Current Trends in Pharmacology and Clinical Trials
ISSN: 2642-0848

Review Article *Volume 7 Issue 2*

Heavy Metals Accumulation and its Effects on Humans Health

Kotasthane T*, Chandak R and Padhatare D

Department of Pharmaceutics, R G Sapkal Institute of Pharmacy, India

***Corresponding author:** Tanmay Kotasthane, Department of Pharmaceutics, R G Sapkal Institute of Pharmacy, Sapkal Knowledge Hub, Nashik-422212, India, Tel: +919603180159; Email: ktanmay25@yahoo.com

Received Date: September 13, 2024; **Published Date:** October 01, 2024

Abstract

Heavy metals represent a wide interest category of pollutants due to their impacts on the environment and on human health. Contaminated soil with heavy metal is hazard to humans, since the metal ions can enter the food chain through direct ingestion. This review discusses about human diseases caused by heavy metal accumulation and animals, plants which act as a bioindicator for metal contamination available in the environment.

Keywords: Bioindicator; Heavy Metals; Pollutants; Human Health

Introduction

Since ancient times plants have been used in different kind of therapies to cure disease. Herbal products considered as safer, less toxic and accessible compared to conventional medicine. Environmental pollution poses serious concerns on quality and safety issues related to its uses Ozyigit II, et al. [1,2]. Inorganic pollutants, such as heavy metals, represent a wide interest category of pollutants for risk studies due to their impacts on the environment and on human health [3,4]. According to the World Health Organization (WHO), heavy metals are some of the most dangerous pollutants; non-degradable, they accumulate in the environment, transfer through the food chain, and induce negative effects on the environment and human health [5].

According to Pruteanu, et al. [6], medicinal plant abilities are different and selection of them have demonstrated the ability: (i) to tolerate elevated levels of heavy metals and accumulate them in very high concentrations; (ii) to remove, contain, inactivate or degrade harmful environmental contaminants, such as: Cd, Ni, Pb, Zn, Cr; (iii) to absorb a high number of elements from soil and water; and (iv) to be compared to solar driven pumps which can extract and concentrate several elements. Chemical composition of plants depends on soil, geographical conditions and its composition. Herbs are even better for phytoremediation, as they are grown primarily for processing and also have the ability to accumulate and eliminate heavy metals from environment, as well as to reduce risks on human health [7,8].

Background

Environmental pollution is one of the major problem all over the world. Polluting agents should be recognized and remediated by using technological tools. The basic problem includes environmental pollution [9,10] and methods for diagnosing high concentrations of toxic elements [9-12]. Biological indicators are living entity, i.e., animals, plants and/or microorganisms, which are utilize to detect pollutants in a polluted ecosystem. It is subject of study to explore residence time of pollutants and correlation with past, current, and future ecosystem. Biological entity are supportive reproducible and applicable to various scale. In nature biological indicators are regularly used to assess positive and negative changes in a given ecosystem.

By definition, pollution is undesirable change in a given ecosystem liable to cause adverse impacts responsible for deteriorating health, harming biota, damaging structures or amenity, and/or interfering normal functioning of ecosystem and environment. Air pollution poses a significant threat to human health, causing approximately 4.2 million premature deaths in 2019, as reported by the World Health Organization [13]. Anthropogenic activity led to serious pollution problems in aquatic, as well as soil ecosystems and food web. Pollution is hazardous for many biological communities and human may face various health issues. Biological ecosystems are complex physical, chemical and biological phenomena to act towards a dynamic equilibrium. Polluting agents consequences directly governed by reactivity under different ecological circumstances.

"Biological Indicators" describes all sources of living and non-living reactions related to changes in a given ecosystem. Effects of natural changes, reactivity depend on type of biological entity plants, animals or microorganisms. These observations could also be used to find out changes in ecosystems due to the occurrence of pollution that might affect the biodiversity therein. Evolution has played a fundamental part in the adaptation processes of land plants, by enhancing the attributes necessary to thrive under various environments. This has occurred through multiple events, including speciation, duplication, and gene fixation among their genomes [14]. Ancient species and local disturbances in a environment are suitable for selecting the biological markers species or groups of species. Ecologists have established a comprehensive set of worthy biological indicators.

