

REVIEW ARTICLE

Mechanisms of Bacterial Resistance to Heavy Metals: A Mini Review

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ABSTRACT

Because of rising levels of heavy metal pollution in the environment, microbial resistance to heavy metals has become an increasing concern. Heavy metal resistance in bacteria is typically achieved through a combination of passive and active mechanisms, including heavy metal sequestration, efflux, or transformation within the microbial cell. During the efflux mechanism, a membrane protein's energy-dependent ion efflux from the cell is necessary for heavy metal removal. Understanding the physicochemical parameters of the environment, structure and diversity of microbial communities, nature and concentration of heavy metals is critical for developing effective strategies for the remediation of heavy metal-contaminated sites. Many microbes play a significant part on functioning ecosystem more especially in the biogeochemical cycling of heavy metals by removing the metals from the environment. As, Pb, Cd, and Hg are among heavy metals that are associated with the most common ecologically hazardous metals that can be toxic to microbes and still nature has evolved few groups of microbes that were found to resist the effect of heavy metals while thriving within their ecosystem such as Pseudomonas sp., Escherichia coli and Serratia marcescens that can resist Hg. Pseudomonas putida, Cupriavidus necator, Exiguobacterium sp., Bacillus aquimaris, Bacillus cereus and Alcaligenes sp. can also resist Cu, Cd, Pb, Cr and Ni. The exposure of local and regional soil with heavy metal pollution due to smelting causes which poses major environmental issues that is currently on rise in human ecosystem. Therefore, studying the mechanisms of bacterial resistance to heavy metal is critical for developing strategies to reduce the environmental impact of heavy metal pollution.

INTRODUCTION

Heavy metals are metallic elements with a large atomic weight and density. They exist abundantly and are essential for many industrial and technological processes (Singh et al., 2023; Duffus 2002). However, their excessive use and improper disposal have resulted in widespread environmental contamination, seriously threatening human health and the ecosystem (Velusamyet al., 2021). Microorganisms dealt with heavy metals through various mechanisms, including adsorption, accumulation, oxidation, reduction, volatilization, and precipitation. Understanding these mechanisms is critical for developing effective bioremediation strategies to ARTICLE HISTORY

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mitigate the negative effects of heavy metal pollution (Ayangbenro and Babalola, 2017).

Microbial resistance to heavy metals is extremely important in biogeochemical cycles (Kishore et al., 2023). They can tolerate and even thrive in environments with high concentrations of heavy metals by employing various mechanisms to detoxify or immobilize them, which can be intra or extracellular (Roy et al., 2023). Some microorganisms also produce chelating agents, such as siderophores, which are used to sequester heavy metals and make them bioavailable for uptake (Mondal et al., 2-

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023). The diversity of microbial mechanisms for heavy metal detoxification offers an intriguing avenue for developing long-term and cost-effective bioremediation strategies (Mohammed et al., 2011).

The exposure of local and regional soil with heavy metal pollution that smelting causes poses major environmental issues that are on rise in human ecosystem (Luo et al., 2023; Gautam et al., 2023). Understanding the pollution issue and where it comes from in the contaminated soils is crucial (Grabias-Blicharz and Franus, 2023). According to the findings, Pb, Zn, As, and Cd were frequent pollutants found in soils at exceptionally high quantities (Luo et al., 2023). Remediation of the smelted soils is urgently needed due to the severe carcinogenicity, genotoxicity, and neurotoxicity that heavy metals pose (Aslam et al., 2023). The possibility of biomineralization for soils with heavy metal contamination was possible with microbes with good resistance mechanism to heavy metals (Kumar et al., 2023). The present mini review is aimed to explore different mechanisms of bacterial resistance to heavy metals that are vital for the future application of heavy metal resistant bacteria in the bioremediation of different heavy metals polluted environments.

