormones and siderophore production, phosphate solubilization, etc.) (Zhuang et al., 2007; Bashan et al., 2008; Das et al., 2014). Some of the well-known bacterial genera that are encompassed with a dual potential, such as metal detoxification and plant growth promotion (PGP), are as follows: Pseudomonas spp., Psychrobacter spp., Bacillus sp., Bradyrhizobium spp., Achromobacter spp., Rhizobium spp., Methylobacterium spp., Azotobacter spp., Variovox spp., and Ochromobacter spp. (Ahemad, 2019). Although there are ample reports that describe the isolation and characterization of potential microbial candidates with desired traits from various habitats, in depth knowledge regarding the genomic basis of the aforementioned physiologic potential is still lacking. It is noteworthy to mention that, with the rapid development of industrialization processes and anthropogenic activity, the increase of new pollutants will occur endlessly along with existing ones in our ecosystem. Thus, improved understanding regarding the genetic make-up of potential microbial candidates will help us to design engineered recombinant microbial strains with trait-specific desired properties, encompassed with better efficacy.

In this review, we aimed to unravel the comprehensive molecular mechanistic details or metabolic capacities of heavy-metal-metabolizing microbiota isolated thus far from diverse habitats and their potential use in the agroeconomic sector in the light of plant-growth-promoting attributes. Furthermore, we also tried to summarize the information on how modern meta-omics-based approaches are used in the revelation of bacterial community architecture and complex interactions of bioremediating microbiome. Further discussion has also been extended in relation to the prospects of microbe-mediated phytoremediation processes with special references to metallophytes.

Overview of the Physiological Strategy of Metal Detoxification or Immunization Used by Potential Microbial Members

High concentrations of different heavy metals, like arsenic (As), mercury (Hg), cadmium (Cd), chromium (Cr), and lead (Pb), pose a very serious threat to our environment, causing different toxic effects both at the physiological and cellular/molecular level (see Table 1; for detailed information) viz., inhibition of several enzyme actions due to the binding of Hg$^{2+}$, Cd$^{2+}$, and Ag$^{+}$ with SH groups of concerned enzymes, generation of oxidative stress, and inhibition of activity of sulfate and phosphate groups containing compounds by structurally-related chromate and arsenate (Cervantes and Campos-García, 2007; Ventura-Lima et al., 2011). Although metals like manganese (Mn) Zinc (Zn), copper (Cu), nickel (Ni), molybdenum (Mo), and cobalt (Co) participate in the regulation of some important biochemical metabolic pathways in both prokaryotes and eukaryotes, higher concentrations of these heavy metals exert toxicity on humans, animals, and plants (see Table 1). Commonly, six widely known heavy metal resistance mechanisms have been characterized so far in different bacterial members (see Figure 1).

Exclusion of Heavy Metals by Permeability Barriers

Several bacteria (strains of Klebsiella aerogenes, Pseudomonas putida, and Arthrobacter viscosus) undergo structural alteration of the cell envelop, cell wall, plasma membrane, and surface layer (S-layer) in response to higher concentrations of certain heavy metals in their extracellular milieu. These changes ultimately reduce the permeability of different heavy metals (Bruins et al., 2000). Upon exposure to metal stress, such microbes started to secrete numerous components like exopolysaccharides (EPS), extracellular proteins, carbohydrates, and hemic acids. These components in turn interact with heavy metals and prevent them from entering into the cell. Moreover, anionic functional groups like hydroxyl, carboxyl, amine, sulphydryl, or sulfonate amide, which are the major constituents of EPS/S-layer and cell envelop, also caused unspecific entrapment of different heavy metals (Bruins et al., 2000; Etesami, 2018). A recent study by Wani et al. (2020) reported the biosorption of Cr(VI) by EPS and the biofilm-producing strain of Paenibacillus thiaminolyticus. Similarly, Upadhyay et al. (2017) also reported the involvement of...
| Heavy metals     | Most Toxic forms | Permissible levels in drinking water (recommended by WHO) and in agricultural soil (based on European union standard) | Adverse effect on plants                                                                 | Adverse effect on animals                                                                 | References                                                                 |
|------------------|------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Arsenic (As)     | As(III) and As(V) | 0.01 mgL$^{-1}$ in drinking water and 20 ppm in agricultural soil                               | ➢ Reduction in root and shoot length and plant biomass.                               | ➢ Long term exposure arsenic contaminated drinking water first resulted in blackfoot disease which later may become precursor of skin cancer. | Pandey et al., 2009; Martelli et al., 2006; Edition, 2011; Garg and Singla, 2011; Jomova et al., 2011; Yoon et al., 2015; Armendariz et al., 2016; Srivastava et al., 2017; Chauhan et al., 2020. |
| Mercury (Hg)     | Hg (II) and CH$_3$Hg$^+$ | 0.006 mgL$^{-1}$ in drinking water                                                             | ➢ Reduction in plant growth and subsequent crop yield.                               | ➢ Mercury toxicity can adversely affect nervous, renal, cardiovascular, immune and reproductive system in both humans and animals. | Zahir et al., 2005; Shiyab et al., 2009; Edition, 2011; Sahu et al., 2012; Srivastava et al., 2017; Sadej et al., 2019; |
| Chromium (Cr)    | Cr(VI)            | 0.05 mgL$^{-1}$ in drinking water and 150 mg kg$^{-1}$ in agricultural soil                    | ➢ Significant reduction in mitotic activity; genetic stability; soluble protein levels and phytohormone production. | ➢ On prolonged ingestion orally can cause stomach and gastrointestinal cancer. | Edition, 2011; Dias et al., 2013; Xu et al., 2013; Wu et al., 2015; Srivastava et al., 2017; Mitra et al., 2018; Sager et al., 2020. |
| Cadmium (Cd)     | Cd(II)            | 0.003 mgL$^{-1}$ in drinking water and 3 mg kg$^{-1}$ in agricultural soil                     | ➢ Reduction in plant dry weight, number of leaves.                                   | ➢ Cd(II) toxicity may cause generation of reactive oxygen species, alteration of vital signaling events and expression of different genes, trigger cell cycle arrest. | Martelli et al., 2006; Edition, 2011; Dias et al., 2013; Xu et al., 2013; Wu et al., 2015; Srivastava et al., 2017; Mitra et al., 2018; Sager et al., 2020. |

TABLE 1 | Detailed information regarding permissible limit and adverse effect of different studied heavy metals/metalloid on plants and animals.

(Continued)
| Heavy metals | Most Toxic forms | Permissible levels in drinking water (recommended by WHO) and in agricultural soil (based on European union standard) | Adverse effect on plants | Adverse effect on animals | References |
|--------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------|------------|
| Lead (Pb)    | Pb(II)          | 0.01 mgL⁻¹ in drinking water and 300 mg kg⁻¹ in agricultural soil                                                                 | ➢ Decrease in root and shoot growth, biomass and subsequent crop yield.  
➢ Reduction in cellular sodium, calcium, magnesium, potassium and phosphate concentration.  
➢ Reduction in cellular carbohydrate and protein content, along with inhibition of several enzyme activities.  
➢ Decrease in chlorophyll content and chlorosis in leaves.  
➢ Elevation of oxidative stress by ROS; found in crops like Oryza sativa (rice), Triticum aestivum (wheat), Lycopersicon esculentum (tomato) etc. | ➢ Pb(II) toxicity can adversely affect reproductive, nervous, renal and cardiovascular systems.  
➢ Induces oxidative stress and causes reduction in antioxidants activity.  
➢ Caused impaired function of several cellular metabolic enzymes, metallothionein and protein kinase activity  
➢ Stimulate the membrane lipid peroxidation in human and animals. | Chatterjee et al., 2004; Akinci et al., 2010; Edition, 2011; Lamhamdi et al., 2011; Gillis et al., 2012; Srivastava et al., 2017 |
| Copper (Cu)  | Cu(II)          | 2 mgL⁻¹ in drinking water and 140 mg kg⁻¹ in agricultural soil                                                                 | ➢ Reduction in plant growth, biomass and crop yield.  
➢ Increase production of several ROS like malondialdehyde  
➢ Massive decrease in chlorophyll and carotenoid content of leaves; reported in crop plants like Oryza sativa (rice), Linum usitatissimum and in medicinally important plant like Withania somnifera (Indian ginseng/ ashwagandha)  
➢ Increased oxidative damage by ROS  
➢ Young leaves suffered from chlorosis.  
➢ Reduction in translocation of essential elements (phosphate, iron, sulfur, manganese etc.) from roots to above ground parts.  
➢ Impaired transpiration, stomatal conductance and intercellular CO₂ concentration; reported in crops like Oryza sativa (rice), Triticum aestivum (wheat), Hordeum vulgare (barley), Brassica napus (oilseed rape), Lycopersicon esculentum (tomato) etc. | ➢ Excessive copper can cause several neurodegenerative diseases like Alzheimer.  
➢ Excessive copper toxicity can cause Wilson’s disease.  
➢ Toxicity may resulted into liver disease.  
➢ Adversely affect the endocrine, nervous and cardiovascular systems.  
➢ Resulted into generation of excessive ROS, and lipid peroxidation, impaired copper, iron homeostasis and mitochondrial function. | Uru-Adams and Keen, 2005; Xu et al., 2006; Khatun et al., 2008; Edition, 2011; Srivastava et al., 2017; Saleem et al., 2020 |
| Cobalt (Co)  | Co(II)          | Not available                                                                                                                                  | ➢ Reduction in root and shoot biomass, chlorophyll content, photosynthetic activity.  
➢ Increased oxidative damage by ROS.  
➢ Young leaves suffered from chlorosis.  
➢ Reduction in translocation of essential elements (phosphate, iron, sulfur, manganese etc.) from roots to above ground parts.  
➢ Impaired transpiration, stomatal conductance and intercellular CO₂ concentration; reported in crops like Oryza sativa (rice), Triticum aestivum (wheat), Hordeum vulgare (barley), Brassica napus (oilseed rape), Lycopersicon esculentum (tomato) etc. | ➢ Adversely affect the endocrine, nervous and cardiovascular systems.  
➢ Toxicity can also resulted in acute hypoxia like disorders ultimately responsible for irreversible cell damage and apoptosis. | Chatterjee and Chatterjee, 2000; Li et al., 2009; Edition, 2011; Leyssens et al., 2017; Srivastava et al., 2017; Ozfidan-Konakci et al., 2020 |
| Zinc (Zn)    | Zn(II)          | 3 mgL⁻¹ in drinking water and 300 mg kg⁻¹ in agricultural soil                                                                                   | ➢ Significant reduction in root and shoot growth, plant biomass, chlorophyll content in leaves.  
➢ Increased oxidative stress and reduction in antioxidant enzymes activity.  
➢ Upward rolling of leaf edges and reduction in cellular concentration of nitrogen, potassium, manganese and magnesium levels; observed in crops like Lycopersicon esculentum (tomato), Beta vulgaris (sugar beet) and Hordeum vulgare (barley).  
➢ Massive reduction in root nodules; as reported in plants like Zea mays (maize), Oryza sativa (rice), Vigna mungo (blackgram), Vigna radiata (mung bean) Vigna cylindrica (catjang) etc. | ➢ Excessive zinc accumulation caused programmed cell death, especially neurons in brain, causing several neurodegenerative diseases.  
➢ High concentration of Zn(II) adversely affect the immune system and caused suppression of lymphocyte and T-cell function.  
➢ High amount of Zn(II) also causes impaired copper homeostasis and cause massive copper deficiency in humans and animals. | Sagardoy et al., 2009; Plum et al., 2010; Edition, 2011; Srivastava et al., 2017; Akanbi-Gada et al., 2019; Mossa et al., 2020 |
| Nickel (Ni)  | Ni (II)         | 0.07 mgL⁻¹ in drinking water and 75 mg kg⁻¹ in agricultural soil                                                                             | ➢ Reduction in growth, yield and nutrient content of crops.  
➢ Reduction in seed germination as well as high mortality rate of seedlings at increased Ni(II) concentrations.  
➢ Chlorosis and yellowing of leaves, along with reduction in Chl-a and Chl-b content.  
➢ Massive reduction in root nodules; as reported in plants like Zea mays (maize), Oryza sativa (rice), Vigna mungo (blackgram), Vigna radiata (mung bean) Vigna cylindrica (catjang) etc. | ➢ Chronic exposure of Ni(II) may resulted into lungs, cardiovascular and kidney diseases.  
➢ Caused increased oxidative stress, DNA damage and inhibition of DNA repair system.  
➢ Nickel is a known carcinogen and caused cancer.  
➢ Toxicity can also resulted in acute hypoxia like disorders ultimately responsible for irreversible cell damage and apoptosis. | Denkhaus and Sahikow, 2002; Edition, 2011; Shabnam and Seema, 2011; Nie et al., 2015; Nazir et al., 2016; Srivastava et al., 2017. |
EPS and biofilm in Zn(II) adsorption as well as Zn(II) resistance by plant-growth-promoting members of *Pseudomonas* sp. Apart from extracellular adsorption, a few earlier studies also reported the periplasmic binding of heavy metals such as for Cu(II) ([Cha and Cooksey, 1991; Silver and Walderhaug, 1992; Silver and Ji, 1994; Bruins et al., 2000](#)). However, both of these extracellular and periplasmic adsorptions strategy ultimately immobilized heavy metals in diverse environments (see Figure 1).

