

# Fungal endophyte: a promising tool of heavy metal bioremediation

<sup>1</sup>Usman, M. M., <sup>1</sup>Idi, A. and <sup>2</sup>Aisami, A.

<sup>1</sup>Department of Biotechnology, Faculty of Life Sciences, Modibbo Adama University, Yola. Adamawa State. Nigeria

<sup>2</sup>Department of Biochemistry, Faculty of Science, Gombe State University, Gombe State. Nigeria

## Paper History

Received: 31<sup>st</sup> May, 2023

Accepted: 26<sup>th</sup> June, 2023

Published: 06<sup>th</sup> July, 2023

## Abstract:

*In recent years, heavy metal pollution has become an increasingly serious global problem. As such, considerable research has been devoted to finding effective ways to remove these potentially toxic substances from contaminated soils and water sources. Bioremediation is one of the most promising methods of achieving this, as living organisms are often capable of substantial pollutant removal. Fungal endophytes, which are microorganisms living within the tissues of plants without causing any detectable pathology, have been identified as an especially promising component of bioremediation processes. This review focuses on the current understanding of endophytic fungi, with an emphasis on the potential for their use in heavy metal bioremediation, the review then explores the bioremediation potential of endophytic fungi, including their ability to reduce the toxicity of heavy metals such as cadmium, lead, zinc, and chromium. Overall, this review suggests that endophytes hold considerable potential for heavy metals bioremediation. In particular, more research is needed into the mechanisms of heavy metal uptake and detoxification by endophytic fungi. Moreover, the effect of environmental conditions on the efficacy of such processes needs to be studied further.*

Corresponding author

Usman, M. M.

[mmusmanu@mau.edu.ng](mailto:mmusmanu@mau.edu.ng)

**Keywords:** Bioremediation, Endophytic, Fungi, Heavy Metals

## 1. Introduction

With industrial development, there has been a significant rise in waste discharge from industries to the environment, mainly water and soil, which resulted the heavy metals accumulation (HMs), particularly in urban regions. The depletion of HMs occurs slowly via erosion, plant uptake, leaching and deflation. The indiscriminating discharge of the HMs into the waters and soils is a main health distress globally. Many HMs can cause harm even at very low concentrations; arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb), mercury (Hg), nickel (Ni), selenium (Se), silver (Ag), zinc (Zn) etc. [1]. HMs are metal and metalloid groups whose atomic density exceeds 4 g cm<sup>-3</sup>, or five times or more, greater than water [2]. Environmental pollution by HMs has become a serious concern for ecosystem health and aquatic life [3]. Environmental pollution occurs when the natural environment is not capable of destroying an element without causing damage. The elements involved are not nature-generated, and the destruction process can range from a few days to thousands of years. Elemental pollutants have been found to be emerging contaminants [4, 5]. Bioaccumulation and consequent biomagnification of HMs and the high levels of toxicity they confer on biological systems indicate an obligation to remove them from contaminated soil and water [6].

Endophytes are microorganisms which colonize the internal tissues of their host plants at a specified time in their lives. Endophytes are one of the most assorted groups of

microbes with an estimate of 1 million species [3]. Endophytes are fungal or bacterial microbes that colonize the tissues of healthy plants intracellular and/or intercellular without producing any seeming symptoms of infection [7].

Microorganisms are universally found in nature and play an important role in basic biotransformation. Metallic-microbe connections can have advantageous or harmful values. Apart from the nature of the microorganisms and the chemistry of the metals concerned, transformation processes are driven by additional environmental factors, for example temperature, moisture, pH, other ions and living organisms and their adversaries that play a critical role in microbial colonisation and biofilm formation [8]. The application of microorganisms to clean up contaminated environments is a speedily moving and growing the field of environmental biotechnology [9]. The chemical and physical approaches for HM remediation are very costly, often leading to the destructive effects to the local ecosystem. In addition, it involves the handling of a great quantity of harmful waste [10]. One emergent, inexpensive, and most economical method is the use of microorganisms to remediate HM. Microorganisms utilize their metabolic potentialities to remediate HMs biochemically [11].

## 2. Sources of the Heavy metals

A metal or metalloid species can be considered "contaminant" when undesirable, or in a concentration or a form that causes harmful effects to the environmental or human. Metals or metalloids include arsenic (As), cadmium

(Cd), chromium (Cr), copper (Cu), lead (Pb), mercury (Hg), nickel (Ni), selenium (Se), silver (Ag), and zinc (Zn). Other metallic pollutants that are less common include aluminium (Al), cobalt (Co), cesium (Cs), molybdenum (Mo), manganese (Mn) and strontium (Sr) [12, 13].