Any kind of biological systems whether plant, animal insects or microorganism might functions as a biological indicator for its surroundings. Occurrence of a given biological indicator certainly acts as warning signal for pollution. They are frequently used to diagnose expected harmful impacts of pollutants towards biosphere. An imperative criterion for the biological indicator is the prompt and correct response to pollution, ability to detect changes, pollution, and/or climate changes in a given ecosystem. Responses to bio-indicators are essentially within a physiological context are complex in nature. However, growth, nourishment, and reproduction are exceptions as they are under direct observation; despite being among the most valuable biological indicators evidences. Physiological responses are visible but their exact use is the most problematic since they seen at the end of a process initiated by the causative pollutant. Pollutants occurring in low concentration requires highly sensitive technologies to identify them at a prohibitive cost. After identification they should be linked with all potential biological hazards. Biological markers has ability to exhibit the indirect biotic effects of pollutants which is not possible by many physical or chemical investigations.

In addition, a clear signal of biological indication might be obscured by a Zaghloul, et al. [15] disproportionate number of responses of divergent species, as some species might increase while others decrease. When incorporating all of a pollutant's direct and indirect effects, emphasis should only be put on sub-set biotas or single species to explain what is happening. This restricted approach makes more appropriate and cost-effective biological measures. Biological indicators often depend on the ecosystem's troublesome intricacies and use a representative and/or totaled reaction to provide a complex image of the ecosystem's state. There are numerous benefits of biological indicators that drove legislative authorities for their use and inclusion in several international accords. But species of biological indicators might be affected by factors other than disruption or stress, such as disease, parasitism, competition, and/or predation, which obscure the image of the causal mechanisms of change. The use of biological indicators is also limited to their ability as scale-dependent. For instances, fish might fail to indicate the biodiversity response to pollutants at a local insect community. In contrast, in their natural ecosystem, species of biological indicators typically have different habitat requirements than other species. The monitoring of ecosystems for specific biological indicators according to their habitat requirements could fail to protect rare species with different requirements. Finally, the overall goal of biological indicators is to use a single species, or a small group of biotas to evaluate the quality of a given ecosystem and how it changes over time, but this could be a gross oversimplification of a complex ecosystem. Nkwoji, et al. reported that biological indicators continuously integrate knowledge from their ecosystem's genetic, physical, and chemical components and manifest as changes in individual fitness, population density, community structure, and ecosystem processes. Biological metrics distinguish between what is and is not biologically stable from a management point of view.

Through biological criteria, the effect of human disruptions could be detected before doing anything to deter them is too late. The ultimate goal of any remediation process should not only be to eliminate pollution, but also to preserve the ecosystem health. Consequently, when assessing the efficiency of a remediation technique, accurate biological health measures are required. Nowadays, biological indicators are exploited and endorsed by several organizations, e.g., the World Conservation Union, International Union for Conservation of Nature, as tools to handle biological monitoring. It seems reasonable to state that the limitations of biological indicators are obviously overshadowed by their benefits Table 1.

Sr No	Plant species	Biomonitoring	Habitat	References
1	(O) Diptera-(F) Chironomidae	Heavy metals	Aquatic	Arimoro FO, et al. [16]
2	(F) Syrphidae	Heavy metals	Terrestrial	Anna M, et al. [17]
3	(O)Diptera- (F) Sarcophagidae	Heavy metal (e.g., asbestos)	Terrestrial	Bartosova M, et al. [18]
4	(O) Odonata-	Heavy metals	Aquatic	Nummelin M, et al. [19]
5	(O) Hymenoptera- (F) Formicidae	Heavy metals	Terrestrial	Nummelin M, et al. [19]
6	(O) Hymenoptera- (F) Apidae	Heavy metals	Terrestrial	Porrini C, et al. [20]
7	(O) Coleoptera- (F) Carabidae	Heavy metal	Terrestrial	Lagisz M, et al. [21]
8	(O) Lepidoptera-(F) Geometridae & Noctuidae	Heavy metal	Terrestrial	Heliövaara K, et al. [22]
9	(O) Hemiptera- (F) Gerridae	Heavy metal (eg Cd)	Aquatic	Jardine TD, et al. [23]
10	(O) Neuroptera- (F) Myrmeleontidae	Heavy metal	Terrestrial	Nummelin M, et al. [19]

*(O):Order (F):Family

Table 1: Bioindicators for variables in terrestrial and aquatic habitats.

