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REVIEW

Inorganic polyphosphates and heavy metal resistance in microorganisms

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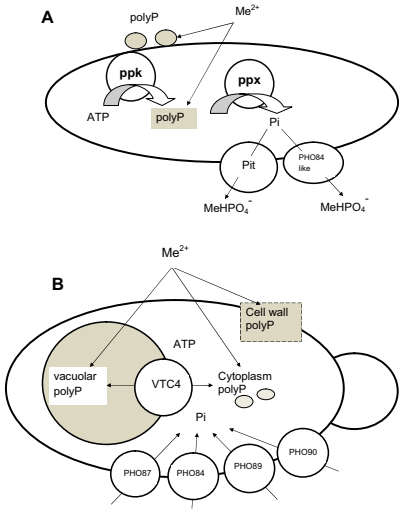
Abstract

The mechanisms of heavy metal resistance in microbial cells involve multiple pathways. They include the formation of complexes with specific proteins and other compounds, the excretion from the cells via plasma membrane transporters in case of procaryotes, and the compartmentalization of toxic ions in vacuoles, cell wall and other organelles in case of eukaryotes. The relationship between heavy metal tolerance and inorganic polyphosphate metabolism was demonstrated both in prokaryotic and eukaryotic microorganisms. Polyphosphates, being polyanions, are involved in detoxification of heavy metals through complex formation and compartmentalization. The bacteria and fungi cultivated in the presence of some heavy metal cations contain the enhanced levels of polyphosphate. In bacteria, polyphosphate sequesters heavy metals; some of metal cations stimulate an exopolyphosphatase activity, which releases phosphate from polyphosphates, and $MeHPO_4^-$ ions are then transported out of the cells. In fungi, the overcoming of heavy metal stresses is associated with the accumulation of polyphosphates in cytoplasmic inclusions, vacuoles and cell wall and the formation of cation/polyphosphate complexes. The effects of knockout mutations and overexpression of the genes encoding polyphosphate-metabolizing enzymes on heavy metal resistance are discussed.

Graphical abstract



Keywords Heavy metal · Tolerance · Polyphosphate · Polyphosphatase · Polyphosphate kinase · Phosphate uptake

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Introduction

Heavy metals are the widespread environmental pollutants hazardous to human health. The exposure to the toxic metal ions results in growth cessation, apoptosis and cell death of many microorganisms.

The study of heavy metal resistance of microorganisms is important for:

- Applications of microorganisms as biosorbents for water, food, soil and waste remediation (Bayat and Sari 2010; Monachese et al. 2012; García-García et al. 2016; Hansda et al. 2016);
- Development of microbial biosensors for heavy metal pollution monitoring (Gutiérrez et al. 2015; García-García et al. 2016; Kim et al. 2018).

Microorganisms realize a variety of pathways to overcome the stresses caused by toxic heavy metals. Inorganic polyphosphate (polyP), a linear polymer of orthophosphoric acid, belong to the compounds participating in this adaptation. PolyP is highly effective complexing agent for metal ions. This polymer is cheaply obtained by fusing phosphates at high temperature and is a common compound in filters for controlling scale formation in households and industry. The studies of new sorbents containing polyP revealed the high potential of sodium polyphosphate modified kaolinite clay as an adsorbent for the removal of Ni^{2+}, Co^{2+}, Cr^{2+} (Tarasevich and Klimova 2001), Pb^{2+}, Zn^{2+}, and Cd^{2+} (Amer et al. 2010) from aqueous solutions. Microbial cells often contain large amounts of polyP. It seems obvious that polyP is involved in heavy metal ions detoxification.

PolyP role in heavy metal ions tolerance in bacteria (Keyhani et al. 1996; Keasling and Hupf 1996; Gonzales and Jensen 1998) and yeast (Okorokov et al. 1983) was found quite a long time ago. In the review on phosphate-mediated remediation of metals (Martinez et al. 2014) it is stated: "polyphosphate metabolism promoting intracellular or extracellular sequestration of metals and radionuclides represents a remediation approach that harnesses the physiologies of extant microorganisms within contaminated environments".