Metals and metalloid are categorized into three classes. The first class consists of metals which are toxic to the lowest level including; cadmium, lead and mercury. The second category is considered less dangerous, examples include bismuth and arsenic. The third category consists of critical metals that are involved in certain biochemical processes in the biological system and are toxic when their concentrations exceed a certain level, examples are cobalt, copper, selenium [14, 15]. In an environment HM is naturally

derived from pedogenic processes involving alteration/weathering of parent materials and from anthropogenic sources as shown in Figure 1. Mineral weathering, erosion and volcanic eruptions are the most important naturally occurring sources of HMs whereas anthropogenic sources are dependent on human actions such as electroplating, mining, smelting, pesticide and biosolid application (Examples; municipal sewage sludge and livestock manure) [1]. Forest fires are also part natural sources of HMs [16]. In addition, metal-based fertilizers contribute also to the environment pollution with HMs [17]. Food safety threatens due to HM pollutants released in agricultural soil, surface runoff to the surrounding rivers, and groundwater leaching is a major concern [18].

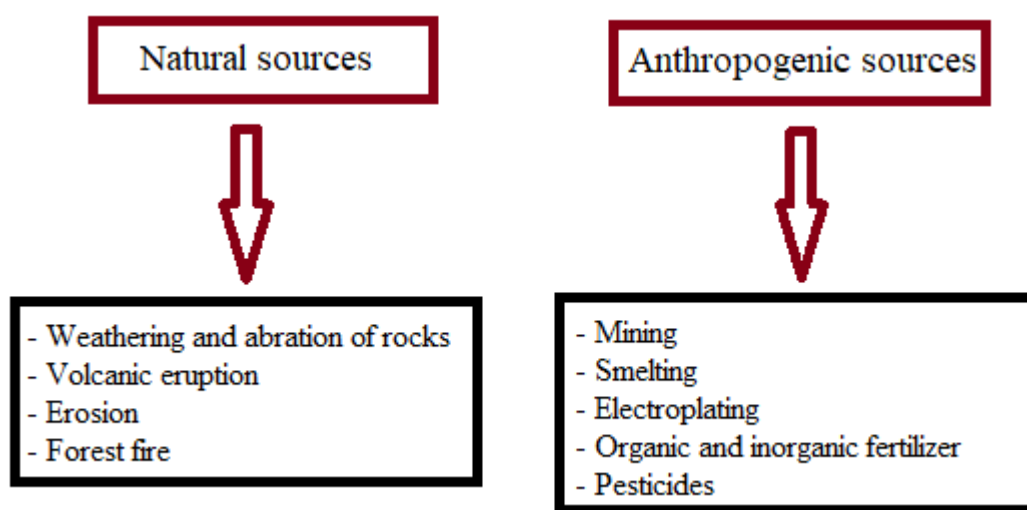


Figure 1: Sources of the heavy metals

### 3. Effects of the heavy metals on plants

Consumption of HM beyond the permissible limits exhibit toxic effects on both plants and humans [19]. Plants grown in the soils polluted with HMs are able to absorb substantial amounts of metal ions, which in turns affect the human health if taken via the food chain [20]. In plant nutrition, plants need some metals as an essential nutrient for the proper development, on the other hand, others are considered potentially toxic when taken by the plant extremely, and which attribute to the change in different physiological and biochemical activities [21]. In several plant systems, symptoms of HM toxicity have been studied under different conditions. Metal toxicity can be grouped into direct targets or indirect impairments of physiological pathways, direct targets involve attack of metals on metalloproteins and metal binding molecules such as chlorophyll [22]. Elevated levels of HMs in soil and subsequent exposure to plants adversely affect a number of biochemical and physiological activities, thus leading to stunted growth and small yield of plants [23]. Accumulation of HMs in the soil is extremely worrisome in agricultural production in view of the adverse effects on quality of food as well as crop growth (course by phytotoxicity). The HMs are hazardous to health either directly by inhaling dust or indirectly by consumption of vegetables grown on polluted soils [24]. HMs may interfere with cell elongation, photosynthesis, respiration