HEAVY METALS

As defined by Koller and Saleh (2018), heavy metals are class of elements with a high density and atomic weight. Because they can accumulate in tissues and interfere with cellular processes, they are frequently toxic to living organisms (Jaishankar *et al.*, 2014). Heavy metals are naturally present in the environment, but are also released by human activities such as mining, industrial processes, and agriculture (Akhtar *et al.*, 2021). Some common examples of heavy metals include:

i. Lead

Lead is a highly toxic heavy metal that can harm the nervous system, cause developmental problems, and have a negative impact on the cardiovascular and reproductive systems. It is frequently found in old paint, polluted soil, and water pipes (Charkiewicz and Backstr, 2020).

ii. Chromium is a chemical element with the symbol Cr and atomic number 24. It is a lustrous, hard, and brittle metal that is widely used in various industrial applications such as stainless steel production, chromate production, and leather tanning. Chromium is also commonly found in the environment, both naturally and as a result of human activities, and is considered a heavy metal. (Farhan *et al.*, 2023).

- iii. Nickel is a chemical element with the symbol Ni and atomic number 28. It is a hard, silvery-white metal that is commonly found in the Earth's crust. Nickel is used in a wide range of industrial applications, such as stainless steel production, battery manufacturing, and electronics. While nickel is an essential trace element for some organisms, it can also be toxic in high concentrations and is considered a heavy metal. (Su *et al.*, 2023).
- iv. Mercury

Mercury is a highly toxic metal that can harm the nervous system development, kidneys and lungs. It is frequently found in contaminated fish as well as dental amalgam fillings (Kim *et al.*, 2016).

v. Cadmium

Cadmium is a toxic metal that can harm the kidneys and bones, as well as have a negative impact on the cardiovascular and reproductive systems. It is frequently found in polluted soil and water, as well as in cigarette smoke (Genchi *et al.*, 2020).

vi. Arsenic

Arsenic is a carcinogenic metalloid that can cause skin, lung, and bladder cancer, as well as neurological and developmental problems. It is frequently found in polluted groundwater and rice (Matta and Gjyli 2016).

CLASSIFICATION OF HEAVY METALS

Heavy metals can be classified based on their toxicity and properties, including:

i. Essential and non-essential metals

Some heavy metals, such as iron, copper, and zinc, are necessary for life in low concentrations but toxic in high concentrations. Others, such as lead, cadmium, and mercury, are non-essential and serve no biological purpose (Jyothi, 2020).

ii. Redox properties

Heavy metals are classified based on their ability to accept or donate electrons, which affects their toxicity and reactivity. For example, metals like chromium and manganese are highly reactive and can produce free radicals that harm cells (Ghori *et al.*, 2019).

iii. Solubility

Heavy metal solubility in water and soil influences their bioavailability and toxicity. Lead and mercury are highly soluble metals that can easily enter the food chain, whereas cadmium and nickel are less soluble and accumulate in soils (Rahman *et al.*, 2019).

SOURCES OF HEAVY METAL CONTAMINATION

i. Natural Sources

Heavy metals are naturally present in rocks, soil, and sediments and can be released into the environment during weathering processes. Natural minerals rich in heavy metals, such as arsenopyrite, galena, and sphalerite, can contribute to heavy metal contamination. Volcanic activity can also cause heavy metals to be released into the atmosphere, and volcanic ash can pollute soil and water. Furthermore, natural deposit erosion can transport heavy metals into surface and groundwater (Tabelin *et al.*, 2018).

ii. Anthropogenic Sources

Anthropogenic activities are the main sources of heavy metal contamination in the environment. Mining and processing of ores, such as copper, lead, and zinc, can release large amounts of heavy metals into the environment, contaminating soil, water and air. Smelting of metal ores and production of metal products can also release heavy metals into the environment, as can electroplating, which uses heavy metals such as chromium, cadmium, and nickel. Industrial and agricultural activities, such as the use of fertilizers, pesticides, and sewage sludge, can also contribute to heavy metal contamination. Improper disposal of waste, including electronic waste and batteries, can also release heavy metals into the environment (Vareda *et al.*, 2019).

BACTERIAL RESISTANCE TO HEAVY METALS

Heavy metals are toxic to microorganisms, as they can interfere with cellular processes and cause damage to DNA and proteins (Bhat *et al.*, 2019). However, some microorganisms have developed strategies to counteract these toxic effects and survive in heavy metal-contaminated environments (Pal *et al.*, 2022). Bacterial resistance refers to the ability of bacteria to withstand exposure to heavy metals, antimicrobial agents such as antibiotics, disinfectants, and antiseptics. This resistance can arise through a variety of mechanisms, including genetic mutations, horizontal gene transfer, and selective pressure from repeated exposure to such agents (Guo *et al.*, 2021).