Contamination with Heavy Metals: Sources

Metal industries and burning of fossil fuels are the sources of heavy metal pollution. Metal industries produces metal compounds which accumulate in the environment and causes pollution. The fine particles of fine and coarse particles has longer persistence and homogenously dispersed in the environment. These metal particles not degraded in atmosphere their removal is depend on wet and dry deposition. The heavy metals are generally found with a single predominant oxidation state in air borne mixture. Industrial developments and anthropogenic activities have boost the geochemical cycling of metals but have also released significant quantities in all kinds of ecosystems. All of these reasons led to increase of heavy metals levels almost in all kind of environments. The occurrence of heavy metals is mostly in the soil, which makes soil as reservoir for accumulation of metals from different sources and therefore it can pose risks and hazards to the Salami SJ, et al. [24] Tables 2 -6.

Category	Bioindicator	Location of Study	References
liPvlianngtscreatures and th			
since the metal ions ca	Mecaonsgyos(tMeman. gCifoernatamin		
indica)	aPteladtesaouilstwatieth heavy m	tal is a Salami SJ, et al. [24]	
	nGeunmteArrtahbeicfToroede chain		

Table 2: Commonly used bioindicators for copper detection.

Category	Bioindicator	Location of Study	References
Fungi	*Aspergillus flavus*	Cairo, Egypt	Gomaa OM, et al. [25]
Algae	Giant Kelp (*Macrocystis pyrifera*)	Point Loma kelp forest	Evans LK, et al. [26]
Parasite	Spiny headed worm (*Acanthocephala* ns	Antarctica	Ali D, et al. [27]

Table 3: Commonly used bioindicators for mercury detection.

Category	Bioindicator	Location of Study	References
Lamiaceae	Water mint (*Mentha aquatica*)	Lebanon	Zurayk R, et al. [28]
Fabaceae	Alfalfa (Medicago sativa)		Sobrino-Plata J, et al. [29]
Bryophyta	*Brachythecium* sp.,	Obrenovac (Serbia)	Vukojević V, et al. [30]
	Hypnum moss		
Category	Bioindicator	Location of Study	References
Moss	Red stemmed feather	Poland (*Upper Silesia*)	Samecka-Cymerman A, et al. [31]
	cupressiforme)		
Magnolio phyta	Seedlings of Barley	In Laboratory	Liu W, et al. [32]
	schreberi)		
	(*Hordeum vulgare*)	Experiment	
Algae	Green algae	Acid Mine Drainage	Tshumah-Mutingwende, et al. [33]
	(*Cladophora sp*)	(AMD) waters, South	
		Africa	
Mollusca	Mediterranean Limpet (*Patella caerulea*)	Mediterranean area	Storelli MM, et al. [34]
Reptiles	Watersnakes (*Nerodia*	Savannah	Haskins DL, et al. [35]
	taxispilota)	River,United States	

Table 4: Commonly used bioindicators for cadmium detection.

Category	Bioindicator	Location of Study	References
Amoeba	Testate lobose amoebae (*Lacustrine*	Yellowknife, Northwest Territories,	Riou L, et al. [36]
	arcellinina)	Canada	
Bryophyta	Aquatic bryophytelike	Sudetes Mts., Poland;	Samecka-Cymerman A, et al. [37]
	Pale Liverwort (*Chiloscyphus pallescens*)	and east Sudetic Rychlebske Mts. And Jesenik Mts. (Czech Republic).	
	Brachythecium sp., Hypnum moss (*Hypnum cupressiforme*), Silvergreen Bryum		Sabovljević M, et al. [38]
	moss (*Bryum argenteum*)		
		Obrenovac (Serbia)	
Pteridophyta	(*Vallisneria gigantean*)		Iriel A, et al. [39]
	and Water Fern (*Azolla filiculoides*)	Latin America	
Fabaceae	Nodule bacteria of red clover (*Trifolium praténse*), Alsike clover (*Trifolium hibridum*)	North Caucasus Research Institute of the Vladikavkaz Scientific Center of	Bekuzarova SA, et al. [40]
		the Russian Academy of Sciences.	

Table 5: Commonly used bioindicators for arsenic detection.