and several other physiological processes. The HMs toxicity of heavy metals depends on their in their generation of reactive oxidative species directly by oxidation and by Fenton reaction or by hindering the vital functional groups of biomolecules or by substitution of essential metallic ions by other ones [25]. Lead (Pb) treatment was found to cause uncertainty in ion uptake by plants even at low concentration, which as a result course significant metabolic changes in photosynthetic ability and eventually inhibit plant growth strongly [26]. The HMs that led to harmful effects to plants include; cadmium, chromium, copper, lead, mercury and nickel. HMs inflict stress on plants, they decrease profitability as well as damaging agro-biologic systems. Plants are persistently exposed to negative environmental conditions over their life cycle that adversely affect their development, growth and productivity [20, 27]. The plant roots are the critical connection point for the HM ions that are transported from the soil. They are responsible for stabilizing and connecting the pollutants in the soil, consequently decreasing their bioavailability. The mechanisms involved in of HMs transmission to plants consist of phytoextraction (phytoremediation approach through which plants remove harmful components from polluted soil), phytostabilization (process of immobilizing and reducing HM mobility in the ground), and rhizofiltration (phytoremediation technique through which plant roots are used to absorb toxic substances) [28, 29].

#### 4. Effects of the heavy metals on human

Pollution of dietary substances by HMs have a range of well-known conflicting effects on human systems [30]. Intake of many HMs in the diet via the intake of plants has lasting damaging effects on human health [31]. Consumption of vegetables having HMs is one of the key ways through which these elements move in the human body. Once pass on, HMs are dumped in fat and bone tissues. When HMs are released into the body, they can cause an assortment of diseases [32]. Once HMs are consumed they are oxidized to several oxidation states that can freely bind to biomolecules such as protein enzymes and other forms of protein [33]. Generally, toxicity exhibited by heavy metals in human system is as a result of chemical reactions of ions with the cellular structural enzymes and components of membrane [34]. The presence of essential or non-essential metals in excess above the normal levels can lead to physiological or morphological anomalies or gene mutations, such as reducing or preventing growth or the formation of mutations [35]. It has been reported that cell organelles and constituents of the cell have been affected by HMs, organelles affected include mitochondria, cell membrane, lysosomes, nuclei and enzymes. It has occurred that HM ions interact with deoxyribonucleic acid (DNA) and nuclear proteins, in consequence causing damage to DNA molecule, subsequently leading to cell cycle modulation and carcinogenesis [21, 36].

##### 4.1 Lead (Pb)

Pb is extremely harmful [37]. Acute contact toxicity of Pb can cause fatigue, headache, sleeplessness, abdominal pain, loss of appetite, hypertension, renal dysfunction, arthritis and vertigo, whereas chronic contact/toxicity can cause in allergies, muscular weakness, brain damage, paralysis, birth defects, intellectual disability, weight loss, kidney damage, hyperactivity, and even death [38, 39].

##### 4.2 Cadmium

Cadmium toxicity has been proven in some organs, it promotes tissue damage by generating oxidative stress [40]. Exposure to Cd upsets male reproductive organs/system in human and weakens spermatogenesis, thereby affecting the quality of sperm particularly motility of sperm and hormonal production/release [41]. Cd has a capacity to connect with aspartate, cysteine, histidine and glutamate ligands and can cause iron deficiency [26, 42].

##### 4.3 Arsenic

Arsenic causes redox reactions in biological systems, thereby causing cancer. The free radicals generated by this type of reactions leading to oxidative destruction to DNA and proteins [43]. Arsenic is not causing mutation or does bind to DNA and form DNA adducts directly, but is capable to bring genotoxicity interfering with DNA repair mechanism and prompting chromosomal uncertainty in the cell. Inhibiting the DNA repair by upsetting the expression of DNA repair genes is significant mechanism involved for arsenic-induced genotoxicity [44].

#### 4.4 Chromium

Hexavalent form of chromium has a cancer-causing ability with various complex mechanisms by which it induces cancer development. The most important mechanism through which  $\text{Cr}^{+6}$  result in cell damage include chromosome breaks, elevated levels of oxidative stress and the formation of DNA adduct [45]. Chronic contact and bioaccumulation of Cr, as HM, can lead to toxicity and several pathophysiological weaknesses, comprising anemia, allergy reactions, burns and wounds specifically in the small intestine and stomach, destruction of semen alongside with the male reproductive system [46].

##### 4.5 Nickel

It has been established that nickel was found to harmfully affect the female reproductive system, and leading to teratogenesis [47]. Severe skin allergy, kidney problems, nasal cancer and cardiovascular diseases have been diagnosed and reported amongst workers in the nickel industry. Nephrotoxicity and hepatic toxicity have been reported in numerous animal model studies. Besides, nickel contact has also been described to yield haematological imperfections in humans [48, 49].