Considering the role of polyP in the heavy metal resistance, it is necessary to take into account the great difference between prokaryotes and eukaryotes in phosphate uptake systems and polyP metabolism pathways. The polyP-metabolizing enzymes in bacteria are:

- Polyphosphate kinases (ppk), which reverse transfer the energy-rich phosphate residues from ATP to polyP and from polyP to ADP (Rao et al. 2009);
- Exopolyphosphatases ppx and gppA which split phosphate from the end of the polyP chain (Rao et al. 2009).

In yeast the set of polyP-metabolizing enzymes is represented by:

- Vacuolar membrane polyphosphate polymerase VTC4 (Hothorn et al. 2009);
- exopolyphosphatase PPX1 which splits phosphate from the end of the polyP chain (Wurst et al. 1995);
- Endopolyphosphatases DDP1 (Lonetti et al. 2011) and PPN2 (Gerasimaitė and Mayer 2017) which split long-chained polyP molecules into shorter ones;
- Dual endo- and exopolyphosphatase PPN1 (Sethuraman et al. 2001; Andreeva et al. 2015)

No direct homology was found between polyphosphate-metabolizing enzymes of prokaryotic and eukaryotic microbial cells.

The comparative analysis of new data on the interrelation between polyP metabolism and heavy metal resistance in prokaryotes and eukaryotes is the purpose of this review.

Polyphosphate and heavy metal resistance in archaea

The data on polyP in archaea are few. It has been reported on the substantial role of polyP in the resistance of some archaea to Cu^{2+} (Remonsellez et al. 2006; Soto et al. 2018; Rivero et al. 2018). *Sulfolobus acidocaldarius, Sulfolobus metallicus* and *Sulfolobus solfataricus* synthesized polyP during growth, but only *S. metallicus* accumulated polyP granules (Remonsellez et al. 2006). *S. solfataricus* could not grow in the presence of more than 1–5 mM Cu^{2+}, most likely due to its low polyP level. *S. metallicus* could grow in the presence of 200 mM Cu^{2+}, the polyP level decreased with increasing copper concentration (Remonsellez et al. 2006). Shifting *S. metallicus* cells to copper sulfate concentrations up to 100 mM led to rapid increase in exopolyphosphatase activity, decrease in polyP level and stimulation of phosphate efflux (Remonsellez et al. 2006).

A recombinant strain of *S. solfataricus* overexpressing the endogenous *ppx* gene was incapable of polyP accumulation. This strain showed an increased copper sensitivity and an earlier transcriptional up-regulation of the *copA* gene coding for the P-type copper-exporting ATPase (Soto et al. 2018). It implies a complementary function of both copper resistance systems. These results strongly suggest that the lack of polyP makes this hyperthermophilic archaeon more sensitive to toxic metals (Soto et al. 2018).

In addition to having a CopA/CopB copper efflux system, the thermoacidophilic archaeon *Metallosphaera sedula* contains electron-dense polyP-like granules, a putative exopolyphosphatase, and four presumed pho84-like phosphate transporters (Rivero et al. 2018). *M. sedula* accumulated the high levels of phosphorous in the form of granules, and the polyP

level was highly reduced when the cells were subjected to an 8 mM $CuSO_4$ shift. The purified exopolyphosphatase PPXMsed hydrolyzed polyP in vitro. The *ppx, pho84*-like, and *copTMA* genes of *M. sedula* were upregulated upon copper exposure, as determined by the qRT-PCR analysis. The findings confirm the existence of a polyP-dependent copper-resistance system that may be of great importance for the adaptation of this thermoacidophilic archaeon to its environment (Rivero et al. 2018).

Polyphosphate and heavy metal resistance in bacteria

In bacteria polyP participates in heavy metal ions detoxification by two ways. First, polyP binds with heavy metal ions to non-toxic complexes. For example, the cells of *E. coli* (Keasling and Hupf 1996) and *Anacystis nidulans* (Keyhani et al. 1996) with high polyP levels were more tolerant to Cd^{2+} than those with low polyP levels. Second, the polyP degradation by exopolyphosphatase in the presence of heavy metals is significant for the heavy metal resistance (Keyhani et al. 1996; Keasling and Hupf 1996; Keasling et al. 2000). The mutant strain of *E. coli* carrying the multiple copies of ppk gene *ppk1* and exopolyphosphatase gene *ppx* showed no increase in the cell doubling time in contrast to mutant carrying the multiple copies of ppk gene *ppk1* only over the same Cd^{2+} concentration range. The high polyP level and the enzymes both synthesizing and degrading polyP were necessary for bacterial tolerance to heavy metals (Keasling et al. 2000). It was proposed, that polyP sequesters heavy metal ions and the metal cations stimulates the exopolyphosphatase, which releases phosphate from polyP, the $MeHPO_4^-$ ions are transported out of the cells (Keasling 1997; Keasling et al. 2000).