Category	Environment	Bioindicator	References
Flowers	Land terrain	Sunflower (*Helianthus*)	Macek T, et al. [41]
Lichens	Fog Belts	Script lichen (*Graphis scripta*)	Hasairin A, et al. [42]
Trees	Landy terrain	Sacred fig (*Ficus religiosa*)	Agrahari P, et al. [43]
Aquatic Animals	Marine	Starfish (*Asteroidea*)	Temara A, et al. [44]

Table 6: Commonly used bioindicators for lead detection.

A Path for Human Health Risks Caused by Contaminated Medicinal Plants

Cosmetics containing heavy metals are injurious to human health. Personal care products manufacturing is very competitive. Innovation and strategies is needed for competitive brands to reduce risks to human health, with consumer requirements, so as to nullify heavy metals use. Products contaminated with heavy metals are no longer considered safe. High contaminants of heavy metals in cosmetics is due to source of raw materials used, techniques involved, stock, and transportation. Sometimes heavy metal contamination is unavoidable but should be removed to certain extent. Table 1 to 6 shows bio-indicators for metal detection.

The Interactions between Heavy Metals and Medicinal Plants

Survival mechanism of plants is very complex. In stress condition plants use their mechanism of genetically engineered programmed cell death to survive. Depending on the tolerance of the medicinal plant species and the nature of the metal ions, the responses of defense in tissues may vary. Usually, the accumulation of heavy metal ions starts in the soil through the roots, at which point signals are transmitted to the plant tissues responsible for producing substances that have the ability to counteract them. A number of metabolites are secreted from certain organs.

Assessment of Risks to Human Health

Heavy metal accumulation causes wide variety of human health issues few of them discussed in detail.

Gastrointestinal: The gut microbiota has a major role in the intestinal homeostasis. It is observed in several studies that exposure to heavy metals pollutants may contribute progression of diseases lead to perturbations in the gut leading to dysbiosis. Presence of toxic heavy metals prevalent in the environment effects on the gut microbiota function and composition upon exposure to toxic heavy metals. The disturbance in gut microbial ecology also affects the biochemical pathway which may alter the state and bioavailability heavy metals therefore affecting metal uptake detoxification mechanisms related to heavy metal metabolism. The toxic effects of various heavy metals require studies with important consideration for therapeutic and protective strategies against the damage to gut microbiota. Children and young people are especially vulnerable to heavy metal intoxication [45,46].

Kidney dysfunction: Heavy metals are used for various purposes in agriculture and industrial applications such as production of pesticides, batteries and metallic utensils. Exposure to heavy metals for longer period may cause systemic disorders. Kidney is a organ for ultrafiltration of urine because of its ability to filter, reabsorb and concentrate divalent ions it is a target organ for toxic heavy metal accumulation. The renal damage depends on type of metal, quantity and exposure time. Acute kidney impairment differs from serious renal failure in its mechanism and its magnitude. As a result, clinical features, diagnosis and treatments are also different. Heavy metals exist in an ionized form, that is toxic and a bound, inert form when metal is conjugated with metal lothionein and then delivered to the liver causing the kidney chronic damage. Treatment include chelation therapy, intensive care, renal replacement therapies and decontamination procedures.

Nervous system disorder: Genetic and Environmental cause, Multiple sclerosis and the major sporadic neurogenerative disorders, Parkinson disease, and Alzheimer. Advances have been made to find out genetic relation to these disorders, but it is difficult to know environmental agents that initiate them. Environmental toxic metals have been implicated in neurological disorders, since human activities and natural source cause exposure to toxic metals .Toxicity of metals have damaging properties that are main cause of these disorders. This is area of research that how metals or combinations of metals are enough to precipitate disease and how toxic metal exposure leads to different patterns of nerve and white matter loss. Toxic metals cause dysfunction of the blood–brain barrier. This makes toxicants to enter astrocytes, from where they are transferred to, and damage, oligo dendrocytes, and neurons. The type of neurological disorder depends on (i) locus ceruleus neurons are damaged, (ii) genetic variation that give rise to susceptibility to toxic metal intake, cytotoxicity, (iii) the age, duration and frequency of toxicant exposure. Proof supporting this hypothesis is presented, targeting on studies that have examined the distribution of toxic metals in the humans [47-50]. Clinicopathological features can be linked to toxic metals. In conclusion, environmental toxicity of metals may leads to several common neurological disorders. While further study to support this hypothesis is needed, to protect the nervous system necessary steps should be taken to reduce environmental toxic metal pollution from industrial, mining, and manufacturing sources, and from the burning of fossil fuels.