#### 5 Endophytic fungi

Fungi constituted an important constituent within each ecosystem, very well associated with critical processes such as transportation, recycling and decomposition nutrients in diverse environments. There may be more than a million different fungi species on Earth, according to reports, out of which only a small portion, about 5% have been recognized [50]. Endophytes refers to as microbes (bacteria and fungi) which colonize living, inner tissues of healthy plants without instigating any instant, harmful effects. The term *endophyte* was first familiarized by De Bary in 1886 for microbes including; bacteria, fungi and yeast capable of colonizing internal tissues of plants [51, 52]. Endophytic fungi exist in the tissues of healthy plant devoid of displaying any disease symptoms, consequently supportive to the physiological as well as ecological qualities of the host plant. [53]. Endophytic fungi, therefore, has been drawing the interest of the scientist due to their potential valuable impression on vegetation, comprising bioremediation of HM contaminated environments and facilitation of plant growth [54]. The association of plants and endophytic fungi has been for over four hundred million years. [55]. Roughly, all vascular plant species well-known to harbor endophytic bacteria and/or fungi [56]. It has been reported that approximately 300,000 different plant species exist on Earth, and each individual plant can host one or several types of endophytes [52, 57-59]. Endophytic fungi possess enormous varieties of metabolic pathways that render them appreciated tools for bioremediation processes.

##### 5.1 Role of endophytic fungi

Endophytes control the morphologic and physiological functions of the host plant, and advance its resistance to HMs by providing diverse decontamination routes, like binding the cell wall of the fungi, extracellular scavenging and precipitation, intracellular scavenging and

complexation, compartmentalization and volatilization [60]. Knowing the effect of HMs on plant and animal health is of paramount importance so as to find a solution for this issue if great concern. In this regard, bioremediation with endophyte fungi is becoming increasingly important day after day [61].

Endophytic fungi joined with phytoremediation strategy could improve plant's adaptation to HM stress and ecological refurbishment success [62]. Phytoremediation (bioremediation using plants) is an encouraging cleanup tool for soils contaminated HMs. Nevertheless, this method has some shortcomings, like slow growth rate of HM-accumulating plant species, short bioavailability of HMs and lengthy period of remediation [63]. Table 1 indicates the bioremediation processes using endophytic fungi from different plants.

## 6 Conclusion

Involvement of fungal endophytes in remediation of HMs has an important value to both plants and human health. Hence, better knowledge of fungal activities and the effects of the heavy metals to plants and human help to articulate the effectual bioremediation approach. In this review, we reported the effects of heavy metals pollution on plants as well as human. In addition, bioremediation potentials of endophytic fungi were discussed toward management of harmful pollutants. The current research works on the potential of endophytic fungi in bioremediation of heavy metals contamination is indicating an excellent success. Further work needs to be done, such as on the mechanisms involved in bioremediation processes. Furthermore, considering the availability of different plant species on earth more work need to be done in isolation of endophytic fungi from the diverse plants available and screen for their bioremediation potentials.

Table 1: Endophytes-assisted bioremediation processes of some heavy metals

Plant source	Endophytic fungi	Bioremediation process	Reference
<i>Parthenium</i> sp.	<i>Mucor</i> sp	The <i>Mucor</i> sp. was able to remove 60–87% of the HMs ( $\text{Cr}^{6+}$ , $\text{Mn}^{2+}$ , $\text{Co}^{2+}$ , $\text{Cu}^{2+}$ and $\text{Zn}^{2+}$ ) from broth culture medium delivered with $300 \mu\text{g mL}^{-1}$ of these metals. The strain effectually endured up to $900 \mu\text{g mL}^{-1}$	[64]
Root of <i>Aeschynomene fluminensis</i> and <i>Polygonum acuminatum</i>	<i>Aspergillus</i> sp. A31 and Lindgomycetaceae P87,	The concentration of Hg in the polluted soil was reduced by 7.69% and 57.14% in <i>A. fluminensis</i> plants inoculated with <i>Aspergillus</i> sp. A31 + Lindgomycetaceae P87 and Lindgomycetaceae P87, respectively	[60]
<i>Beta vulgare</i> , <i>Parthenium argentatum</i> , <i>Zea Mays</i> , <i>Saccharum officinarum</i> , <i>Colocasia esculenta</i> , <i>Cucurbita maxima</i> , and <i>Ficus carica</i>	The strains were identified as <i>Aspergillus fumigatus</i> , <i>Rhizopus</i> sp., <i>Penicillium radicum</i>	The fungal isolates were found to remove Cr from soil and culture media. They also as bio-transformed it from highly toxic $\text{Cr}^{6+}$ to least toxic $\text{Cr}^{3+}$ .	[61]
leaves of <i>Cupressus torulosa</i>	<i>Alternaria alternata</i>	<i>Alternaria alternata</i> isolated was most effective in elimination of varying number of HMs with respect $\text{Cu}^{+2}$ , $\text{Pb}^{+2}$ , $\text{Ag}^{+}$ , $\text{Hg}^{+2}$ which displayed the extreme uptake of lead of 80% and the least uptake of Ag of 63.1% at concentration of $50 \mu\text{g/mL}$	[65]
<i>Convolvulus arvensis</i>	<i>Fusarium falciforme</i> and <i>Fusarium</i> sp.	The results shown that <i>F. falciforme</i> and <i>Fusarium</i> sp. have a important capability for bio-removal of Cd from aqueous solutions as their tolerance indexes were $>1$ . The bioaccumulation ability stretches to 276.5 and $101.6 \mu\text{g/g}$ with percentages bioremediation values of 82.4% and 76.5%, respectively.	[66]
<i>Prosopis laevigata</i>	<i>Aspergillus</i> closest to <i>Aspergillus luchuensis</i>	The isolated strain offered a noticeable tolerance to high concentrations of Cu, Pb and Zn. It favors the translocation of the HMs from the roots to the leaves in <i>Prosopis laevigata</i> .	[67]