The evidence in favor of this concept was obtained for various bacterial species and for different heavy metal ions. The stationary phase wild-type cells of *E. coli* grown in a high phosphate medium were significantly more tolerant to copper than those grown in a complete phosphate medium (Grillo-Puertas et al. 2014). The addition of Cu^{2+} to tolerant cells induced polyP degradation by exopolyphosptahase ppx and phosphate efflux. The null mutants in the *ppk1* and *ppx* genes (unable to synthesize/degrade polyP), in the *ppx* gene (unable to degrade polyP), and the Pit system mutants were highly sensitive to Cu^{2+} even in high phosphate media (Grillo-Puertas et al. 2014). The cells of *Pseudomonas putida* lacking ppk, which expectedly low intracellular polyP level, were more sensitive to Cd^{2+} and Cu^{2+} (Nikel et al. 2013). The inhibition of the hydrolysis of polyP by the bisphosphonate strongly increased the toxic effect of copper towards the biofilm-producing *Streptococcus mutans* (Müller et al. 2012).

The importance of phosphate efflux for heavy metal resistance was shown in the acidophilic bacterium *Acidithiobacillus ferrooxidans*, which can grow in the presence of 100 mM Cu^{2+}. Under these conditions, cells showed an increased exopolyphosphatase activity, a rapid decrease in polyP level, and a stimulation of phosphate efflux (Alvarez and Jerez 2004). Cd^{2+} and Zn^{2+} showed similar effects. This result supports the hypothesis, where heavy metals stimulate polyP hydrolysis and the formed metal-phosphate complexes are transported out of the cells. It is believed that in acidophilic bacteria the phosphate released from polyP is excreted from cells through the Pho84-type transporter (similar to the *S. cerevisiae* transporter), since the acidophiles have no standard Pit-like bacterial phosphate transporters (Alvarez and Jerez 2004). The detailed analysis of the role of polyP in metal resistance of acidophilic bacteria and the organization of their PHO regulon is given in the review (Navarro et al. 2013).

Despite polyP is accumulated in bacteria mainly intracellularly, the role of cell envelope polyP in metal sequestration should be taken into account. The methods of light, fluorescence and electron microscopy coupled with Energy Dispersive X-ray (EDX) spectroscopy demonstrated the presence of surface-associated polyP bodies in the filamentous, heterocystous, nitrogen-fixing marine cyanobacterium *Anabaena torulosa* (Acharya and Apte 2013). These bodies concentrate uranium from the medium (Acharya and Apte 2013).

The design of bacteria with genetically modified polyP metabolism and of transgenic plants with enhanced polyP levels may be effective for bioremediation biotechnologies. The bacteria transformed by the metallothionein and ppk expression vectors were highly resistant to mercury and accumulated up to 100 µM of mercury from the media containing 120 µM Hg (Ruiz et al. 2011). The transgenic tobacco expressing the bacterial *ppk1* was more resistant to cadmium and mercury and accumulated more heavy metals that the wild-type plant (Nagata et al. 2008, 2009). Probably, the excess polyP formed by *ppk1* decreased heavy metal toxicity by the chelation mechanism.

The simplified scheme illustrating the role of polyP in heavy metal resistance in bacterial cell is shown in Fig. 1a. The participation of polyP in heavy metal resistance of bacteria includes:

- PolyP accumulation in the cells and/or on cell surface and heavy metal ions complexing;
- PolyP hydrolysis by exopolyphosphatase;
- Phosphate and heavy metal ion excretion via the Pit system or PHO84-like phosphate-metal transporters.