Skin leisons: Contact dermatitis is an inflammatory skin reaction caused by direct contact with chemical substances in the environment and can either be irritant or allergic in nature. The clinical symptoms of contact dermatitis, include local rash, itching, redness, swelling, and lesions of skin. Acids and alkalis such as drain cleaners, nail polish remover, plants such as poinsettias and hair colors, are all prominent causes of irritant contact dermatitis (ICDs). Heavy metals are metallic elements with a high atomic weight that are hazardous in low quantities and are known to cause dermatitis after systemic or local exposure. Nickel (Ni), chromium (Cr), lead (Pb), and copper (Cu) are among the common heavy metals used in various industries. Contact dermatitis is detected by laboratory tests such as patch testing, lymphocyte stimulation test (LST), and evaluation of cytokine production by primary cultures of peripheral blood mononuclear cells.

Vascular damage: Heavy metals are polluting agents and has various health hazards to human heart disease. Heavy metals, like cadmium,lead, mercury, chromium, and arsenic, are found in various sources such as air, water, soil, food, and industrial products. There is strong evidence to show connection between heart disease and exposure to heavy metals. Heavy metals can enhance the production of reactive oxygen species, which can then worsen reactive oxygen species generation and induce inflammation, resulting in endothelial dysfunction, lipid metabolism distribution, homeostasis disturbance, and epigenetic changes. Over a period of time, heavy metal exposure eventually leads to an increased risk of hypertension, arrhythmia, and atherosclerosis. Public health prevention and the application of antioxidants, such as vitamins and β-carotene, along with micronutrients, like selenium and zinc, can diminish the burden of vascular disease.

Immune system dysfuntion: Heavy metal exposure as a form of environmental pollution cause serious health problem all over the world .Children are more prone to have ill effects of heavy metal exposure because of imperfect physical development. Research shows that heavy metal exposure is associated with low immune response in children. Although there are lot of studies describing the evidence for the negative effects of heavy metal exposure on the immune system in children. Heavy metals such as (lead (Pb), cadmium (Cd), arsenic (As), mercury (Hg), nickel (Ni), and manganese (Mn)) have effects on children's innate immune cells, WBCs, cytokines, total and specific immunoglobulins. Exposure to heavy metals, particularly Pb, Cd, As, and Hg, not only shows suppressed adaptive immune responses in children, but also altered the innate immune system to impair the body's capacity to fight pathogens. Heavy metal exposure alters cytokine levels which induce inflammatory responses in children. Pb, As, and Hg exposure was associated with decreased antibody titers, and high risk of immune-related diseases in children by changing specific immunoglobulin levels. Cd, Ni and Mn showed activation effects on the immune response to childhood vaccination. Age, sex, nutritional status, may influence the effects of heavy metals on immunity in children.

Birth defects: Polluting metals; such as lead (Pb), cadmium (Cd), and mercury (Hg), in the ecosystem have potential risk factors and negative effects on pregnant women and the embryonic developments in humans, including reproductive disorders, reduced weight. Several studies have explored the association between air pollution exposure and MN frequencies, yielding interesting findings. O'Callaghan-Gordo C, et al. [51] demonstrated the genotoxic repercussions of air pollution on pregnant women. Environmental pollution with heavy metals may cause congenital diseases.

Cancers: Heavy metals are highly toxic, have environmental persistence, and accumulation in living organisms. Human health is a main concern poisoned by harmful heavy metals. Most heavy metals pollute all the strata of atmosphere which can be fatal to humans. All living beings can be exposed to heavy metals through water, soil, or air). Their entry into the food chain confirms effects on macromolecules DNA, RNA and proteins in living systems, resulting in undesirable outcomes. Combustion of fossil fuels, industrial discharge cause spread of metals like mercury, lead, chromium, cadmium, and arsenic through all medium. These spread causes dysfunction of organ and organ system. These heavy metals are carcinogenic. Heavy metals interfere with human metabolism, including proliferation, differentiation, repair and apoptosis.