**Extra and Intracellular Sequestration**

An extracellular sequestration mechanism detoxifies heavy metals by forming stable complexes with them and ultimately reducing their bioavailability (Etesami, 2018). For instance, siderophore (Pyridine-2,6-bis thiocarboxylic acid type; pyoverdine, pyochelin, hydroxamate) of bacterial origin (*Pseudomonas* spp., *Streptomyces* spp. etc.) is able to form such complexes with several heavy metals (As, Cd, Hg, Cu, Ni, Zn, and Pb) and reduce their toxicity ([Zawadzka et al., 2007; Dimkpa et al., 2008](#)). Notably, a study conducted by Zloch et al. (2016) reported increased production of three different types of siderophore (hydroxamates, catecholates, and phenolates) by members of *Streptomyces* spp. under cadmium stress. They also suggested a possible role of ferrioxamine B (a hydroxamate type siderophore) in enhancing cadmium tolerance in *Streptomyces* sp. Apart from siderophore, several microbes (such as *Bacillus* spp. and *Pseudomonas* spp.) are able to produce different types of biosurfactants (surfactin, rhamnolipids, etc.) which can bind with diverse heavy metals (such as Cu or Zn) and reduce their bioavailability ([Mulligan et al., 2001; Yang et al., 2018; Md Badrul Hisham et al., 2019; Sun et al., 2021](#)).

However, in the case of intracellular sequestration, cytoplasmic hyperaccumulation of heavy metals involved several metal binding proteins like metallothioneins, metallo-chaperons, and many other low-molecular-weight cystine-rich proteins. In general, metallothioneins are low-molecular-weight cystine-rich proteins which reduce the bioavailability of noxious heavy metals by binding with them ([Bruins et al., 2000; Blindauer et al., 2002; Naik et al., 2012](#)). Several divalent cations of Cu, Cd, Zn, Pb, and As are found to be sequestered intracellularly in this manner ([Bruins et al., 2000](#)). For example, *Synechococcus* PCC 7942 strain-derived SmtA protein is able to sequester four zinc ions per molecules ([Blindauer et al., 2002](#)). Similarly another plant growth-promoting strain of *Pseudomonas* was found to produce metallothioneins for extracellular sequestration of Pb(II) ([Naik et al., 2012](#)). Moreover, several bacteria are also able to accumulate large amounts of heavy metal ions

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**FIGURE 1** Thematic representation of microbe-assisted heavy metal remediation and its consequence on plant systems.
in intracellularly by compartmentalization or by cytoplasmic sequestration where various cellular proteins were involved for this (glutathione, metallothioneins, cystein rich proteins, etc.), thereby reducing the bioavailability of free metal ions (Etesami, 1999). A similar kind of observation by Kotoky et al. (2019) reported the involvement of glutathione S-transferase enzymes mediated Cd(II) detoxification system in members of Serratia marcescens.

**Enzymatic Detoxification and Active Transport of Heavy Metals**

Enzyme-mediated metal-detoxification mechanisms involve oxidation and/or reduction and demethylation and/or methylation reactions. This mechanism was found to be very effective in a wide range of bacteria for certain heavy metals e.g., Hg(II), As(V), and Cr(VI) (Bruins et al., 2000). For instance, organomercurial lyase and mercuric ion reductase are two such enzymes which can bind to the active site of Hg(II) (containing cystine sulfhydryl residue) and participate in hydrolyzing the stable carbon-mercury bond, finally forming a mercury thiolate adduct. This mercury thiolate adduct in turn was used as a substrate for mercuric ion reductase that finally reduced the Hg(II) into metallic mercury (Hg⁰) and forced it to diffuse back (mercury volatilization) into its natural environment (Bruins et al., 2000; Etesami, 2018). Moreover, Calzada Urquiza et al. (2017) reported that several plant growth-promoting members of Bacillus spp. were also capable of mercury volatilization. Enzymatic detoxification of arsenic involves oxidation of the more toxic As(III) into the less toxic As(V) by arsenite oxidase and conversion of arsenate (As⁵⁺) to the more toxic form arsensite (As³⁺) by the enzyme arsenate reductase, which may be exported out through some efflux system in response to the chemiosmotic gradient across the plasma membrane (Nies, 1999). So far as the other mechanisms are concerned, formation of metal sulfides and phosphate by anaerobic sulfur reducing bacteria (e.g., production of Cds and PbS by Klebsiella spp. or Aliszewanella sp.), bacteria assisted heavy metal volatilization (conversion of arsenic into volatile derivatives by Clostridium spp.), and formation of gaseous substances has also been reported in several cases (Sharma et al., 2000; Meyer et al., 2007; Shi et al., 2018). Enzymatic detoxification system of Cr(VI) involves reduction of highly reactive Cr(VI) into less toxic Cr(III) by chromate reductase that has been observed in many bacteria like Sphingomonas spp. or Variovorax spp (Han et al., 2011; Bilal et al., 2018). Additionally, Wani et al. (2020) also reported an NADPH-dependent chromium reductase in Paenibacillus thiananolicus PS 5, having chromium resistance potential.

Notably, in certain cases, active transport of heavy metals is reported as a dominant mechanism in several bacteria (Bruins et al., 2000). These efflux systems can be linked to ATPase or not, but always have higher specificity for relevant cation or anion (Bruins et al., 2000). These efflux systems include Cd, Zn, and Pb by Cad-A system or active transport of Cd, Zn, and Co by Czc system, which have been reported in various bacteria such as Bacillus spp. or Pseudomonas spp. (Nies, 2003; Silver and Phung, 2005a). Furthermore, several plant growth-promoting bacteria are also known to have such an efflux system mediating their heavy metal resistance mechanism (see Supplementary Table 2 for detailed information).

On several occasions it has been observed that heavy-metal-induced oxidative stress can cause DNA damage which can in turn be countered by an indigenous DNA repair mechanism to some extent (Bruins et al., 2000). These resistant mechanisms may serve as potential plots for several remediation as well as industrial strategies, starting from metal recovery of industrial waste to remediation of metal contaminated soil. However, to achieve these, a comprehensive and improved understanding regarding the complex molecular mechanistic details of metal resistance in bacteria is very much necessary.

**Molecular Mechanistic Insight Into Heavy Metal Resistance in Bacteria**

Though there are no generalized resistance patterns for different heavy metals in bacteria, previous research has pointed out some major mechanisms which either solely or in combination are operating in diverse organisms. However, the genetic determinants for any heavy metal resistance in bacteria are either plasmid-born or a genome-integrated feature. Several factors, like concentration of heavy metals in the environment, types and toxicities of heavy metals, exposure time of organisms against those metals, and horizontal gene transfer through evolutionary time scale, play an imperative role in the development of their indigenous resistance property (Gadd, 1990). Here, we discuss the various molecular mechanisms of metal resistance in bacteria along with their utility in bioremediation purposes.