## References

- [1]. Dixit, R., Malaviya, D., Pandiyan, K., Singh, U. B., Sahu, A., Shukla, R., Singh, B. P., Rai, J. P., Sharma, P. K., and Lade, H., (2015). Bioremediation of heavy metals from soil and aquatic environment: an overview of principles and criteria of fundamental processes. *Sustainability*, 7(2), 2189-2212.
- [2]. Asati, A., Pichhode, M., and Nikhil, K., (2016). Effect of heavy metals on plants: an overview. *International Journal of Application or Innovation in Engineering & Management*, 5(3), 56-66.
- [3]. Sharma, P. and Kumar, S., (2021). Bioremediation of heavy metals from industrial effluents by endophytes and their metabolic activity: Recent advances. *Bioresource Technology*, 339, 125589.
- [4]. Das, A. and Osborne, J. W. (2018). Bioremediation of heavy metals. *Nanotechnology, food security and water treatment*, Springer, 277-311.
- [5]. Yu, H., Ni, S. J., He, Z. W., Zhang, C. J., Nan, X., Kong, B., and Weng, Z. Y. (2014). Analysis of the spatial relationship between heavy metals in soil and human activities based on landscape geochemical interpretation. *Journal of Geochemical Exploration*, 146, 136-148.
- [6]. Govarthanan, M., Mythili, R., Selvankumar, T., Kamala-Kannan, S., Rajasekar, A., and Chang, Y.-C. (2016). Bioremediation of heavy metals using an endophytic