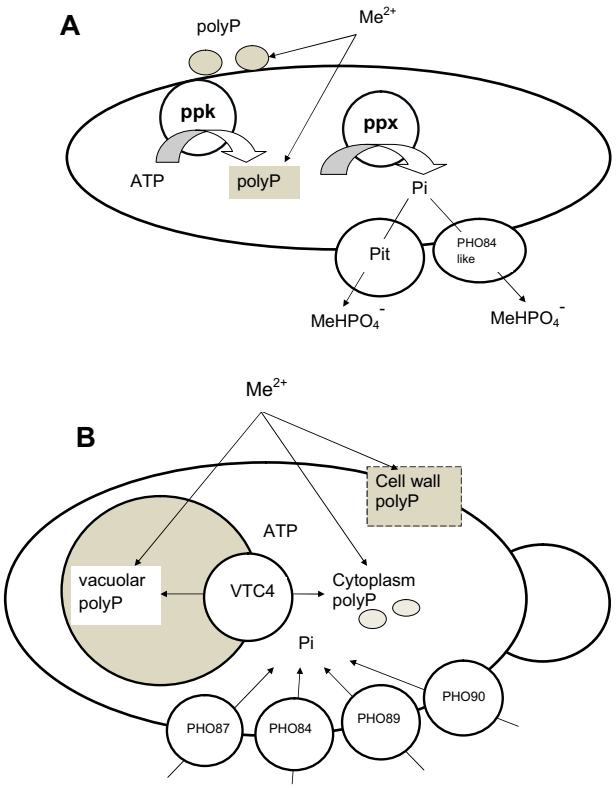

Fig. 1 The role of polyP in heavy metal resistance in bacterial (**a**) and yeast (**b**) cells. **a**—the participation of polyP in heavy metal resistance of bacteria includes: polyP synthesis by ppk and accumulation in cytoplasm and/or on cell surface and heavy metal ions complexing; polyP hydrolysis by exopolyphosphatase; phosphate (Pi) and heavy metal ion excretion via the Pit system or PHO84-like phosphate-metal transporters. **b**—at the excess of heavy metal the expression of the genes encoding phosphate transporters PHO87, PHO84, PHO89 and PHO90 increases and the cells take up more phosphate; the synthesis of polyP by polyphosphate polymerase VTC4 increases; polyP accumulated in cell wall, vacuoles and cytoplasmic inclusions form complexes with heavy metal ions

Polyphosphate and heavy metal resistance in fungi

The yeast species differ in heavy metal tolerance. For example, *Candida tropicalis* from wastewater was resistant to Zn^{2+}, Ni^{2+}, Hg^{2+}, and Pb^{2} (Rehman and Anjum 2011). *Cryptococcus humicola* was resistant to Cd^{2+}, Co^{2+}, Ni^{2+} and Mn^{2+} (2.5 mM), while the growth of *Cryptococcus terreus* and *Rhodotorula bogoriensis* was blocked by the same concentration of heavy metal ions (Andreeva et al. 2014; Ryazanova et al. 2016).

Multiple genes and signaling pathways including environmental sensing, sulfur and glutathione biosynthesis, vacuolar and endosomal transport and sorting are responsible for yeast viability under heavy metal excess (Culotta et al. 2005; Jin et al. 2008; Reddi et al. 2009; Thorsen et al. 2009; Wysocki and Tamas 2010; Kennedy et al. 2008).

The adaptation of *S. cerevisiae* to the toxic Mn^{2+} concentration (4 mM) after an abnormally long lag phase correlated with the accumulation of polyP and an increase in the chain length of acid soluble polyP (Andreeva et al. 2013). The upregulation of cytoplasmic membrane phosphate transporters Pho84, Pho87, Pho89 and Pho90 was observed in manganese-adapted cells (Andreeva et al. 2017). Pho84 is responsible for phosphate and manganese uptake under manganese excess (Rosenfeld et al. 2010). The upregulation of phosphate transporters explains the increase in phosphate accumulation by manganese-adapted cells (Andreeva et al. 2017). This increase may stimulate the synthesis of polyP by the vacuolar VTC4 polyphosphate synthetase which is activated by manganese ions (Hothorn et al. 2009). No upregulation of polyphosphate hydrolases were found; moreover, the exopolyphosphatase PPX1was downregulated. Thus, the enhanced phosphate uptake and polyP synthesis and the decreased polyP degradation are responsible for polyP accumulation in manganese-adapted cells of *S. cerevisiae* (Andreeva et al. 2017). It should be noted that no increase in sensitivity to manganese (Andreeva et al. 2013) and cadmium (Trilisenko et al. 2017) in PPX1 and PPN1 null mutants was observed. Apparently, the ability to degrade polyP is not particularly important for adaptation of *S. cerevisiae* to heavy metals.