**Resistance for Arsenic (As)**

Arsenic is one of the most abundant elements on earth, often categorized as a heavy metalloid due to the presence of both metal and nonmetal moiety (Garg and Singla, 2011). It can exist in over 200 different forms, of which arsenopyrite is the most abundant (Mandal and Suzuki, 2002; Garg and Singla, 2011). Arsenic is a non-essential toxic element which mostly have two highly toxic forms, arsenite or As(III) and arsensate As(V), that can cause serious health hazards both in plants and animals (see Table 1 for detailed information). Among As(III) and arsenate As(V), As(V) is most abundant on the earth’s crust whereas As(III) is mostly predominant in reducing environments (Nies, 1999; Mandal and Suzuki, 2002; Garg and Singla, 2011). Between them, As(III) has been found to be more soluble and toxic compared to As(V) (Mandal and Suzuki, 2002; Jomova et al., 2011). Arsenic, when present in combination with sulfur, oxygen, and chlorine, is generally referred to as inorganic arsenic; when in combination with carbon and hydrogen, it is commonly referred to as organic arsenic which is much less toxic than its inorganic counterparts (Mandal and Suzuki, 2002; Jomova et al., 2011). Having close structural similarities with (PO₄)³⁻, As(V) frequently accumulates into cells via (PO₄)³⁻ transporting Pit or Pst system and results in 100-fold higher accumulation (Nies and Silver, 1995). Thus, arsenate toxicity often causes the inhibition of different phosphate transport systems (Nies and Silver, 1995; Nies, 1999). Bacteria had several arsenic resistance mechanisms viz. reduction of arsenate to arsenite and efflux of arsenite, oxidation of arsenite to arsenate, or intracellular
accumulation and methylation of this metal (Andres and Bertin, 2016). In this context, operons like arsRBC and arsRDABC are well-characterized in diverse bacteria and located either in chromosome or in plasmid. For instance, arsRBC contain three genes, arsR, arsB, and arsC, which were discovered in the chromosome of E. coli (Diorio et al., 1995) and in plasmids pL258 (Ji and Silver, 1992) and pSX267 (Rosenstein et al., 1992) of Staphylococcus aureus and S. xylosus, respectively. On the contrary, arsRDABC operon contain two extra set of genes, arsA and arsD, that were initially discovered in plasmids R773 (Figure 2) and R46 of strains of E. coli (Chen et al., 1986; Bruhn et al., 1996). Both aforementioned operons are As(III) inducible. ArsR is a repressor protein which, in the absence of As(III), constitutively produce and bind to the operator region of both operons and prevents the transcription initiation process (Wu and Rosen, 1991). ArsD protein serves as a corepressor of arsRDABC operon (Wu and Rosen, 1993). ArsC is an intracellular arsenate reductase which reduced As(V) into As(III) (Ji and Silver, 1992). Though arsenic reductase performs the same function in diverse organisms, their sequences vary greatly (Silver and Phung, 1996). ArsB is a transmembrane arsenite efflux pump protein that extruded the As(III) from cytoplasm to cell surface in response to a chemiosmotic gradient (Chen et al., 1986), while ArsA is an As(III) stimulated ATPase (Chen et al, 1986). According to Dey and Rosen (1995), both ArsA and ArsB formed a heterodimer (ArsA2B) which served as an ATP dependent efflux system of As(III). Moreover, in Microbacterium sp., arsenic resistance is also conferred by both ars and acr systems (see Figure 2), whereas arsC3 and acr3 are reported to transcribe in the opposite direction (Achour-Rokhani et al., 2010). Moreover, another arsenite efflux protein, namely Acr3, was found in various plant growth-promoting bacterial isolates like Pantoaea agglomerans C1, Azospirillum brasilense Az39, Variovorax paradoxus S110, and Pseudomona koreensis AGB-1 (Han et al., 2011; Armendizari et al., 2015; Babu et al., 2015; Luziatelli et al., 2020).

Notably, two other respiratory periplasmic, arsenite and arsensate oxidase (Anderson et al., 1992; Ahmann et al., 1994) enzymes, are known to be involved in arsenic resistance in bacteria (Silver and Phung, 2005a). Among all other bacterial isolates, arsenite oxidation system (another prime mechanism for arsenic resistance) is well-characterized in Alcaligenes faecalis where the first “arsenic gene island” was reported (Silver and Phung, 2005b; Phung et al., 2012). Arsenite oxidase is a heterodimeric protein that consists of two subunits: one large molybdopterin-containing subunit with an iron (3Fe-4S) center encoded by asoa/aoaA and another small rieke active subunit (Anderson et al., 1992) encoded asob/aoxB genes (Silver and Phung, 2005b; Phung et al., 2012; Mallick et al., 2015). Upstream of the aoxA, there is a Twin Arginine Translocation (TAT) leader sequence which is involved in assemblage of arsenite oxidase and its translocation from cytoplasm to periplasm (Mallick et al., 2015). On the other hand, an anaerobic form of arsenite reductase (Arr) is a heterodimer (Mallick et al., 2015) and is encoded by arrA and arrB genes that were primarily characterized in Shewanella spp. (Saltikov and Newman, 2003) and in Bacillus selenitireducens (see Figure 2) (Afkar et al., 2003). Both cytoplasmic and periplasmic arsenite reductase, encoded by two different operons, i.e., arsDABC and arrAB respectively, were characterized in members of Shewanella (Saltikov et al., 2003). A few other arsenite oxidase encoding genes (e.g., aoxA, aoxB, arsB, and aroA) were also reported in different bacterial isolates, like Centibacterium arszenoxidans, and in Chemolithoautotrophic strain NT-26 (Muller et al., 2003; Santini and vanden Hoven, 2004; Silver and Phung, 2005b). Another gene, arsH encoded NAFDP:FMN oxidase (ArsH) that oxidizes As(III) into As(V), has been reported in a few plant growth-promoting bacterial isolates (Pantoaea agglomerans and Azospirillum brasilense; see Supplementary Table 2 for detailed information) (Armendarizari et al., 2015; Luziatelli et al., 2020).

Both arsenite and arsensate reductase are coupled with inner membrane respiratory chain (Silver and Phung, 2005a), where arsenite oxidase serves as an electron donor while arsensate reductase serves as an electron acceptor (Ahmann et al., 1994). So far as the other mechanisms are concerned, biosorption of As(V) and As(III) on bacterial cell surface and methylation of inorganic arsenic in organic compounds (Thomas et al., 2004) are some of the most vital strategies for arsenic resistance, which have been reported in various bacteria. For example, Babu et al. (2015) reported the presence of gene bmtA (encoding metallothionein) in Pseudomona koreensis, along with other arsenic resistance genes. On the other hand, methylation of arsenic and its subsequent volatilization is a multistep complex process and information is significantly lacking in this regard (Mallick et al., 2015). Another gene, namely arsM, was found to be responsible for arsenic methylation (Bertin et al., 2011). Mostly, arsenic resistance plant growth-promoting gram positive bacterial isolates belong to the phyla firmicutes and actinobacteria where Bacillus spp. was found to be the most abundant member. On the other hand, in the case of gram-negative bacterial isolates, they mostly belong to the phylum proteobacteria where Pseudomonas spp. holds a significant position. Among several bioremediation strategies used by bacterial isolates, biotransformation of As(V) and As (III) by enzymatic reduction and oxidation are found to be predominant, followed by arsenite efflux, bioaccumulation, and bio-adsorption strategy.

However, a few recent proteome-level investigations in Brevibacterium spp. and Exiguobacterium spp. shows that under metal stress [in the presence of 750 mg L\(^{-1}\) arsenic; As(III) and As(V)] conditions, various housekeeping proteins (ribosomal proteins or lipid metabolism-related proteins) are downregulated while proteins like superoxide dismutase, thioredoxin disulfide reductase, lipid hydroperoxide reductase, ArsR, ArsA, Cdr (encoding Co-enzyme A disulfide reductase), and ABC transporter are be upregulated (Castro-Sevynt et al., 2019; Shah and Damare, 2020). Additionally, transcriptome analysis by Liu et al. (2020) also revealed the upregulation of areB gene in plant growth-promoting Paenibacillus polymyxa YCO136 in the presence of root exudates of tobacco.

Resistance for Mercury (Hg)
The most toxic bioavailable forms of mercury (Hg) are mercuric ions (Hg\(^{2+}\)) and methyl mercury (CH\(_3\)Hg\(^{+}\)) (Nies, 1999). In general, microbe-assisted mercury detoxification mechanism
FIGURE 2 | Schematic diagram illustrating the organization of heavy-metal-resistant related gene clusters reported from some major representative bacterial genera.
involves enzymatic reduction of highly toxic mercuric ions (Hg$^{2+}$) into less toxic volatile metallic mercury (Hg$^0$), which passively diffuses from bacterial cells upon aeration (Silver and Walderhaug, 1992). A previous study identified that mercury resistance in microbes is conferred by mer operon that is located either in plasmid or in chromosomal DNA, and occasionally in the form of a transposons (see Figure 2) such as Tn21, characterized from plasmid NR1 in Shigella flexneri (Liebert et al., 1999; Silver and Phung, 2005a). This mer operon comprised of several functional genes, such as merRTPCADB, although their copy number and gene orientation synteny varied widely in different organisms (Silver and Walderhaug, 1992; Silver and Phung, 1996, 2005a). For instance, in Thiobacillus ferrooxidans, instead of one, two merR genes, merR$_1$ and merR$_2$, are present at a separate genetic locus (Inoue et al., 1991). MerR is a regulatory protein which contains a DNA binding region at carboxy terminal and a Hg$^{2+}$ binding region at amino terminal (Silver and Phung, 2005a). MerR can both repress (in absence of Hg$^{2+}$) and activate (in presence of Hg$^{2+}$) the transcription initiation process of mer operon in taxonomically distantly related organisms (Silver and Phung, 1996).

MerT is an inner membrane Hg$^{2+}$ transport protein encoded by merT gene, while merP and merC genes encode a periplasmic Hg$^{2+}$ binding and transport protein respectively (Kusano et al., 1990). Notably, mer operon of gram-positive Streptomyces lividans is comprised of two divergent gene clusters (see Figure 2), out of which one cluster is encompassed with genetic determinants for MerR and MerT that are transcribed from right to left and another cluster contained gene merA and merB, transcribed from left to right (Sedlmeier and Altenbuchner, 1992). Mercuric reductase and organomercurial lyase are encoded by merA and merB, respectively (Silver and Phung, 1996). merB gene can also be found in bacterial isolates such as in plasmid pDU1358 of Serratia marcescens (Griffin et al., 1987) and in mer operon of several members of Pseudomonas spp. This operon-derived resistance sometimes represents the “narrow spectrum” that only contain merA gene and provides resistance for mercuric ions only, or it can be a “broad spectrum” which contains genes merA and merB that provide resistance against both Hg$^{2+}$ and CH$_3$Hg$^+$ (Silver and Phung, 1996). Often, there is another genetic determinant, merD (encoding secondary regulatory protein), present at the end of mer operon that has been reported in many organisms (Mukhopadhyay et al., 1991). Under mercury-stressed conditions, bacterial mer operon activates its genes. A small periplasmic protein MerP binds with the Hg$^{2+}$ in the periplasm. Eventually, MerP protein is transferred from the Hg$^{2+}$ to inner membrane protein MerT (Silver and Phung, 2005a). In this transfer event, no outer membrane protein is involved; therefore it can be considered as a passive process (Silver and Phung, 1996, 2005a). However, sometimes inner membrane proteins like MerC and MerF are also found to play similar roles in Hg$^{2+}$ transport in some members (Kusano et al., 1990). Once on the inner surface of the cell membrane, Hg$^{2+}$ is transferred to the homodimeric mercuric reductase, and then reduces Hg$^{2+}$ into Hg$^0$. Being volatile, Hg$^0$ passively diffused out from an intracellular environment. On the other hand, more toxic organomercurials are detoxified by organomercurial lyase which follow a SE$_2$ reaction pathway that break down the Hg-C bond by concerted proton attack. Subsequently, Hg$^{2+}$ ions and reduced organic compounds are formed, such as methane after lysis of methyl mercury or benzene after lysis of phenylmercury (Silver and Phung, 1996; Begley and Ealick, 2004). A recent work related to Hg$^{2+}$ resistance shed new light on MerT/MerP/MerA-mediated bioremediation potency in a marine strain of Pseudomonas pseudoalcaligenes (Zhang J. et al., 2020).