- bacterium *Paenibacillus* sp. RM isolated from the roots of *Tridax procumbens*. *3 Biotech*, 6, 1-7.
- [7]. Krishnamurthy, Y. L. and Naik, B. S (2017). Endophytic fungi bioremediation. *Endophytes: Crop Productivity and Protection*, 2, 47-60.
  - [8]. Kapahi, M. and Sachdeva, S (2019). Bioremediation options for heavy metal pollution. *Journal of health and pollution*, 9(24).
  - [9]. Iwamoto, T. and Nasu, M (2001). Current bioremediation practice and perspective. *Journal of bioscience and bioengineering*, 92(1), 1-8.
  - [10]. RoyChowdhury, A., Datta, R., and Sarkar, D (2018). Heavy metal pollution and remediation, in *Green chemistry*, Elsevier, 359-373.
  - [11]. Hassan, Z.u., Ali, S., Rizwan, M., Ibrahim, M., Nafees, M., and Waseem, M., (2017). Role of bioremediation agents (bacteria, fungi, and algae) in alleviating heavy metal toxicity. *Probiotics in agroecosystem*, Springer, 517-537.
  - [12]. McIntyre, T (2003). Phytoremediation of heavy metals from soils. *Phytoremediation*, Springer, 97-123.
  - [13]. Singh, R., Gautam, N., Mishra, A., and Gupta, R (2011). Heavy metals and living systems: An overview. *Indian journal of pharmacology*, 43(3), 246.
  - [14]. Odošić, A., Šestan, I., and Begić, S., (2019). Biosensors for determination of heavy metals in waters, In T.Rinken and K. Kivirand (Eds), *Biosensors for environmental monitoring*, IntechOpen. 139-155.
  - [15]. Zaynab, M., Al-Yahyai, R., Ameen, A., Sharif, Y., Ali, L., Fatima, M., Khan, K.A., and Li, S., (2022). Health and environmental effects of heavy metals. *Journal of King Saud University-Science*, 34(1), 101653.
  - [16]. Jyothi, N.R., (2020). Heavy metal sources and their effects on human health. In M. Nazal and H. Zhao (Eds), *Heavy Metals-Their Environmental Impacts and Mitigation*, IntechOpen, 21-31.
  - [17]. Sim, C. S. F., Chen, S. H., and Ting, A. S. Y., (2019). Endophytes: Emerging tools for the bioremediation of pollutants. *Emerging and eco-friendly approaches for waste management*, Springer, 189-217.
  - [18]. Salem, M. A., Bedade, D. K., Al-Ethawi, L., and Al-Waleed, S. M., (2020) Assessment of physiochemical properties and concentration of heavy metals in agricultural soils fertilized with chemical fertilizers. *Heliyon*, 6(10), e05224, 1-10.
  - [19]. Sandeep, G., Vijayalatha, K., and Anitha, T (2019). Heavy metals and its impact in vegetable crops. *International Journal of Chemical Studies*, 7(1), 1612-1621.
  - [20]. Diaconu, M., Pavel, L. V., Hlihor, R. M., Rosca, M., Fertu, D. I., Lenz, M., Corvini, P. X., and Gavrilescu, M., (2020). Characterization of heavy metal toxicity in some plants and microorganisms: A preliminary approach for environmental bioremediation. *New Biotechnology*, 56, 130-139.
  - [21]. Tchounwou, P. B., Yedjou, C. G., Patlolla, A. K., and Sutton, D. J., (2012). Heavy metal toxicity and the environment. *Molecular, clinical and environmental toxicology: volume 3: environmental toxicology*, Springer, 133-164.
  - [22]. Viehweger, K., (2014). How plants cope with heavy metals. *Botanical Studies*, 55(1), 1-12.
  - [23]. Bilal, S., Shahzad, R., Imran, M., Jan, R., Kim, K. M., and Lee, I. J., (2020). Synergistic association of endophytic fungi enhances *Glycine max* L. resilience to combined abiotic stresses: Heavy metals, high temperature and drought stress. *Industrial Crops and Products*, 143, 1-10 111931.