Microbial resistance to heavy metals is a phenomenon in which microorganisms develop the ability to survive and grow in environments that contain high levels of heavy metals (Dweba *et al.*, 2018). This resistance can arise through a variety of mechanisms, including the production of efflux pumps, metal-binding proteins, and detoxification enzymes (Sharma *et al.*, 2021). Some bacteria were reported by different authors to resist an individual or groups of heavy metals (Table 1 : next page).

MECHANISMS OF MICROBIAL RESISTANCE TO HEAVY METALS

Mechanisms of heavy metal resistance by microbes are how microorganisms can survive and grow in environments that contain high levels of heavy metals (Pal *et al.*, 2022). The ability of microorganisms to resist heavy metals is a complex process involving a variety of extracellular and intracellular mechanisms.

Extracellular Mechanisms

i. Efflux pumps

It is important to take into account how bacteria acquire necessary metal ions from the exterior of cells. Metal ions must go via the periplasmic space, outer membrane, and inner cytoplasm of every Gram-negative bacterium in order to reach the cytosol. In contrast, Gram-positive bacteria do not have periplasm, and the presence of porins on the outer membrane allows metal ions to passively diffuse through the membrane in an unselective manner (Frei et al., 2023). А membrane protein's energy-dependent ion efflux from the cell is necessary for heavy metal removal. Instead of carrying out chemical detoxification, this efflux functions as an ATPase or chemiosmotic cation/proton antiporter (Kanekar and Kanekar, 2022). Heavy metals are pumped out of the cell by these transporters. They are energy-dependent and capable of actively pumping heavy metals against the gradient concentration (Ayangbenro and Babalola, 2020).

ii. Extracellular sequestration

Heavy metal-binding molecules can be secreted by microorganisms, resulting in the formation of complexes that are insoluble and can be expelled from the cell (Kosakivska *et al.*, 2021).

iii. Biosorption

Biosorption is defined as the ability of living organisms particularly microorganisms to

accumulate heavy metals from contaminated media (wastewater, soil etc) through metabolically mediated or spontaneous physicochemical pathways of uptake, or as a property of certain types of inactive, non-living microbial biomass which bind and concentrate heavy metals from even very dilute aqueous solutions (Ibrahim et al., 2022). It is a complex process that depends on different- factors like cell physiology, physicochemical factors such as pH, temperature, contact time, ionic strength, and metal concentration, chemistry of the metal ions, cell wall composition of microorganisms (Shamim, 2016).

Heavy metals can be taken up by microorganisms and adhered to their cell surfaces by chelation, ion exchange, or electrostatic interactions (Priya *et al.*, 2022).

iv. Biofilm formation

A biofilm is a group of cells coated in an extracellular polymer matrix that some microbes can create. By physically preventing the entry of

Table 1: Bacterial Resistance to Some Heavy Metals

heavy metals into the cell or by encasing them inside the matrix, biofilms can guard against them. For instance, a study discovered that bacterial biofilms can shield humans from the harmful effects of copper ions (Mahto *et al.*, 2022).

v. Precipitation

Extracellular substances secreted by some bacteria, like carbonates, sulfates, and phosphates, can interact with heavy metals to generate intractable precipitates. Then, these precipitates may be eliminated from the environment or may build up inside the cells of microorganisms (Zhu *et al.*, 2019).

vi. Complexation

Extracellular ligands made by microorganisms can interact with heavy metals to lessen their toxicity and bioavailability. For instance, microbes can create siderophores, which are tiny molecules that can bind to heavy metals and enhance the cell's uptake of those metals (Roskova *et al.*, 2022).