In recent years, a number of plant growth-promoting bacterial isolates (see Supplementary Table 2 for detailed information) were found to use mer operon encoded gene-mediated detoxification mechanisms (e.g., biotransformation). Notably, some other important mechanisms include merB gene-mediated detoxification of Hg$^{2+}$ and CH$_3$Hg$^+$ (found in members of Bacillus) (Amin and Latif, 2016) and conversion of Hg$^{2+}$ into less toxic and soluble Hg$^0$ by plant growth-promoting members of Pseudomonas spp. or Enterobacter spp. (Tariq et al., 2015). Interestingly, gram positive bacterial isolates are mostly used for bioremediation of both Hg$^{2+}$ and CH$_3$Hg$^+$ due to the existence of functional merA and merB genes, while gram-negative members mostly have a mercuric ion detoxification system, but lack an organomercurial system, except for a few Pseudomonas spp. which have merB gene for organomercurial lyase. However, a recent study by Calzada Urquiza et al. (2017) reported the presence of a merR gene for the first time in plant growth-promoting Bacillus spp. along with merA gene.

**Resistance for Chromium (Cr)**

Chromium (Cr) is one of the most abundant metals in the earth’s crust, with an average concentration of 125 mg kg$^{-1}$, while Cr(VI) or chromate and Cr(III), the trivalent cation, are two copious bioavailable forms of chromium, of which Cr(VI) is far more toxic than Cr(III) to all living cell (Nies, 1999; Sun et al., 2015). In bacteria, Cr(VI) is generally accumulated in the cell by sulfate uptake system which used Cr(VI) as an alternative substrate (Silver and Walderhaug, 1992). Reduction of intracellular Cr(VI) concentration by reducing its uptake system or by extrusion of Cr(VI) using membrane efflux pump or enzymatic reduction of Cr(VI) into Cr(III) are some of the imperative mechanisms of chromate resistance that have been reported in bacteria. The two most important genes, namely chrB and chrA (encode chromium efflux protein), for chromate resistance were initially sequenced and characterized from plasmid pUM505 (Cervantes et al., 1990) and pMOL28 (Nies et al., 1990) in Pseudomonas aeruginosa and Alcaligenes eutrophus CH34 (later named as Cupriavidus metallidurans CH34) respectively (Figure 2). The gene (chrB and chrA) expression system in Pseudomonas was found to be constitutive, while in Alcaligenes it is inducible nature (Cervantes et al., 1990; Nies et al., 1990). Viti et al. (2014) briefly reviewed genetic determinants of chromate detoxification system in bacteria (e.g., Cupriavidus metallidurans and Ochrobactrum tritici) which include several chr genes located in chr operons (chrECAB) and encode proteins that belong to CHR superfamily (Branco et al., 2008; Monsieurs et al., 2011). ChrB served as a regulatory protein and was only activated by Cr(VI) or Cr(III) and sulfate in various
organisms (Juhnke et al., 2002). However, chrC gene encoded a superoxide dismutase (SOD) (Juhnke et al., 2002). Gene clusters like chrABC are also found in plasmid of Shewanella sp. (Figure 2) (Aguilá-Barajas et al., 2008; Viti et al., 2014).

Notably, reduction of Cr(VI) to Cr(III) catalyzed by chromate reductase (ChrR), which was encoded by chrR or bio-adsorption of Cr(VI), is an alternate chromate resistance mechanism identified and characterized from several PGP bacteria (Sphingomonas sp.; Variorovax sp. etc.) (Han et al., 2011; Bilal et al., 2018). Among different chromate bioremediating PGP bacterial members (see Supplementary Table 2 for detailed information), most are members of firmicutes, followed by actinobacteria. Whereas, gram negative isolates mostly belong to phylum proteobacteria where γ-proteobacteria were found to be the predominant class, followed by α-proteobacteria and other subsequent classes.

Resistance for Cadmium (Cd)
Cadmium is not an abundant metal in the Earth’s crust and is mostly found in association with other elements such as Zinc, copper, and lead. The most toxic bioavailable redox form of cadmium is Cd²⁺ which is often taken up by Mg(II) uptake system (Nies, 1999). In bacteria, enzymatic detoxification of cadmium resistance mechanism is completely absent, because several divalent cations, like Cd(II), Zn(II), Co(II), and Ni(II), are quickly reoxidized into their former highly reactive toxic states, unlike passive removal of volatile Hg⁰ (Bruins et al., 2000). Efflux-pump-mediated resistance mechanism is the most predominant one for Cd(II) (Nies, 1999). Silver and Phung (2005a) summarized seven different types of metal ion efflux systems, of which CadA-, CzcCBA-, and CzcD-mediated efflux systems were responsible for Cd(II) efflux in various organisms. The CadA system (encode P-type ATPase protein) of Cd(II) efflux are well-characterized and were first discovered in plasmid p258 of gram positive Staphylococcus aureus (Novick et al., 1979). Moreover, cadC encodes for a DNA binding repressor protein (able to bind at the operator-promoter site of DNA and prevent transcription) (Yoon et al., 1991) for transcriptional regulation of inducible cad operon. This cad operon was also found in a transposon element like Tn5422 in Listeria monocytogenes (Lebrun et al., 1994). When divalent metal ions like Zn²⁺/Pb²⁺/Co²⁺ and Ni²⁺ bind with CadC protein, it is released from DNA and a transcription event occurs (Silver and Phung, 2005a).

Another well-characterized chemiosmotic efflux system is CzcCBA, driven by proton motive force. Necessary genes for Czc system are located in czcCBAD operon, either in chromosome or in plasmids of various organisms (e.g., plasmid pMOL30 of Cupriavidus metallidurans CH34, see Figure 2) (Nies et al., 1989; Gutiérrez-Barraquer et al., 2013). CzcD protein is a single membrane polypeptide efflux pump that belongs to the cation diffusion facilitator family (CDF) (Haney et al., 2005; Silver and Phung, 2005a). Whereas, CzcCBA protein complex is comprised of three polypeptides, of which a large inner membrane protein is CzcA, a smaller outer membrane protein is CzcC, and CzcB is a periplasmic protein. These CzcA and CzcB together formed a continuous channel from cytoplasm to the outside of the plasma membrane (Rensing et al., 1997; Silver and Phung, 2005a). Sometimes, CzcA alone can provide low levels of resistance for Cd(II), Co(II), and Zn(II), while CzcB creates a pathway for the removal of metal ions. CzcC creates a hole on the outer membrane surface for the release of those metal ions (Rensing et al., 1997). Moreover, adsorption of Cd(II) on cell surface by physical entrapment, ion exchange, or complexation prevents metals from entering inside the cell, and is also functional in several organisms (Bruins et al., 2000). However, resistance by Czc Cd(II) efflux pump and bio-adsorption on cell surface was found to be the predominant mechanism for cadmium resistance in different PGP bacterial isolates (e.g., Bacillus spp., Pseudomonas spp., Sphingomonas spp., Klebsiella spp., Enterobacter spp., Serratia spp., and Rhizobium spp. See Supplementary Table 2 for detailed information). Notably, a recent proteome-level investigation in Pseudomonas aeruginosa revealed that one third of the total upregulated proteins in cadmium amended culture are metalloproteins, suggesting their role in cadmium resistance (Izrael-Živković et al., 2018). Another separate proteomics-based study conducted by Zhang et al. (2019) shows that upregulation of Cd²⁺/Zn²⁺ exporting ATPase, type-VI protein secretion system, and glutathione-S-transferase under cadmium stress, which might be responsible for cadmium homeostasis in Burkholderia cepacia strain GYP1 (Zhang et al., 2019). In this connection, a recent comparative transcriptome analysis by Wang H. et al. (2020) revealed a unique strategy: using montmorillonite(Mt) for enhanced cadmium tolerance in Chryseobacterium sp. WAL2. They put forward the fact that, in the presence of Mt and Cd(II) stress, the expression of genes related to efflux systems in strain WAL2 are found to be up-regulated. It has been observed that in the presence of Mt, expression of certain genes like czcA, czcB, and zntA increased several fold in Chryseobacterium sp. WAL2.

Resistance for Lead (Pb)
Divalent cation Pb²⁺ or Pb(II) is the most common bioavailable form, thus resistance against Pb(II) is mostly conferred by different efflux systems (Bruins et al., 2000). The Pb(II) resistance genetic determinants which are responsible for uptake, efflux, and accumulation of Pb(II) were first discovered in plasmid of Cupriavidus metallidurans strain CH34 (formerly known as Ralstonia metallidurans) (Borremans et al., 2001). All six genes for Pb(II) resistance are organized in two different operons: pbrABC and pbrRT (Borremans et al., 2001). An earlier study revealed that the entire pbrABC operon is co-transcribed into a single mRNA (Borremans et al., 2001; Silver and Phung, 2005a). However, pbr operon is an inducible one which is regulated by PbrR, a metal-sensing regulatory protein that belongs to Mer family (Chen et al., 2005). Another permease type protein, PbrT, is also involved in uptake of Pb(II). Gene pbrA encoded a P-type Pb(II) efflux ATPase of Cys-Pro-Cys soft metal efflux family and shared general sequence features with other P-type ATPase (Solioz and Vulpe, 1996). PbrB is an outer membrane protein involved in Pb(II) removal from periplasmic space to the extracellular side, whereas PbrC is a signal peptidase that cleaved off the signal peptide from a protein in periplasm (Borremans et al., 2001). Protein PbrD has Cys-rich metal binding sites and an important role in intracellular
sequestration of Pb(II). Some other notable Pb(II) resistance mechanisms are adsorption of Pb(II) by EPS or by functional groups on cell wall or intracellular accumulation of Pb(II) as lead phosphate, reported in several organisms like *Citrobacter freundii* or *Staphylococcus aureus* (Levinson and Mahler, 1998). Notably, several reports revealed the involvement of *phrA* gene in Pb(II) resistance in different plant growth-promoting bacteria which include members of *Agrobacterium* sp., *Rahnella* spp., *Pseudomonas* spp., *Rhizobium* spp., and *Bacillus* spp. (Jebraa et al., 2015; Abdelkrim et al., 2018) Naik et al. (2012) reported another gene, namely *bmtA*, which encodes metallothionein and is involved in Pb(II) sequestration in several PGP bacteria like *Pseudomonas aeruginosa*. The occurrence of bio-adsorption was found to be key to the Pb(II)-resistant mechanism among PGP bacteria, followed by bioaccumulation and efflux by P-type ATPase.

**Mechanism of Copper (Cu) Resistance**

Unlike other heavy metals, Cu served as a vital micronutrient to all life forms. Cupric oxide [Cu(II)] and cuprous oxide [Cu(I)] are found to be the most abundant chemical forms that exist in the natural environment. Although it is necessary for certain physiological functions, excessive concentration of Cu(II) often imparts toxic side effects on various living entities. During the course of evolution, bacteria developed different mechanisms for Cu(II) resistance in response to high Cu(II) contaminants. Several such well-characterized systems include *copYZAB* system in *Enterococcus hirae* (Odermatt et al., 1992), *cus* (Franke et al., 2003; Gutiérrez-Barranquero et al., 2013), *pco* operon in plasmid pRJ1004 (Brown et al., 1995), *cut* systems in *E. coli* (Silver and Phung, 1996), and *cop* operon in *Pseudomonas syringae* (see Figure 2) (Gutiérrez-Barranquero et al., 2013).