The sensitivity to Cd^{2+}, an important environmental pollutant, was studied in the cells of *S. cerevisiae* strains with genetically altered polyP metabolism (Trilisenko et al. 2017). The strains overproducing polyphosphatases PPX1 or PPN1 were more sensitive to Cd^{2+} than the parent strain. The half maximal inhibitory concentrations were 0.02 mM and 0.05 mM for the transformants and the parent strain, respectively. Transformant strains cultivated in the presence of Cd^{2+} showed a decrease in the content of acid-soluble polyP. These data support the significant role of acid-soluble polyP in the binding and detoxification of heavy metal ions. There are evidences on localization of these short-chained polyPs in cytoplasm (Lichko et al. 2006).

Vacuoles play a fundamental role in storage of phosphorus and metal ions (Lichko et al. 1980; Yang et al. 2017) and in heavy metal detoxification (Ramsay and Gadd 1997; Reddi et al. 2009; Sousa et al. 2015; Kane 2016). The mutant strains of *S. cerevisiae* with impaired vacuolar function display enhanced sensitivity to heavy metal ions (Kane 2016). It is associated, on the one hand, with the fact that the vacuole is a cellular compartment where these ions are accumulated and isolated. On the other hand, the mutants with impaired vacuolar function, in particular, V-ATPase knockout mutants are characterized by a drastic decrease in the level of polyP, not only the fractions localized in the vacuoles but also the acid-soluble polyP (Trilisenko et al. 2013). Thus, the vacuolar membrane turns out to be responsible for two pathways of detoxification of heavy metal ions: their transport into the

vacuole and the synthesis of polyP forming complexes with these toxicants.

PolyP content increased in many yeast species cultivated in the presence of toxic manganese concentration (Table 1). Species that accumulate more polyP were characterized by a smaller decrease in the growth rate caused by this toxicant. The more resistant species accumulated large amounts of acid soluble polyP at manganese excess. The content of acid-soluble polyP increased in the tolerant *Cr. humicola* at cultivation in the presence of Cd, Co, Ni and Mn^{2+} (2.5 mM), but did not in the sensitive *Cr. terreus*. The data on the localization of polyP in the cells of both species were obtained using florescence microscopy with DAPI (4′,6′-diamino-2-phenylindole. 2HCl) (Andreeva et al. 2014). Staining with DAPI is an effective method of study of polyP localization in living cells (Aschar-Sobbi et al. 2008). As it has been revealed by DAPI fluorescence, the polyPs accumulating in *Cr. humicola* in response to the excess of heavy metal cations are localized mainly in cytoplasmic inclusions and in cell wall, while in *Cr. terreus* they are localized mainly in vacuoles (Andreeva et al. 2014). Moreover, the vacuoles of *Cr. terreus* underwent morphological changes and their function was probably disturbed (Andreeva et al. 2014).

The cells of *C. terricola* demonstrated a relatively high growth velocity at Mn^{2+} excess, while the content of polyP was not increased (Table 1). The enhanced DAPI fluorescence of the cell wall in *C. terricola*, indicating the increase in polyP content, was observed during the cultivation with manganese (Ryazanova et al. 2016). Probably, the forming of polyP-Mn^{2+}complexes in the cell wall of this microorganism protect it from toxic effect of manganese excess. The increase of DAPI fluorescence of the cell wall at heavy metal excess was observed also in the cells of other yeast species (Andreeva et al. 2013, 2014; Ryazanova et al. 2016). The origin of polyP of the cell wall remains in question. Probably, the dolichyl-diphosphate: polyphosphate phosphotransferase is responsible for biosynthesis of this polyP (Shabalin and Kulaev 1989).

In some cases, the DAPI staining did not allow to reveal the accumulation and localization of polyP, probably because these polymers were in the form preventing DAPI staining (Andreeva et al. 2013; Ryazanova et al. 2016).