  - [24]. Mohammadi, R. M., Sobhan, A. S., Karimi, H., and Sorooshnia, R., (2015). Natural and anthropogenic source of heavy metals pollution in the soil samples of an industrial complex; a case study, *Iranian Journal of Toxicology*, 9(27), 1336-1341.
  - [25]. Houri, T., Khairallah, Y., Al Zahab, A., Osta, B., Romanos, D., and Haddad, G., (2020). Heavy metals accumulation effects on the photosynthetic performance of geophytes in Mediterranean reserve. *Journal of King Saud University-Science*, 32(1), 874-880.
  - [26]. Jaishankar, M., Tseten, T., Anbalagan, N., Mathew, B. B., and Beeregowda, K. N., (2014). Toxicity, mechanism and health effects of some heavy metals. *Interdisciplinary toxicology*, 7(2), 60-72.
  - [27]. Yaashikaa, P., Kumar, P. S., Jeevanantham, S., and Saravanan, R., (2022). A review on bioremediation approach for heavy metal detoxification and accumulation in plants. *Environmental Pollution*, 301, 119035.
  - [28]. Alengebawy, A., Abdelkhalik, S. T., Qureshi, S. R., and Wang, M. Q., (2021). Heavy metals and pesticides toxicity in agricultural soil and plants: Ecological risks and human health implications. *Toxics*, 9(3), 42.
  - [29]. Tangahu, B. V., Sheikh Abdullah, S. R., Basri, H., Idris, M., Anuar, N., and Mukhlisin, M., (2011). A review on heavy metals (As, Pb, and Hg) uptake by plants through phytoremediation. *International journal of chemical engineering*, 2011, 1-31
  - [30]. D'Souza, C. and Peretiak, R., (2002). The nexus between industrialization and environment: A case study of Indian enterprises. *Environmental Management and Health*, 13 (1), 80-97.
  - [31]. Pirhadi, M., Shariatifar, N., Bahmani, M., and Manouchehri, A., (2022). Heavy metals in wheat grain and its impact on human health: A mini-review. *Journal of Chemical Health Risks*, 12(3), 421-426.
  - [32]. Guerra, F., Trevizani, A. R., Muraoka, T., Marcante, N.C., and Canniatti-Brazaca, S. G., (2012). Heavy metals in vegetables and potential risk for human health. *Scientia agricola*, 69, 54-60.
  - [33]. Engwa, G. A., Ferdinand, P. U., Nwalo, F. N., and Unachukwu, M. N., (2019). Mechanism and health effects of heavy metal toxicity in humans. *Poisoning in the modern world-new tricks for an old dog*, 10, 70-90.
  - [34]. Mahurpawar, M., (2015). Effects of heavy metals on human health. *International Journal of Research Granthaalayah*, 530, 1-7.
  - [35]. Mitra, S., Chakraborty, A. J., Tareq, A. M., Emran, T. B., Nainu, F., Khushro, A., Idris, A. M., Khandaker, M. U., Osman, H., and Alhumaydhi, F. A., (2022). Impact of heavy metals on the environment and human health: Novel therapeutic insights to counter the toxicity. *Journal of King Saud University-Science*, 34 (3), 101865.
  - [36]. Briffa, J., Sinagra, E., and Blundell, R., (2020). Heavy metal pollution in the environment and their toxicological effects on humans. *Heliyon*, 6(9), 1-26, e04691.
  - [37]. Kumar, A., Kumar, A., MMS, C. P., Chaturvedi, A.K., Shabnam, A.A., Subrahmanyam, G., Mondal, R., Gupta, D. K., Malyan, S. K., and Kumar, S. S., (2020). Lead toxicity: health hazards, influence on food chain, and sustainable remediation approaches. *International journal of environmental research and public health*, 17(7), 1-33, 2179.
  - [38]. Jan, A. T., Azam, M., Siddiqui, K., Ali, A., Choi, I., and Haq, Q. M. R., (2015). Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants. *International journal of molecular sciences*, 16(12), 29592-29630.
  - [39]. Papanikolaou, N. C., Hatzidaki, E. G., Belivanis, S., Tzanakakis, G. N., and Tsatsakis, A.M (2005). Lead