For the last few decades, a number of seminal papers have been published in this regard which critically bring to the light the molecular tuning of Cu-metabolizing genes. For instance, in *Enterococcus hirae*, copper resistant gene cluster *CopYZAB* is organized in *cop* operon which activates upon copper starvation as well as in the presence of excessive copper concentration (Odermatt et al., 1992). In another separate study, deletion mutation of *copA* results in higher resistance in *E. hirae*, indicating that CopA might be involved in copper ions’ uptake, especially Cu(I), while deletion of *copB* resulted in copper sensitivity (Silver and Phung, 1996). The expression of *copA* and *copB* are regulated by proteins CopY and CopZ protein, where CopY is an apo-repressor that is unable to bind directly with the DNA; instead, it forms CopY-Cu\(^{+}\) complex which in turn binds to the operator region and prevents transcription initiation process of *cop* operon (Odermatt and Soliz, 1995). On the other hand, CopZ is an anti-repressor protein which forms a CopZ-Cu\(^{+}\) protein complex and interacts with the CopY-Cu\(^{+}\) and finally results in removal of the repressor (Odermatt and Soliz, 1995). Similar to *copYZAB* in *E. hirae*, another operon, namely *tcrYZAB* in *E. hirae*, has also been reported to be involved in copper homeostasis in *E. faecium* and *E. faecalis* (Hasman, 2005).

In *Pseudomonas syringae*, *cop* operon encompassed with *copABCD* genes to encode four structural proteins: periplasmic copper binding protein (CopA), outer membrane protein (CopB), periplasmic copper binding protein (CopC), and inner membrane protein (CopD) (Silver and Phung, 1996). The regulation of this operon is solely dependent on two regulatory proteins, *copR* and *copS*; together they form two component regulation systems (Silver and Phung, 1996). Both CopA and CopC proteins are able to bind with the Cu(II) in the periplasmic site and reduce the Cu(II) toxicity. In this context, several earlier works suggested that bacteria can undergo colony color change under Cu stress. For instance, colonies of *Pseudomonas* turned to a blue color from a whitish one when they were grown in Cu(II)-containing medium (Cooksey, 1994; Silver and Phung, 1996). However, Cu resistance also came from some other operons like *pco* (encompassed with genes like *pcoABCD* and *pcoRS*) that were initially characterized in plasmids of *E. coli* (Cooksey, 1994). Although, gene clusters of *pco* operon encode *cop* operon-related proteins; only the former contain an additional genetic determinant *pcoE*, that is located downstream of other regulatory genes (Brown et al., 1995). Notably, *cus* system, which is characterized in *E.coli*, potentially encodes an RND efflux chemiosmotic carrier protein complex *CusCFBA* and *cusRS* (*cusS* encodes histidine kinase while *cusR* is a response regulator) involved in Cu(II) resistance only under anaerobic conditions (Franke et al., 2003). *CusA* is a member of the resistance-nodulation-division related (RND) protein and CusB is a membrane fusion protein (MFP). CusF is a copper-binding protein (Franke et al., 2003). Flow of Cu(II) and other heavy metals back and forth from the natural environment to inside the bacterial cell through proper uptake and efflux system is a vital eco-strategy that engaged a large portion of bioavailable heavy metals and ultimately reduced the possibility of their entry from soil to plant systems and eventually other living forms. The abovementioned Cu(II) resistance mechanisms can also be observed in different plant growth-promoting bacterial isolates (see Supplementary Table 2 for detailed information) and served as bioremediation agents and reduced Cu(II) toxicity in agricultural fields. Amongst such isolates, abundance of gram-negative bacteria occupied a higher position and mostly belonged to class α and γ proteobacteria, where members of *Pseudomonas* spp. holds a significant position. Use of P-type ATPase, which is either CopA- or CueA- (Adaikkalam and Swarup, 2002; Zhang and Rainey, 2007; Wei et al., 2009; Asaf et al., 2018) based efflux system of Cu(II), is found to be predominant in the Cu-remediating mechanism in PGP members. However, a few recent reports also exhibited the functionality of Cu(II) resistance by CusAB system in plant growth-promoting rhizobacteria i.e., *Mesorhizobium amorphae* 186 (Hao et al., 2015). Notably, Glibota et al. (2020) detected several genetic determinants (*copA*, *copB*, *copC*, *pcoR*, *pcoA*, and *pcoD*) that were responsible for conferring copper resistance in a large number of bacterial genera that include *Bacillus* spp., *Chryseobacterium* spp., *Pseudomonas* spp. *Variovorax* spp., and *Stenotrophomonas* spp. These were initially isolated from copper-compound-treated soil of an olive tree farm. Additionally, more copper resistance genetic determinants, *tcrB* (encoding copper export ATPase) and *sile* (encoding silver/copper periplasmic metal binding protein), were also detected in members of *Enterobacter aerogenes* and *Pseudomonas* sp.
Mechanism of Co(II) Resistance

The uptake of Cd(II) inside the cell by CorA system caused rapid accumulation of Co(II) (Smith et al., 1993). Mostly, Co(II) resistance occurred as a by-product of other resistance systems such as Cd(II), Zn(II), and Ni(II) (Nies, 1999). In gram-negative bacteria, Co(II) resistance is driven by trans envelope efflux system by RND protein (Nies, 1999). However, a widely reported Co(II) resistance system is the cation antipporter CzcCAB system, responsible for resistance to Cd(II), Co(II), and Zn(II), whereas CnrCBA and NccCBA efflux systems are responsible for Cd(II), Ni(II), Co(II), and Cd(II) resistance (Nanda et al., 2019). Notably, in Staphylococcus aureus, ZntA protein is responsible for Co(II) efflux (Xiong and Jayaswal, 1998) whereas in E. coli, gene yohM (rcnA) encodes a protein, RcnA/YohM, involved in Co(II) an Ni(II) resistance (Eitinger et al., 2005). There are several PGP bacteria that exhibited Co(II) resistance through different mechanisms. Out of these, CzcCAB-mediated efflux system was found to be the most prevalent and significant, followed by bio-adsorption and bioaccumulation mechanisms.

Mechanism of Zn(II) Resistance

Zinc is an important micronutrient required in trace amounts to maintain cellular function, thus zinc solubilization by bacteria is considered important event in nature (Kamran et al., 2017). However, at higher concentrations, Zn(II) can also cause severe health hazards in plants and animals (see Table 1). A study performed by Islam et al. (2014) exhibited reduction in the biomass of maize in the presence of 50 μM of Zinc. Generally, several unspecific cation transporters are responsible for the accumulation of Zn(II) in an intercellular environment. Among many, two such central Zn(II) uptake systems are CorA (a chemiosmotically driven transporter from the MgtE family) and MgtA type zinc transporter (a P-type ATPase transporter) (Nies, 1999). Bacterial Zn(II) resistance potency came from ccc operon that encodes for chemiosmotic Zn(II) efflux pump. Another important efflux system is P type ATPase ZntCAB encoded by znt operon (Silver and Phung, 2005a). Glibota et al. (2020) reported the frequent presence of zntA gene among several bacterial isolates that belong to genera Chryseobacterium spp., Pseudomonas spp. Varioroxar spp. and Stenotrophomonas spp. Another study by Hao et al. (2012) using genomic reverse transcriptase PCR and a transposon-based gene disruption approach revealed the zntA and zntR genes mediated resistance of Zn(II) and Cd(II) in PGPB members like Agrobacterium tumefaciens. Apart from this, several microbes also have the ability to produce metallothionein (a cytoplasmic metal cation binding protein) which can effectively reduce metal toxicity (Silver and Phung, 2005a). Nonetheless, several plant growth-promoting bacterial isolates (Pseudomonas spp., Sphingomonas spp., Serratia spp., and Rhizobium spp. See Supplementary Table 2 for detailed information) are also known to exhibit Zn(II) resistance potency via the ccc operon (Arroyo-Herrera et al., 2020; Kang et al., 2020).

Another transcriptomic study in Pseudomonas putida strain KT2440 revealed that under Zn(II) stress, along with zinc resistance genes (e.g., cadA1, cadA2, czcCBA1, and czcD), several arsenic resistance genes belonging to two arsenic operons - arsRBCH1 and arsRBCH2 - are significantly upregulated. A downstream proteomic study in that organism also exhibited that, under zinc stress, the multidrug and metal efflux system related genes were upregulated whereas genes related to membrane proteins were found to be downregulated (Peng et al., 2018). Comparative transcriptomic analysis by Wang H. et al. (2020) also revealed the upregulated expression of gene zntA in Chryseobacterium sp. WAL2 in the presence of montmorillonite. This study hinted toward the role of montmorillonite as a positive regulator of metal detoxification related genes in diverse microbial groups, but requires further in-depth investigation in future.

Mechanism of Ni(II) Resistance

Intercellular accumulation of Ni(II) followed two different uptake systems. These include either a single polypeptide chemiosmotic system or a five component ABC uptake system (Mulrooney and Hausinger, 2003). An earlier study by Navarro et al. (1993) also reported the presence of two separate energy dependent Ni(II) uptake systems in E. coli, which include a non-specific high affinity magnesium uptake system and another highly specific, low capacity system encoded by nik operon. The nik operon (comprised of five genes: nikA, nikB, nikC, nikD, and nikE) remain activated at high Ni(II) concentrations, the transcription is ceased and Ni(II) is found to be transported using magnesium uptake system. Another study by Liu et al. (2020) reported the upregulation of nikB and nik genes in PGPB isolates Paenibacillus polymyxa YCO136 in the presence of root exudates of tobacco. So far, Ni(II) resistance in several bacteria involve cnc/ncr/nreB like tolerance system (Stoppel and Schlegel, 1995) which encode Ni(II) efflux proteins that extruded out Ni²⁺ from cytoplasm to the extracellular environment. Generally, cnc or ncr gene clusters responsible for the synthesis of efflux protein belong to RND type transporter whereas efflux systems encoded by nreB belong to MFS superfamily (Nanda et al., 2019). However, ncr system in Leptospirillum ferrphilum and cnc system in Cupriavidus metallidurans pMOL-28 are some well-characterized Ni(II) detoxification systems in prokaryotes (see Figure 2) (Tian et al., 2007; Mazhar et al., 2020) Nonetheless, several PGP Ni(II)-resistant bacterial isolates are reported where bio-adsorption of Ni(II) on the cell surface is found to be the most predominant resistance mechanism. Notably, metal-stress-induced transcriptome analysis of Sphingobium spp. revealed the upregulated expression of genes [NerB-like permease, a specific protein of secondary metal transporter family (HupE/UreJ)] coding for nickel resistance and other metal ion efflux systems along with overexpression of CopA, CopB, and CopC proteins that are involved in Copper resistance. This indicates the interlinking metal resistance potential in this organism (Volpicella et al., 2017).