Further evidence of polyP importance for detoxification of heavy metals was obtained for *Candida albicans* (Ikeh et al. 2016). The phosphate-responsive transcription factor Pho4 proved to be vital for the resistance of *C. albicans* to heavy metal stress. The RNA-Seq analysis showed that Pho4 did not induce stress-protective genes directly. Instead, the loss of Pho4 affected the toxicity, accumulation and bioavailability of metal cations. The null *Pho4* mutants were sensitive to metal cations. Pho4-regulated polyP synthesis was suggested to be important for manganese resistance (Ikeh et al. 2016).

As regards mycelial fungi, it is supposed that mycorrhizal fungi protect their host plants from abiotic stress factors, including heavy metals (Daghino et al. 2016). Fungal cells are rich in polyP (Kulaev et al. 2004), and the participation of polyP in heavy metal detoxification is very likely. For example, *Cunninghamella elegans* grown in the presence of cadmium showed a 15% increase in phosphate uptake compared to the control (De Freitas Lima et al. 2011). *C. elegans* accumulated 70–81% of the cadmium added to the culture medium during its growth. Cadmium induced vacuolization, the presence of electron dense deposits in vacuoles, cytoplasm and cell membranes, and the accumulation of acid-insoluble polyP (De Freitas Lima et al. 2011).

Thus, the role of polyP in detoxification of heavy metal ions in yeasts and fungi can be described as follows (Fig. 1b):

- The excess of heavy metal ions leads to enhanced expression of the genes encoding phosphate transporters;
- The cells take up more phosphate;
- This results in enhanced accumulation of polyP in cell wall, vacuoles and cytoplasmic inclusions.

Table 1 The effects of manganese excess on growth velocities and polyphosphate levels in various yeast species. The yeasts were cultivated in YPD medium (control) and in YPD medium supplemented with 2.5 mM $MnSO_4$. The data were data are taken from articles (Andreeva et al. 2013; Ryazanova et al. 2016)

	Species	Growth velocity in logarithmic phase, % of control	Total polyP in stationary phase, % of control	Acid-soluble polyP in stationary phase, % of control
Basidiomycetes	*Cryptococcus humicola*	48	169	274
	Cryptococcus terricola	64	101	174
	Cryptococcus curvatus	29	105	116
Ascomycetes	*Kuraishia capsulata*	44	190	266
	Lindnera fabianii	36	257	583
	Candida maltosa	50	148	370
	Saccharomyces cerevisiae	18	124	230
	Kluyveromyces marxianus	18	125	110

- The polyP form complexes with heavy metal ions, thereby contributing to their detoxification.

Yet, there is an open question about the peculiarities of polyP involvement in such processes in different species and about the signaling pathways involved in activation of phosphate transport and homeostasis, in particular, associated with the transcription factor Pho4.

Conclusion

Despite the well-developed concept explaining the role of microbial polyP in the detoxification of heavy metals, studies in this area encounter some difficulties. Firstly, there are no methods for obtaining viable microbial cells completely lacking polyP. In bacteria, the level of polyP is most reduced in the knockout ppk mutants (Rao et al. 2009). However, these mutants retain a certain amount of polyP and their heavy metal tolerance is reduced only partly. In yeasts, the mutants in VTC4 polyP synthase have simultaneous decrease in the level of polyP and abnormal vacuole functions (Kane 2016). In such mutants, it is difficult to estimate the contribution of vacuole transporters and polyP in the heavy metal tolerance.

It should be noted that the systems for heavy metals resistance in microbial cells are multicomponent, and polyP is only one of their participants.

In eukaryotic microorganisms, the problem of localization of polyP remains important. The DAPI staining methods do not always allow the detection of polyP under heavy metal exposure. Probably, the binding of polyP to metals suppresses binding to DAPI. So, *S. cerevisiae* cells containing high polyP and manganese levels were poorly stained with DAPI (Andreeva et al. 2013).

An prospective task is the detection of signaling pathways providing changes in the metabolism of polyP in the presence of heavy metals. Probably, these pathways are associated with transport systems of plasma membrane and other intracellular membranes in the case of eukaryotes.

Microbial cells have a high potential for heavy metal biosorption and bioaccumulation. The contribution of polyP to detoxification of heavy metal ions is not the same for different microorganisms. The knowledge of the peculiarities of polyP accumulation, localization and utilization is useful for screening of most effective microbial species for development of new bioremediation and biosensor technologies.

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Compliance with ethical standards

Conflict of interest The author declares the absence of a conflict of interest.

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