Heavy metal	Bacteria	Reference
Pb	Alcaligenes faecalis strain UBI	Ibrahim et al. (2022)
As	Enterobacter agglomerans	Hamzah <i>et al.</i> (2013)
	Acinetobacter lwoffii	
Cu, Pb, Cd	Bacillus megaterium X4	Velusamy et al. (2011)
Cu	Sphingomonas sp.	Altimira et al. (2012)
	Stenotrophomonas sp.	
Zn, Pb, Cd	Arthrobacter sp.	Nosalova rt al. (2023)
Cu, Co, Ni, Zn, Cr, Cd, Pb	Pseudomonas aeruginosa ASU 6a	Zhang et al. (2014)
Pb, Cr, Zn, Cu	Streptomyces	Prabhakaran et al. (2016)
	Amycolatopsis	
Hg, Cr, Ag	Bacillus sp.	Zhang et al. (2014),
	Pseudomonas aeruginosa	Ibrahim et al. (2022),
	Enterobacteriaceae strain	Prabhakaran et al. (2016)
	Pseudomonas putida	
	Cupriavidus necator	
	Exiguobacterium sp.	
	Bacillus aquimaris	
	Bacillus cereus	
	Alcaligenes sp.	
As, Pb	Bacillus sp.	Prabhakaran et al. (2016)
As, Hg	Bacillus sp.	Prabhakaran et al. (2016)
	Lysinibacillus sp.	
Hg	Pseudomonas sp.	Prabhakaran et al. (2016)
	Escherichia coli	
	Serratia marcescens	

vii. Siderophores Secretion

Certain microbes have the ability to create siderophores with a high affinity for heavy metal ions, enabling them to scavenge these metals from their surroundings and prevent them from building up inside the cell. For instance, bacteria like Pseudomonas and Bacillus can create siderophores that are particular for heavy metals like cadmium, lead, and nickel (Khan et al., 2018). By boosting the intake of vital minerals like iron and detoxifying heavy metal ions that can be damaging to cells, it also confers heavy metal tolerance in bacteria (Alotaibi et al., 2021). This is especially important in situations with high concentrations of heavy metals because they can compete with iron for binding sites on siderophores (Ahmed and Holmström, 2014).

viii. Biosurfactant

Biosurfactants are surface active biomolecules produced by microorganisms; they are ampiphilic secondary metabolites having various properties and functions (Fardami et al., 2022; Lawal et al., 2022). By making heavy metals more bioavailable, biosurfactants can aid in bacteria' resistance to them. Because of their propensity to firmly bond to soil particles and other surfaces, heavy metals can become less palatable to bacteria (Ali et al., 2022). On the other hand, biosurfactants can assist in solubilizing heavy metals and increasing their availability for microbial absorption (Seneviratne et al., 2017). The increased mobility of the metals is another way biosurfactants can help with heavy metal resistance. To enable heavy metals move more freely through the environment, biosurfactants can assist in their desorption from soil particles or other surfaces. This may be helpful for microorganisms that need to access the metals in order to develop or detoxify (Shah and Daverey, 2020).

Intracellular Mechanisms

i. Intracellular sequestration

Binding to intracellular proteins, enzymes, or other biomolecules can sequester heavy metals inside the cell (Riyazuddin *et al.*, 2022).

ii. Enzymatic detoxification

Enzymes produced by microorganisms can transform heavy metals to make them less harmful. Examples include the methylation of Hg (II) to produce less harmful volatile methylmercury by methyltransferases or the reduction of Cr (VI) to Cr (III) by chromate reductases (Saravanan *et al.*, 2022).

iii. DNA repair

i.

11.

By DNA binding and interference with transcription and replication, heavy metals can harm DNA. Microbes may fix this damage using specific DNA repair mechanisms (Kumari *et al.*, 2021).

FACTORS AFFECTING MICROBIAL RESPONSE TO HEAVY METALS

The type and concentration of the heavy metal, the physicochemical properties of the environment, the presence of other contaminants, and the diversity of the microbial community all have an impact on how microorganisms react to heavy metal pollution. It is crucial to comprehend these variables to create efficient and sustainable bioremediation system (Medfu *et al.*, 2020).

Type and Concentration of Heavy Metals Microbes have diverse levels of heavy metal tolerance; some are more efficient than others at removing particular heavy metals (Nanda *et al.*, 2019). Moreover, microbial response might be impacted by the concentration of heavy metals in the environment. Heavy metals can be tolerated and even used as mineral nutrients by microbes at low concentrations (Medfu *et al.*, 2020). However, heavy metals can be hazardous to microbes at high doses, which reduce microbial activity and diversity (Xu *et al.*, 2019).