- toxicity update. A brief review. *Medical science monitor*, 11(10), RA329.
- [40]. Bernhoft, R. A (2013). Cadmium toxicity and treatment. *The Scientific World Journal*, 2013, 1-7.
- [41]. Kumar, S. and Sharma, A (2019). Cadmium toxicity: effects on human reproduction and fertility. *Reviews on environmental health*, 34(4), 327-338.
- [42]. Castagnetto, J. M., Hennessy, S. W., Roberts, V. A., Getzoff, E. D., Tainer, J. A., and Pique, M. E., (2002). MDB: the metalloprotein database and browser at the Scripps Research Institute. *Nucleic acids research*, 30(1), 379-382.
- [43]. Fu, Z. and Xi, S., (2020). The effects of heavy metals on human metabolism. *Toxicology mechanisms and methods*, 30(3), 167-176.
- [44]. Zhu, Y. and Costa, M., (2020). Metals and molecular carcinogenesis. *Carcinogenesis*, 41(9), 1161-1172.
- [45]. DesMarias, T. L. and Costa, M., (2019). Mechanisms of chromium-induced toxicity. *Current opinion in toxicology*, 14, 1-7.
- [46]. Hossini, H., Shafie, B., Niri, A. D., Nazari, M., Esfahlan, A. J., Ahmadvpour, M., Nazmara, Z., Ahmadianesh, M., Makhdomi, P. and Mirzaei, N., (2022). A comprehensive review on human health effects of chromium: insights on induced toxicity. *Environmental Science and Pollution Research*, 29(47), 70686-70705.
- [47]. Parveen, S., Rizvi, A., and Naseem, I., (2022). Nickel Toxicity with Reference to Female Reproductive Physiology, Pregnancy and Teratogenesis: A Brief Review. *Advanced Chemicobiology Research*, 1 (2), 65-71.
- [48]. Begum, W., Rai, S., Banerjee, S., Bhattacharjee, S., Mondal, M. H., Bhattarai, A., and Saha, B., (2022). A comprehensive review on the sources, essentiality and toxicological profile of nickel. *RSC advances*, 12(15), 9139-9153.
- [49]. Tammaro, A., Narcisi, A., Persechino, S., Caperchi, C., and Gaspari, A., (2011). Topical and systemic therapies for nickel allergy. *DERM*, 22(5), 251-255.
- [50]. Padhi, L., Mohanta, Y. K., and Panda, S. K., (2013). Endophytic fungi with great promises: a review. *Journal of Advanced Pharmacy Education & Research*, 3(3), 152-170.
- [51]. Bary, A., (1884). *Vergleichende morphologie und biologie der pilze, mycetozoen und bacterien*. 1884, Engelmann.
- [52]. Stępniewska, Z. and Kuźniar, A., (2013). Endophytic microorganisms-promising applications in bioremediation of greenhouse gases. *Applied microbiology and biotechnology*, 97, 9589-9596.
- [53]. Manganyi, M. C. and Ateba, C. N., (2020). Untapped potentials of endophytic fungi: A review of novel bioactive compounds with biological applications. *Microorganisms*, 8(12), 1934, 1-25
- [54]. Domka, A. M., Rozpaadek, P., and Turnau, K., (2019). Are fungal endophytes merely mycorrhizal copycats? The role of fungal endophytes in the adaptation of plants to metal toxicity. *Frontiers in Microbiology*, 10, 371, 1-16.
- [55]. Sun, X. and Guo, L. D., (2012). Endophytic fungal diversity: review of traditional and molecular techniques. *Mycology*, 3(1), 65-76.
- [56]. Mishra, Y., Singh, A., Batra, A., and Sharma, M., (2014). Understanding the biodiversity and biological applications of endophytic fungi: a review. *Journal of Microbial & Biochemical Technology*, 8, 4,1-11
- [57]. Huang, W. Y., Cai, Y. Z., Xing, J., Corke, H., and Sun, M., (2007). A potential antioxidant resource: endophytic fungi from medicinal plants. *Economic botany*, 61(1),14-30.
- [58]. Petrini, O., (1991). Fungal endophytes of tree leaves. in *Microbial ecology of leaves*. 1991. Springer.
- [59]. Strobel, G. and Daisy, B., (2003). Bioprospecting for microbial endophytes and their natural products. *Microbiology and molecular biology reviews*, 67(4), 491-502.
- [60]. Pietro-Souza, W., de Campos Pereira, F., Mello, I. S., Stachack, F. F. F., Terezo, A. J., da Cunha, C. N., White, J. F., Li, H., and Soares, M. A., (2020). Mercury resistance and bioremediation mediated by endophytic fungi. *Chemosphere*, 240, 124874,1-12.
- [61]. Hussain, A., Hamayun, M., Rahman, H., Iqbal, A., Shah, M., Irshad, M., Qasim, M., and Islam, B., (2018). Bioremediation of hexavalent chromium by endophytic fungi; safe and improved production of *Lactuca sativa* L. *Chemosphere*, 211, 653-663.
- [62]. Zheng, J., Xie, X., Li, C., Wang, H., Yu, Y., and Huang, B., (2023). Regulation mechanism of plant response to heavy metal stress mediated by endophytic fungi. *International Journal of Phytoremediation*, 1-18.
- [63]. Khalid, M., Saeed, U.-R., Hassani, D., Hayat, K., Pei, Z., and Nan, H., (2021). Advances in fungal-assisted phytoremediation of heavy metals: A review. *Pedosphere*, 31(3), 475-495.
- [64]. Z ahoor, M., Irshad, M., Rahman, H., Qasim, M., Afridi, S.G., Qadir, M., and Hussain, A., (2017). Alleviation of heavy metal toxicity and phytostimulation of *Brassica campestris* L. by endophytic *Mucor* sp. MHR-7. *Ecotoxicology and environmental safety*, 142, 139-149.
- [65]. Verma, D., Bhatt, A., and Agrawal, P., (2016) In-vitro study on bioaccumulation and tolerance of heavy metals by endophytic fungi *Alternaria alternata* isolated from *Cupressus torulosa* D. DON. *Octa Journal of Environmental Research* 4:146-154.
- [66]. Saad, M.M., Saad, M.A., Saad, B.S., Zakaria, F.A., Husain, A.-R.A., and Abdelgaleil, S.A. (2022). Bioremediation and microbial-assisted phytoremediation of heavy metals by endophytic *Fusarium* species isolated from *Convolvulus arvensis*. *Bioremediation Journal*, 1-11.
- [67]. Tovar-Sánchez, E., Concepción-Acosta, C. M., Sánchez-Reyes, A., Sánchez-Cruz, R., Folch-Mallol, J. L., and Mussali-Galante, P., (2023). *Aspergillus luchuensis*, an Endophyte Fungus from the Metal Hyperaccumulator Plant *Prosopis laevigata*, Promotes Its Growth and Increases Metal Translocation. *Plants*, 12(6), 1338, 1-22.