Summarizing the Genomics of Major Plant-Growth-Promoting Attributes, Characterized so Far in Diverse Bacteria

Organisms with physiological potential, such as production and distribution of plant growth-promoting hormones...
like IAA/GAs, phosphate solubilization, nitrogen fixation, siderophore production, ACC deaminase production, and biofilm formation, are usually considered as potential plant growth-promoting candidates. Current advancements and the emerging picture of high-throughput genomic data helps in decoding a number of PGP bacterial genomes and relevant gene encoding proteins in distantly related microbial group isolated from diverse habitats.

Although microbes have the ability to produce multiple phytohormone, here we restricted our discussion to auxin. However, so far as the auxin-producing genes are concerned, mostly it has been characterized from bacteria thriving in rhizosphere (Spaepen and Vanderleyden, 2011); however, we detected a number of auxin-producing genes in the genome of several gut bacteria with high auxin production efficiency (Cox et al., 2018). A study by Indiragandhi et al. (2008) also revealed the presence of auxin-producing genes in several PGPB members isolated from gut environment, however delineation of the genetic basis of such attributes were not reported in that study. Microbes with such auxin production efficiency can significantly influence the plant growth and root architecture. In this context, the trp gene cluster plays a critical role in the biosynthesis of tryptophan (central metabolic precursor of auxin) from the chorismite. There are at least five different biochemical pathways for auxin production characterized so far in various PGP bacteria (e.g., members of Azospirillum spp., Bacillus spp., Bradyrhizobium spp., Enterobacter cloacae, Paenibacillus spp., Pseudomonas spp., Rhizobium spp., Acinetobacter spp., and Aeromonas spp.) (Spaepen et al., 2007; Yadav et al., 2017). For instance, pathways like indole-3-acetaldehyde (IAAld), indole-3-acetamide (IAM), indole-3-acetamide (IPDC), indole-3-pyruvate decarboxylase (IPAc), and tryptophan (Trp) were found to be operative either singly or in combination (Spaepen et al., 2007). Relevant genes for auxin production are either found to be present in plasmid (Agrobacterium spp.) or in chromosme (P. syringae, Pantoaea agglomerans) of diverse bacteria (Mole et al., 2007). High-throughput genetic and proteome level investigation emphasized the involvement of some major auxin-producing enzymes: Amino transferase, Trp monoxygenase, Nitrilase, Nitrile hydratase, IAM-hydrolase, Trp decarboxylase, Amine-oxidase, tryptophanase, tryptophan, and synthase (Spaepen et al., 2007). Transcriptomic study of PGPB members of Paenibacillus polymyxa YCO136 showed the upregulation of several metal resistance genes along with genes that are related to auxin production as well as phosphate solubilization (Liu et al., 2020). Due to the presence of multiple biochemical pathways, in-depth knowledge regarding genetic systems of auxin production still requires some more attention as these organisms could be used as important bioresources toward sustainable agriculture in the near future.

From the perspective of PGP attributes, microbe-mediated phosphate solubilization (conversion of insoluble phosphate into bioavailable form to the plants) potential holds substantial importance in the agricultural sector. Bacteria with such potential are being characterized and isolated from diverse ecosystems/niche (soil ecosystem/ectorrhizospheric region/ as an endosymbionts). These currently include Acinetobacter spp., Pseudomonas spp., Enterobacter spp., Arthrobacter spp., Cellulosimicrobium spp., Desemzia spp., Flavobacterium spp., Providencia spp., Bacillus spp., Serratia spp., Burkholderia spp., and Erwinia spp. (Goswami et al., 2016; Behera et al., 2017; Yadav et al., 2017; also see Supplementary Table 2 for detailed information). Acidification, chelation, and polymeric substances formation are some of the important mechanisms via which phosphate-solubilizing bacteria (PSB) act on mineral phosphates. However, the most common mechanism shown by maximum PSB is the production of low molecular weight organic acids (e.g., gluconic acid, oxalic acid, citric acid, acetic acid, succinic acid, etc.) with substantial lowering of the soil pH (Suleman et al., 2018; Wei et al., 2018). Genomic surveys of PSB highlighted the presence of several essential genes/enzymes involved in P-solubilization, such as glucose dehydrogenase (gcd), acid phosphatase (AphA), phosphatase, inorganic diphosphatase, alkaline phosphatase (AP), and sugar-phosphatase. Nonetheless, a few other accessory enzymes like phosphoenolpyruvate carboxylase (Pepc) have also been identified in several organisms responsible for the increase in supply of oxaloacetate, a vital anabolic precursor and an intermediate in biosynthesis of organic acids in phosphate (P) solubilization (Buch et al., 2010). Moreover, a previous study reported that enzymes like exopolyporphosphatase (Ppx) and polyporphosphate kinase (Ppk) could also be involved in the hydrolysis of inorganic polyphosphate P to release orthophosphate (Kaur et al., 2016).

Conventionally, siderophores are iron chelating low molecular weight (<1 kDa) compounds that are synthesized by various groups of microbial genera in response to low iron availability in their native environment (Goswami et al., 2016). These components play a considerable role in improving plant health through several mechanisms, i.e., mitigating the iron nutrition deficiency of host plant or preventing the growth of deadliest phytopathogens by limiting their iron availability. Multiple bacterial genera, such as Rhizobium spp., Mesorhizobium spp., Streptomyces spp., Burkholderia spp., Bacillus spp., and Pseudomonas spp. have been isolated with such siderophore production efficiency (Saharan and Nehra, 2011). Among many, some of the well-studied microbe-derived siderophore components are aerobactin, vibriobactin, bacillibactin, and enterobactin. Although functionally all siderophore components are the same, their chemical nature [catecholates (phenolates), hydroxamates, and carboxylates (e.g., derivatives of citric acid)] and genetic determinant vary significantly. For instance, aerobactin (hydroxamate-type siderophore) synthesis is tightly regulated by iuc (iron uptake chelate; encompassed with iucABCD genes) and iut (iron uptake transport; having iutAC genes) operon, identified and characterized in various bacteria such as E. coli, Gluconacetobacter spp., Micromonospora spp., and Acinetobacter spp. (Mihara et al., 2004; Logeshwaran et al., 2009; Ortúzar et al., 2020). On the contrary, genes [viuPDGC ABF (utilization related genes); vibABCDDEH (biosynthesis related genes)] involved in vibriobactin biosynthesis/utilization are not clustered in a single locus; rather they are scattered throughout the genome (Crosa and Walsh, 2002). In the
case of enterobactin biosynthesis, genes such as entA (encode for 2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase), entB (encode for 2,3-dihydro-2,3-dihydroxybenzoate synthetase), entC (encode for isochorismate synthetase), and EntEFB are found to be involved (Crosa and Walsh, 2002). Notably, some siderophore components like anguibactin (encoded by angCNHUTR genes), pyochelin (encoded by pchDCBAEF genes), yersiniabactin (encoded by YbtEUTSXQP genes), and mycobactin (encoded by mbtABCDEFGHIJ genes) are also known to play important roles in iron acquisition/uptake/chelation in various organisms.

In the context of potential PGP traits, 1-aminocyclopropane-1-carboxylic acid deaminase (ACC deaminase; encoded by acdS gene)-producing bacteria perform a vital role by blocking the synthesis of ethylene, thereby improving plant-fitness potentiality under many biotic stresses such as drought, salinity, or floods (Glick 2005). So far as its structural features are concerned, it is a multimeric enzyme (homodimer or homotrimer that uses pyridoxal 5-phosphate per subunit as a critical cofactor) with a molecular weight ranging between 35 and 42 kDa (Ali and Kim, 2018). Interestingly, several previous works report that production of this enzyme can be triggered in bacteria (Pseudomonas spp., Achromobacter spp., Serratia spp., Herbaspirillum spp., Ochrobactrum spp., Mesorhizobium spp., etc.) by inducing stressed conditions (Ali and Kim, 2018). Notably, several studies reported an LRP-like protein-coding region present in the close vicinity of many acdS genes in diverse bacteria (Rhizobium spp., Azospirillum spp. etc), termed acdR (ACC deaminase regulatory protein), which is required for optimum ACC deaminase production (Prigent-Combaret et al., 2008). Nevertheless, the presence of ACC deaminase is not only restricted within bacteria; rather their distribution is also reported in plant and fungal kingdoms, although their sequence composition varied greatly (Nascimento et al., 2014).

Moreover, in the context of PGP traits, nitrogen fixation ability of different PGPBs is considered as a key trait involved in plant growth promotion under heavy metal stress. Vicente and Dean (2017) exhibited the simplest form of molecular mechanism of nitrogen fixation by diazotrophs, while highlighted the promising research endeavor for developing genetically modified cereal plants capable of producing their own functional nitrogenase and subsequently able to perform nitrogen fixation function. Bacteria from a wide range of habitats are found to be capable of nitrogen fixation using oxygen sensitive metallozyme nitrogenase, which share common features of catalytic mechanism and assembly of metal-containing cofactors, which are important for its function. It has been observed that nitrogenase contain two catalytic parts: one is dinitrogenase reductase that serves as a nucleotide dependent system of electron delivery to another part of nitrogenase which, after receiving a sufficient amount of electrons from reductase, binds with nitrogen (N2) and converts it into ammonia (Vicente and Dean, 2017). Moreover, nif genes are found to be responsible for governing such nitrogen fixation. Nonetheless, diversity of diazotrophs is also responsible for altering soil fertility and optimizing plant growth, as it links directly/indirectly with the expression of nifH gene. Notably, nifH gene being highly conserved among diazotrophs serves as an indicator organism of soil (Chakraborty and Islam, 2018). The study by Chakraborty and Islam (2018) pointed out the fluctuation pattern in the abundance of proteobacteria and diazotrophs under arsenic stress. However, qPCR-based analysis of highly conserved 16S rRNA gene and nifH gene at higher arsenic concentration (10 ppm) showed significant reduction in the copy number of nifH gene, which indicated the decrease in diazotrophic population, whereas it remained unaltered where arsenic stress was lower (6 ppm). They have also suggested that factors like pH, arsenic, and (PO4) is also linked with the fluctuation of nifH gene abundance. On the other hand, 16S rRNA gene-based diversity analysis revealed an increase in proteobacterial abundance with increased concentration of arsenic (Chakraborty and Islam, 2018). A similar finding was also reported by Chakraborty et al. (2019); they showed the decrease in expression of nifH gene and EPS production of arsenic oxidizing free living diazotrophs by members of Bacillus spp., Klebsiella spp., and Burkholderia spp. at higher arsenic concentrations.

**Interrelation Between Bacterial Plant Growth Promoting Traits and Metal Resistance Mechanism for Stress Amelioration in Plants**

Association of PGPB with their native host plant plays an instrumental role in their survival, especially during stressed conditions. Out of many components, heavy metals pose serious stress to plants that ultimately causes severe irreversible damage (see Table 1 for detailed information). To combat such issues, PGPB was found to play a critical role and remain associated with their host in metal-contaminated soil. A large number of PGPB have been isolated and characterized from diverse habitats which include rhizospheric soil, phyllosphere, costal sediments, heavy metal mine areas, sewage sludge, tannery effluents, endophytes, and root nodules (see Supplementary Table 2). PGPB have several traits that play important roles in plant growth promotion during heavy metal stress as well as metal detoxification. These are as follows.