Metal speciation

The speciation of heavy metals may also impact microbial resistance. The solubility, bioavailability, and toxicity of heavy metals vary depending on their speciation, which can have an effect on microbial activity and growth. For instance, some heavy metals, like mercury, can exist in several forms, such as elemental mercury, methylmercury, and inorganic mercury, each of which has a unique toxicology and potential to affect microbial communities in a variety of ways (Rahman and Singh, 2019).

iii. Presence of Other Contaminants

The presence of other environmental pollutants can also influence the microbial reaction to heavy metals. For instance, the presence of organic molecules might encourage microbial activity and growth, increasing the elimination of heavy metals (Zhang *et al.*, 2020). However, the presence of some contaminants, such as pesticides and antibiotics, might impede microbial activity and lessen heavy metal removal (Ajiboye *et al.*, 2021).

iv. **Microbial community structure and diversity** The composition and diversity of microbial populations can also influence microbial resistance to heavy metals. A greater variety of resistance mechanisms, such as metal efflux pumps, metal-binding proteins, and biosorption capacities, can be found in microbial communities with higher levels of diversity, which can boost the resistance of those communities to heavy metals. On the other hand, microbial communities with less diversity can be more vulnerable to the toxicity of heavy metals (Biswas *et al.*, 2021).

v. Physicochemical parameters of the environment

Microbial resistance to heavy metals can also be influenced by the physicochemical aspects of the environment, such as pH, temperature, and redox potential (Huang *et al.*, 2022). Heavy metal speciation, microbiological activity, and growth can all be impacted by the pH of the environment (Li and Song, 2020). Although some microbes are accustomed to high-temperature habitats, extreme temperatures can also have an impact on microbial development and activity. While some bacteria can decrease or oxidize heavy metals to less hazardous forms, redox potential can also affect the mobility and toxicity of heavy metals (Ojuederie and Babalola, 2017).

CHALLENGES AND LIMITATIONS OF MICROBIAL MECHANISMS TO HEAVY METALS RESISTANCE

Many difficulties and restrictions still need to be resolved, despite the fact that microbial responses to heavy metals have demonstrated considerable potential for environmental remediation (Saha *et al.*, 2022). Among these difficulties and restrictions are:

i. Toxic Effect of Heavy Metals to Microorganisms Microorganisms can nonetheless suffer detrimental effects from high levels of heavy metal contamination, despite their capacity to tolerate and convert heavy metals. As a result, their activity and bioremediation efficiency may decline (Yin *et al.*, 2019).

ii. Specificity of Microbial Mechanisms

Various microbes have distinct strategies for coping with and converting heavy metals. Finding the best microorganisms for a given bioremediation scenario may be challenging as a result (Raklami *et al.*, 2022).

 iii. Lack of Understanding of Microbial Interactions
 In natural environments, microorganisms

In natural environments, microorganisms frequently live in diverse communities, and these interactions can be extremely important to the cycling of heavy metals. Unfortunately, there is still having a limited grasp of these interactions (Kayiranga *et al.*, 2023; Ramanan *et al.*, 2016).

 iv. Lack of Standardized Heavy metal Bioremediation Protocols
 The application of microorganisms in heavy metal bioremediation currently lacks a standardized technique. This may result in inconsistent outcomes and make it challenging to evaluate the efficacy of various bioremediation techniques (Shahnawaz et al., 2019).

v. Safety Concerns

When microorganisms are utilized in bioremediation, there may be safety issues, especially if they are genetically engineered. It is crucial to make sure that bioremediation techniques are secure and do not endanger the environment or human health (Hussain *et al.*, 2018).

IMPLICATIONS OF MICROBIAL RESISTANCE TO HEAVY METALS

It can substantially impact the environment and people's health when microbes are resistant to heavy metals (Wang *et al.*, 2021).

Environmental implications

i. Bioremediation potential

The utilization of microorganisms in bioremediation, which involves removing or transforming pollutants from damaged settings, can be significantly impacted by the resistance of microbes to heavy metals (Medfu *et al.*, 2020). Heavy metal-resistant microorganisms can be employed to degrade or change pollutants in heavy metal-contaminated environments and these environments are becoming a reservoir for heavy metal resistant microbes which have potentials in the bioremediation of the heavy metal-contaminated environments (Tarfeen et al., 2022).

ii. Impact on ecosystem functioning

The ability of microbes to withstand heavy metals can also affect how well an ecosystem functions (Hao *et al.*, 2021). The ability of microorganisms to withstand heavy metals can impact ecosystem processes such as nutrient cycling, decomposition, and energy flow (Prasad *et al.*, 2021). Moreover, the consequences of heavy metal pollution on microbial diversity and community structure might have a domino effect on how well ecosystems function (Liang *et al.*, 2022).