Conclusion

Biological indicators acts as warning signal for pollution. They are used to diagnose harmful impacts. They are frequently used to diagnose expected harmful impacts of pollutants towards biosphere. Biological indicator is the prompt and correct response to pollution, ability to detect changes, pollution, and/or climate changes in a given ecosystem. The occurrence of heavy metals is mostly in the soil, which make it reservoir for accumulation of metals from different sources and therefore it can pose risks and hazards to living creatures and the ecosystem. Contaminated soil with heavy metal is hazard to humans, since the metal ions can enter the food chain through direct ingestion or skin contact with the soil, or drinking of contaminated groundwater.

References

1. Ozyigit II, Yalcin B, Turan S, Saracoglu IA, Karadeniz S, et al. (2018) Investigation of Heavy Metal Level and Mineral Nutrient Status in Widely Used Medicinal Plants' Leaves in Turkey: Insights into Health Implications. Biol Trace Elem Res 182(2): 387-406.

2. Suteu D, Rusu L, Zaharia C, Badeanu M, Daraban GM (2020) Challenge of Utilization Vegetal Extracts as Natural Plant Protection Products. Appl Sci 10(24): 8913.

3. Rosca M, Cozma P, Minut M, Hlihor RM, Betianu C, et al. (2021) New Evidence of Model Crop *Brassica napus* L. In Soil Clean-up: Comparison of Tolerance and Accumulation of Lead and Cadmium. Plants 10(10): 2051.

4. Asiminicesei DM, Hlihor RM, Cozma P, Apostol M, Simion IM, et al. (2020) Medicinal Plants: Linking Herbs Contamination with Human Health Risks. In: Proceedings of the 2020 8th (Edn.), E-Health and Bioengineering Conference, pp: 1-4.

5. Joint WHO/Convention Task Force on the Health Aspects of Air Pollution (2007) Health Risks of Heavy Metals from Long-Range Transboundary Air Pollution. WHO Regional Office for Europe: Geneva, Switzerland.

6. Pruteanu A, Muscalu A (2014) Phytoremediation Using Medicinal Plants–A Review. Ann Univ Craiova Agric Montanology Cadastre Ser 44: 186-193.

7. Mishra B, Chandra M (2022) Evaluation of Phytoremediation Potential of Aromatic Plants: A Systematic Review. J Appl Res Med Aromat Plants 31: 100405.

8. Fattahi B, Arzani K, Souri MK, Barzegar M (2019) Effects of Cadmium and Lead on Seed Germination, Morphological Traits, and Essential Oil Composition of Sweet Basil (*Ocimum basilicum* L.). Ind Crops Prod 138: 111584.

9. Wang Z, Pan X, Uno I, Chen X, Wang Z (2018) Importance of mineral dust and anthropogenic pollutants mixing during a long-lasting high PM event over East Asia. Environmental Pollution 234: 368-378.

10. Mendoza LM, Mladenov N, Kinoshita AM, Pinongcos F, Gersberg R (2020) Fluorescence-based monitoring of anthropogenic pollutant inputs to an urban stream in Southern California, USA. Science of The Total Environment 718: 137206.

11. Ermakov VV (2017) A.P. Vinogradov's concept of biogeochemical provinces and its development. Geochem Int 55(10): 872-886.

12. Ermakov VV, Tyutikov SF, Danilova VN (2020) Ecological Monitoring of the Unal Depression, Northern Ossetiya–Alania, Using Techniques of Biogeochemical Indication. Geochem Int 58(3): 332-341.

13. World Health Organization (2022) Ambient (outdoor) air pollution. Air quality and health.

14. Qiao X, Li Q, Yin H, Qi K, Li L, et al. (2019) Gene Duplication and Evolution in Recurring Polyploidization–Diploidization Cycles in Plants. Genome Biol 20(1): 38.

15. Zaghloul A, Saber M, Gadow S, Awad F (2020) Biological indicators for pollution detection in terrestrial and aquatic ecosystems. Bulletin of the National Research Centre 44(127): 2-11.

16. Arimoro FO, Auta YI, Odume ON, Keke UN, Mohammed AZ (2018) Mouthpart deformities in Chironomidae (Diptera) as bioindicators of heavy metals pollution in Shiroro Lake, Niger State, Nigeria. Ecotoxicol Environ Saf 149: 96-100.