**Role of Phytohormones Under Heavy Metal Stress**

It has been known for a long time that a large number of bacterial candidates have the ability to produce different plant growth hormones (gibberellic acid, cytokines, auxins, etc.). Of these, bacterial-derived auxin, especially IAA, gained significant attention as it plays a major role in plant growth promotion under such heavy metal stress (see Supplementary Table 2). Bacteria with such potency thus far include members of Pseudomonas spp., Bacillus spp., Serratia spp., Rhizobium spp., Mesorhizobium spp., Sinorhizobium spp., Burkholderia spp., Achromobacter spp., Azotobacter spp., and Paenibacillus spp. (see Supplementary Table 2). IAA not only helps plants to sustain metal tolerance by physiological changes but also enhances branching of plant roots and thereby aids nutrient uptake capacity under heavy metal stress (Etesami,
2018). Several reports also suggested that, during plant growth, IAA also loosened the cell wall of root cells which resulted in excess secretion of nutrient rich root-exudates in the surrounding environment, which eventually attracted native microbial populations of root rhizosphere (Bacilio-Jiménez et al., 2003). Root-exudates secreted in such a way contained components like phytochelatins and organic acids that subsequently prevent the entry of heavy metals in symplastic path (Manara, 2012).

**Roll of ACC Deaminase Under Heavy Metal Stress**

Under heavy metal stress, ACC deaminase promotes plant growth by inhibiting the generation of plant hormone ethylene which forms during different biotic and abiotic stresses, causing early senescence in plants (Glick, 2005). ACC deaminase cleaves the 1-aminocyclopropane 1-carboxylic acid, which is a precursor of ethylene, into α-ketobutarate and ammonia. (Carlos et al., 2016) reported the positive plant growth promotion effect of two ACC deaminase-producing bacteria Klebsiella Mc173 and Serratia K120 on Helianthus annuus under Ni(II) and Cd(II) stress. It has been observed that ACC deaminase activity of both strains remained unaffected in the presence of Ni(II) and Cd(II). A large number of heavy metal resistant plant growth-promoting bacteria has been isolated and reported to produce ACC deaminase (see Supplementary Table 2 for detailed information).

**Role of Siderophore Under Heavy Metal Stress**

Although plants reportedly produce phyto-siderophore to acquire Fe, it has been reported that bacterial-derived siderophore have a greater affinity toward iron (Etesami, 2018). Additionally, bacterial siderophores are reported to have the ability to bind with a number of different heavy metals, thereby immobilizing them and reducig their bioavailability to plants under heavy metal stress. A large number of PGPB isolates were reported to produce siderophores under such heavy metal stress (Zloch et al., 2016; Yang et al., 2018; Md Badrul Hisham et al., 2019; Sun et al., 2021).

**Role of Nitrogen Fixation Under Heavy Metal Stress**

Nitrogen fixation has been reported in a number of plant growth-promoting diazotrophs isolated from diverse habitats, many of which were found to have multi-metal tolerant potency. Nowadays, nitrogen fixing bacteria serve as key players as bioindicators of heavy metal contamination in soil. In this connection, two important studies by Chakraborty and Islam (2018) and Chakraborty et al. (2019) reported a decrease in population of nitrogen-fixing diazotrophs at higher concentrations of arsenic while the abundance of proteobacteria was found to be increased. Moreover, they also reported a decrease in EPS production among free living diazotrophs under high arsenic stress. However, in general, EPS production was found to be increased along with increased metal concentration to protect bacteria from metal stress. This metal resistance endeavor eventually created a microaerobic environment where free living diazotrophs were able to fix N₂ and subsequently support plant growth under heavy metal stress. This is another classic example of an interdependency relationship between heavy metal resistance and PGP traits in PGPB members.

**Role of Phosphate Solubilization Under Heavy Metal Stress**

Phosphate solubilization by PGPB or other microbes is a major plant growth promoting phenomenon, where the phosphate solubilizing bacteria (PSB) solubilized the mineral phosphate in rock and created a pool of bioavailable soluble phosphate in soil, which is further taken up by plants. Several bacterial-derived organic acids by PSB and lowering of pH and/or phosphatase enzyme activity are thought to be responsible for phosphate solubilization (Chen et al., 2006; Wei et al., 2018). These bioavailable phosphates eventually immobilized different heavy metals by complexation and reduced their bioavailability to plants. For example, immobilization of Pb(II) by formation of pyromorphite has been observed in Enterobacter cloacae (Park et al., 2011). Additionally, binding of heavy metals to the cell surface by forming phosphate-heavy-metal-complex has been reported for Pb(II) and Cd(II) adsorption by amide and carboxyl groups on cell surface of Enterobacter sp., Bacillus sp., and Lactococcus sp. (Yuan et al., 2017). For both instances, concerned heavy metals were found to be immobilized and insoluble, thus reducing the bioavailability and its stress generation capacity. A number of multi-metal tolerant PGPB from diverse habitats with phosphate solubilization ability has been reported and characterized over the past two decades (see Supplementary Table 2 for detailed information). Moreover, organic acid produced by PGPB/PSB members has a higher affinity for heavy metals and was also found to be involved in immobilization of such metals by complexation, thereby reducing heavy metal stress on plants (Najeeb et al., 2009; Gadd, 2010; Islam et al., 2016).

**Role of Antioxidants Under Heavy Metal Stress**

In the generation of reactive oxygen species, superoxide during heavy metal stress is one of the most expected events reported for both plants and animals (for details see Table 1). This heavy-metal-induced oxidative stress was reported to cause massive irreversible damage to DNA and cellular proteins (Islam et al., 2014). Furthermore, heavy-metal-induced oxidative stress resulted in a massive reduction in yield of several economically important crops, including Oryza sativa (rice), Triticum aestivum (wheat), and Zea mays (maize) (already mentioned in brief in Table 1). To combat such oxidative stress, plant cells produce several antioxidant enzymes like superoxide dismutase, catalase, peroxidase, and glutathione reductase. Several reports indicated that PGPBs like Azotobacter chroococcum and Proteus mirabilis can induce antioxidant systems in Zea mays so that the plant becomes more tolerant toward metals like Cu, Zn, and Pb (Islam et al., 2014; Rizvi and Khan, 2018). Additionally, PGPB was also found to produce several such enzymatic (such as catalyze and peroxidise) (Karthik and Arulselvi, 2017) and non-enzymatic (such as proline and glutathione) defense mechanisms that were
eventually found to be involved in lowering the heavy-metal-induced oxidative stresses in plants (Islam et al., 2014; Rizvi and Khan, 2018).

**Meta-Omics Perspective in Exploring the Structure-Function of Metal-Remediating Microbiota**

Nowadays, the “meta-omics”-based approach offered a number of advantageous strategies in exploring microbiome framework, community dynamics, and metabolic networking in diverse environments (metagenomics, metatranscriptomics, metaproteomics, and metabolomics) that curtail different constraints posed by conventional culture dependent approaches. In the context of arsenic remediating microbiome, the work of Bertin et al. (2011) highlighted the use of the genome-binning approach that exhibited the prevalence of seven bacterial strains (contigs affiliated to novel bacterial phylum *Candidatus “Fodinabacter communificans”* β-Proteobacterium *Thiomonas* genus, Acidobacteria clade and *A. ferrooxidans* γ-Proteobacterium) in extreme habitats (e.g., acid mine drainage) with genetic potential for arsenic resistance [oxidizing As(III) into As(V) and their subsequent co-precipitation with sulfur] (Bertin et al., 2011). Among the seven genome bins reconstructed from the metagenomes, CARN6 contained the gene *arsM* encoding arsenite S-adenosylmethyltransferase which was further validated by the presence of monomethylarsonate and dimethylarsinate in their native habitat (Bertin et al., 2011). Subsequent metaproteomic-based investigations by the same group revealed the presence of *Pst* system which potentially influences the controlled uptake of As(V) in their inherent environment. Moreover, this study also unraveled the high-level expression of genes that were potentially involved in biosynthesis of biofilm, capsule, flagella, and pili, indicating that these components indeed have persuasive connection with metal-resistant genes (Bertin et al., 2011). In this connection, the functional importance between biofilm formation and immobilization of different heavy metals in metal-contaminated mine waters is further enlightened by the work of Drewniak et al. (2016). In total, 2% sequence reads were found to be ascribed for genes related to biofilm formation which indicates that biosorption might be a major process for sequestration of those heavy metals (Drewniak et al., 2016). Notably, another omics-based diversity study by Li et al. (2015) revealed that microbial community composition caused significant fluctuation between low and high arsenic containing samples collected from groundwater and sediments. Bacterial genera like *Acinetobacter*, *Pseudomonas*, *Psychrobacter*, and *Alishewanella* were found to be most abundant in high arsenic-containing groundwater systems, while *Thiobacillus*, *Pseudomonas*, *Hydrogenophaga*, *Enterobacteriaceae*, *Sulfuricurvum*, and *Arthrobacter* were found to be prevalent in high arsenic-containing sediment systems. Moreover, another separate metagenomic study by Wang et al. (2016) revealed the selective prevalence of certain bacterial genera (such as *Alishewanella*, *Psychrobacter*, *Methylotenera*, and *Crenothrix*) in high arsenic-containing groundwater systems of diverse geographical distribution, while *Rheinheimera* and the unidentified OP3 group were found to be abundant in low arsenic-containing groundwater systems. In this context, another study by Han et al. (2017) examined the impacts of As on bacterial communities’ structure and their functional genetic determinants in the rhizosphere of *As*-hyperaccumulator plant *Pteris vittata* and reported that *aroA*-like genes were found to be more prevalent than *arsC* genes where As(V) was present in high concentrations in the soil. These studies actually exhibited how arsenic influences the bacterial community architecture in diverse environments. Moreover, another important study by Yu et al. (2020) revealed that cyanobacterial population (85.89%) was found to be present as dominant taxa among the diazotrophic microbial community studied in the citrus orchard where heavy metals like Pb, Cd, Cu, and Zn are present in higher concentrations. However, they also mentioned the dominance of other phylum types, which includes phylum like Proteobacteria, Firmicutes, and Verrucomicrobia, in different habitat types contaminated with the aforementioned heavy metals. High abundance of such candidates in metal-contaminated habitats sheds new light on their roles as key players for natural metal-remediation while maintaining the ecosystem balance. Omics-based functional gene analysis in other habitats, like activated sludge, coastal sediments, mangrove sediments, and contaminated ground water, revealed the functionality of various metal-resistant genes such as *ChrA* (encoding chromate transport protein), *ACR3* (encoding arsenic resistant protein), *CusA* (cation efflux system protein), *CzCA* (cobalt-zinc-cadmium resistance protein) *aioA* (arsenite oxidation), *aroA*, *ACR3*, *arsM* (arsenite methylation), *aroA*, *arrA*, *arsB*, and *arsC* (Cai et al., 2013; Luo et al., 2014; Cabral et al., 2019; Cavalca et al., 2019). However, so far as the metal-remediating microbiome architectures are concerned, microbial taxa like members of Firmicutes, Clostridiales, Verrucomicrobia, Methylococaceae, Methylophilaceae, Rhizobiaceae, *Burkholderia*, *Leptothrix*, *Thiobrix*, *Geobacter*, *Rhodococcus*, *Azoarcus*, *Rhodanobacter*, *Pseudomonas*, and *Beggioa* are reported as predominant groups (Cai et al., 2013; Cabral et al., 2019; Cavalca et al., 2019; Wang L. et al., 2020) in most arsenic-contaminated ecological diverse environments. For the revelation of any pollutant-degrading novel microbial diversity, an amplicon sequencing (sequencing the hypervariable regions of the 16S rRNA gene) based approach is equally as important (cost-effective) as a metagenome approach. Ample work has been published in this regard that highlighted the presence of certain bacterial genera (e.g., *Pseudomonas* spp.; *Methyllobacillus* spp.; *Solirubrobacter* spp., *Ohtaekwangia* etc.) in arsenic-contaminated sites as a major group (Kou et al., 2018; Espinosa et al., 2020). Notably, along with metagenomics, the use of stable isotope probe technique is also found to be effective in the revelation of nitrate dependent As(III) oxidizing bacterial members like *Azoarcus*, *Rhodanobacter*, and *Pseudomonas*, from arsenic-contaminated soil systems (Zhang M. et al., 2020). In meta-omics connection, another term “Fluxomics” has recently been introduced in the scientific community (Chandran et al., 2020). This approach is concerned with the estimating fluctuation and/or rate of metabolic reactions and predicts the fate of different metabolic
process as well as intermediates in biological organisms. For instance, fluxome profiling approach was successfully used in the case of one marine strain of *Shewanella* for deciphering the co-metabolic pathways for the biodegradation of lethal metals, halogenated organic compounds, and radionuclides (Tang et al., 2007). Nonetheless, using a metagenomic survey, several groups also reported the presence of potential arsenic reduction (80% metagenomic reads ascribed for this) by methylating/efflux related genes (6–9% metagenomic reads ascribed for this) in wetland environments like paddy soil (Xiao et al., 2016; Imchen et al., 2018). Notably, in a separate study conducted by Shi et al. (2019), the As(V) and Hg(II) bioremediation efficiency in methanotrophic bacterial members such as *Methylocystis* sp. HL18, whose assembled genome encompassed with operons like mer (having genes like merR, merT, merP, merC and merA), arsRCB, and arsRCCB, were reported (Shi et al., 2019). In this connection it is noteworthy to mention that functional-protein-based phylogenetic analysis (MerA, arsRCCB) indicates acquisition of metal-remediating genes in this organism follow a horizontal path of gene transfer, a phenomenon that hints toward the new possibilities for getting bioremediation potency in novel taxonomically diverse bacterial groups that has not been explored till date.