Microbes play a significant part on functioning ecosystem more especially in the biogeochemical cycling of heavy metals by removing the metals from the environment (Wang *et al.*, 2023). Biological roles and impacts of metals are categorized into three broad groups: (Na, Ca, K, Mn, Mg, V, Fe, Cu, Co, Mo, Ni, Zn, and W) are necessary metals with known biological functions; (Ag, Sn, Cd, Au, Ti, Hg, Pb, Al, and metalloids Ge, Sb, As, and Se) are toxic metals; and (Rb, Sr, Cs, and T) are non-essential, nontoxic metals with no known biological effects. Health risks are posed by the most common ecologically hazardous metals, including As, Pb, Cd, and Hg (Prabhakaran *et al.*, 2016).

Nature has evolved few groups of microbes that were found to resist the effect of heavy metals while thriving within their ecosystem for example *Pseudomonas* sp., *Escherichia coli* and *Serratia* marcescens were reported by Prabhakaran et al. (2016) to resist Hg. *Pseudomonas putida, Cupriavidus* necator, Exiguobacterium sp., Bacillus aquimaris, Bacillus cereus and Alcaligenes sp. were reported by Zhang et al. (2014) to resist Cu, Cd, Pb, Cr and Ni. Also Bacillus sp. was also reported by Prabhakaran et al. (2016) to resist As, Pb and Hg. Acinetobacter Inoffii and Enterobacter agglomerans were also reported by Prabhakaran et al. (2016) to resist As.

Health Implications

i. Antibiotic resistance

Antibiotic resistance is a potential consequence of heavy metal resistance in microbes. Antibioticresistant bacteria can be selected for by exposure to heavy metals since some of their resistance mechanisms are similar to those of some antibiotics. Due to this, antibiotics may no longer be as efficient at treating bacterial infections and may even cause the spread of antibiotic resistance genes (Li et al., 2022).

ii. Human exposure and health risks

The impact of heavy metal resistance in microbes on human health is also possible. Humans may be exposed to heavy metals through contaminated food and water sources as well as through the food chain (Sonone *et al.*, 2020). The chance of infections that are difficult to treat with antibiotics is increased by the ability of heavy metalresistant microbes to transfer resistance genes to pathogenic bacteria (Longhi *et al.*, 2022).

FUTURE RESEARCH

Future research in this field will likely focus on several areas, including:

i. Molecular Mechanisms of Heavy Metal Resistance

Understanding molecular mechanisms by which microbes do resist heavy metal resulted in establishing new techniques that are now highly related to molecular biology and genomics (Manoj *et al.* 2020). Transcriptomics, proteomics, and metabolomics will likely be used in future studies in this field to better understand the genetic and metabolic processes underlying heavy metal resistance (Jamla *et al.*, 2021).

- ii. **Developing New Bioremediation Strategies** Although bioremediation has advanced, the cost, scalability, and effectiveness of current approaches are constrained. The development of new bioremediation techniques that are more successful, economical, and environmentally sustainable is anticipated to be the main focus of future research (Patel *et al.*, 2022).
- iii. Studying Microbial Interactions in Complex Environments

Most research on microbial responses to heavy metals has concentrated on specific strains or species (Alvarez *et al.*, 2017). Yet, in natural environments, microbes frequently live in diverse communities. To better understand the roles of microorganisms in the biogeochemical cycling of heavy metals, future research will probably focus on the study of microbial interactions in these complex ecosystems (Zhu *et al.*, 2017).

CONCLUSION

Bacterial resistance to heavy metals is a complex phenomenon involving a variety of passive and active mechanisms. Understanding the mechanisms, sources, factors and implications of bacterial resistance to heavy metals is critical for developing effective strategies for the remediation of heavy metals contaminated sites and for mitigating the impact of heavy metal pollution on environment and human health. More research is needed to fully understand the molecular mechanisms underlying heavy metal resistance and to identify new strategies that microbes resisting heavy can be beneficial in mitigating and solving environmental problems.

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