On some occasions it has been observed that bioremediating bacteria also has influence in other biogeochemical cycles. For instance, a functional marker gene and metagenome-based study that dealt with bacteria (*Capriavidus metallidurans* MSR33) assisted mercury bioremediation efficiency and microbial community dynamics in a soil ecosystem unveiled that the removal of mercury (82%) from the soil system significantly increased the nitrogen fixing and nitrifying bacterial population (Bravo et al., 2020). On the contrary, a few works also used biomarker genes and metagenomics as ecological-indicator tools to detect some toxic pollutants like “methylmercury.” Genes like *hgcAB* that participate in Hg-methylation process [conversion of mercury (Hg) to MeHg] were efficiently used as biomarkers of diverse mercury-mercury contaminated environments that includes riverine areas, tidal marshes, and arctic permafrost (Christensen et al., 2019). A functional omics approach was also successfully used to explore the metallothionein-related genes [responsible for Cu(II) resistance] in a Cu-contaminated soil environment. Later on, downstream cloning and overexpression of these metallothionein-related genes were also used to develop recombinant strains that had better survival efficacy under metal stress along with greater absorption capacity for certain metals like cadmium, copper, and zinc (Liu et al., 2019). Notably, another important study by Wang et al. (2007) pointed out the effect of heavy metal stress in regulating microbial community composition and enzyme activity in soil environment. Recently, another comparative metatranscriptomic and metagenomic study in industrial wastewater discovered the presence of six novel genes potentially involved in Cr(VI) resistance. Out of six, two genes, *gsr* (general stress response protein) and *mer* (membrane chrome reductase), when cloned and expressed in *E. coli* efficiently remove 50% of Cr(VI) out of 200–600 µm Cr(VI) (Pei et al., 2020). In this context, a recent finding by Ma et al. (2020) sheds new light on the role of minerals like phosphorus in changing bacterial population dynamics and subsequent Cr(VI) reduction efficiency in chromium-contaminated environments (Ma et al., 2020). They used an amplicon sequencing approach for microbial diversity analysis both in the presence and absence of liquid phosphorus (LP) and phosphorus (NP). In an LP system, *Aeromonas* spp. and *Acinetobacter* spp. etc. occurred as a prevalent microbial group, whereas *Alcaligenes* spp. and *Parabacteroides* spp. etc. were found to be abundant in an NP system. Interestingly, genera like *Delftia*, *Stenotrophomas*, and *Comamonas* disappeared in the presence of phosphorus minerals, while genera like *Pseudomonas* and *Clostridium* were found to be enriched in the presence of different types of phosphorus components (Ma et al., 2020).

### Potency and Prospect of Microbe Assisted Phytoremediation of Heavy Metals

Although plants are prime colonizers, they become highly susceptible when they are exposed to high heavy metal containing environments. Interestingly, it has often been observed that several socio-economically important crops have the ability to accumulate high concentrations of heavy metals in metal-contaminated sites. Reasonably, such phenomenon ultimately resulted in severe health hazards through the process of biomagnifications. Nevertheless, there are several non-crop plant species encompassed with high metal resistance/accumulation efficiency that also exist in nature, commonly regarded as metallophytes (e.g., *Thlaspi caerulescens*, *Psyticota vanhennerni*, *Viola calaminaria*, and *Pteris vitata*). Surprisingly, these plant systems have been undervalued since their discovery in remediation purposes (Khan, 2005; Marques et al., 2009). Notably, a number of heavy metal resistant plant growth-promoting bacteria were reported to enhance metal accumulation (e.g., Cr, As, Cd, Cu, Hg, Pb, Ni, and Zn) in large numbers of crop/fodder plants (such as maize, tomato, black mustard, rapeseed, and Indian pea) (Ma et al., 2009; Cruz Medina et al., 2013; Ahmad et al., 2016; Kamran et al., 2016; Franchi et al., 2017; Abdelkrim et al., 2018). In this context, use of these microbes as bioinoculant/biofertilizer was obviously subjected to objectionable concern when they can be employed safely for the growth of hyperaccumulator plants, which are able to remediate agricultural soil due to their massive accumulation potency. Additionally, these plant biomass can also be used in energy production purposes (Ma et al., 2010). Therefore, phytoextraction can be considered as a most pertinent approach in the domain of bacteria-assisted phytoremediation strategies. Notably, a few studies also reported the enhanced accumulation of different heavy metals in plant roots only in the presence of plant growth-promoting bacteria, which suggests their probable future application in remediation strategies like phytofiltration (Moreira et al., 2014; Rojjanateeranaj et al., 2017). Even though these are very promising strategies for remediation of agriculturally important soil, improved understanding on molecular-genomic basis of plant-microbe-metal interaction is a prerequisite before its vast environment application of agronomic benefits for farmers.
FIGURE 3 | Heat map comparing the different levels of heavy metal resistant efficiency in several majorly studied bacterial genera having plant-growth-promotion attributes. Two-dimensional clustering is also shown involving the 10 major heavy metals on one hand and 67 representative bacterial genera on the other. Concentration of heavy metals are calculated and expressed using mg/L unit.
DISCUSSION AND CONCLUSIVE REMARKS

Along with genomics/molecular mechanism-based discussion, here we also tried to summarize the global scenario of bacteria-assisted metal remediation potential using a heat-map approach. Accordingly, Figure 3 exhibited the bioremediation potency of different toxic heavy metals by phylogenetically and ecologically diverse bacteria with plant growth-promoting traits. Remarkably, multi-metal tolerance ability was only found in the case of genera like Bacillus (belong to the phylum Firmicutes), Acinetobacter, Pseudomonas, and Rhizobium (three genera that belong to the phylum Proteobacteria). However, among the studied bacteria, Hg(II) tolerance potentiality was only shown by certain bacterial genera, out of which Bacillus shows very promising results [4,011 mg/l Hg(II)]. Notably, various PGP members of Bacillus, Azotobacter, and Paenibacillus reported so far have high Pb(II) tolerance ability (<5,175 mg/l) while members of Acinetobacter have the highest Pb(II) capability (16,000 mg/l). So far as the As(III) and As(v) metalloids are concerned, the highest tolerance ability was found in Exiguobacterium [13,485 and 52,444 mg/l for As(III) and As(v) respectively], Pseudomonas [59,936 mg/l for As(V)] along with Rhodococcus [52,444 mg/l for As(V)], and Acinetobacter [50,000 mg/l for As(V)]. Notably, several PGP members of proteobacteria were found to be competent for tolerance of other heavy metals. For instance, Sphingomonas efficiently tolerates high concentration of heavy metals like Cd(II), Zn(II), and Co(II) (10,000 mg/l); Cupriavidus can tolerate the highest Ni(II) concentration (2,948 mg/l). Providencia had the highest Cu(II) tolerance ability (63,540 mg/l), whereas Cellulosimicrobium had the ability to tolerate Cr(VI) at a concentration of 23,395 mg/l. Considering the current state of knowledge, it has been observed that most of the bacterial-heavy metal tolerance mechanisms have been reported for As, Pb, Zn, and Cd. In this context, it is noteworthy to mention that other heavy metals, particularly Hg and Cr, needs special attention and indeed require further investigation. From the perspective of socio-economic progress, we cannot overlook the importance of industrial development; at the same time, the necessity of a sustainable pollution-free ecosystem cannot be ruled out. With the rapid development of modern meta-omics, comparative genomics, and molecular and/or system biology techniques, various groups have already made significant progress in the field of pollutant microbiome research. This will help us to combat nefarious heavy metal pollution issues and unravel the complex microbial population dynamics and their trophic interaction. Throughout this review, we have made an effort to decode the molecular genetic basis of heavy metal detoxification/resistance potential (having PGP traits) from bacteria with diverse taxonomical and ecological spectrums. Deeper molecular-genetic understanding of these potential microbes involved in such processes brings to the fore novel or advanced bioremediation technologies that could be used to polish our understanding in this regard.

AUTHOR CONTRIBUTIONS

SM conceived the idea of the review, provided the general concept and inputs for each specific section, drafted part of the manuscript, and wrote the review in conjunction with NM. SM and NM edited, compiled, and finalized the draft. KS participated in manuscript writing and extensive data mining. All authors contributed to the article and vetted the submitted version of the manuscript.

SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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