17. Anna M, Lukasz M, Elżbieta **WŻ (2021) Hoverflies (**syrphidae: Diptera) in areas contaminated with heavy metals (Cd, Zn, Pb). Folia Hortic 33(2): 325-342.

18. Bartosova M, Glovinova E, Povolny D (1997) Use of flesh-flies (Diptera, Sarcophagidae) for eco toxicological bioindication. Ekol Bratisl 16(3): 319-322.

19. Nummelin M, Lodenius M, Tulisali E, Hirvonen H, Alanko T (2007) Predatory insects as bioindicators of heavy metal pollution. Environ Pollut 145(1): 339-347.

20. Porrini C, Sabatini AG, Girotti S, Ghini S, Medrzycki P, et al. (2003) Honey bees and bee products as monitors of the environmental contamination. Apiacta 38: 63-70.

21. Lagisz M (2008) Changes in morphology of the Ground beetle Pterostichus oblongopunctatus Fab. (coleoptera; carabidae) from vicinities of a zinc and lead smelter. Environ Toxicol. Chem 27(8): 1744-1747.

22. Heliövaara K, Väisänen R (1990) Heavy-metal contents in pupae of Bupalus piniarus (Lepidoptera: Geometridae) and Panolis flammea (Lepidoptera: Noctuidae) near an industrial source. Environ Entomol 19: 481-485.

23. Jardine TD, Al TA, MacQuarrie KTB, Ritchie CD, Arp PA,

et al. (2005) Water striders (family Gerridae): Mercury sentinels in small freshwater ecosystems. Environ Pollut 134: 165-171.

24. Salami SJ, Oyere AJ (2010) Mangifera indica as a bioindicator of lead, copper and iron in the vicinity of a metal smelting plant, Bukuru Jos, Nigeria. Global Journal of Pure and Applied Science 16(4): 417- 421.

25. Gomaa OM, Azab KS (2013) Biological indicators, genetic polymorphism and expression in Aspergillus flavus under copper mediated stress. Journal of radiation research and applied sciences

26. 6(2): 49- 55.

27. Evans LK, Edwards MS (2011) Bioaccumulation of copper and zinc by the giant kelp Macrocystis pyrifera. Algae 26(3): 265-275.

28. Ali D, Almarzoug MH, Al AH, Samdani MS, Hussain SA, et al. (2020) Fish as bio indicators to determine the effects of pollution in river by using the micronucleus and alkaline single cell gel electrophoresis assay. Journal of King Saud UniversityScience 32(6): 2880-2885

29. Zurayk R, Sukkariyah B, Baalbaki R (2001) Common hydrophytes as bioindicators of nickel, chromium and cadmium pollution. Water Air and Soil Pollution 127(1): 373-388.

30. Sobrino-Plata J, Ortega-Villasante C, FloresCáceres ML, Escobar C, Del Campo FF, et al. (2009) Differential alterations of antioxidant defenses as bioindicators of mercury and cadmium toxicity in alfalfa. Chemosphere 77(7): 946-54.

31. Vukojević V, Sabovljević M, Sabovljević A, Mihajlović N, Dražić G, et al. (2006) Determination of heavy metal deposition in the county of Obrenovac (Serbia) using mosses as bioindicators II: Cadmium (CD), cobalt (CO), and chromium (CR). Archives of Biological Sciences 58(2): 95-104.

32. Samecka-Cymerman A, Kosior G, Kolon K, Wojtuń B, Zawadzki K, et al. (2013) Pleurozium schreberi as bioindicator of mercury pollution in heavily industrialized region. Journal of Atmospheric Chemistry 70(2): 105-114.

33. Liu W, Li PJ, Qi XM, Zhou QX, Zheng L, et al. (2005) DNA changes in barley (Hordeum vulgare) seedlings induced by cadmium pollution using RAPD analysis. Chemosphere 61(2): 158-167.

34. Mutingwende T, Setswa RRM (2014) Assessment of Algae as Mercury Bioindicators in Acid Mine Drainage waters and their potential for Phytoremediation. Doctoral dissertation, University of the Witwatersrand, Johannesberg.

35. Storelli MM, Marcotrigiano GO (2005) Bioindicator organisms: heavy metal pollution evaluation in the Ionian Sea (Mediterranean Sea-Italy). Environmental Monitoring and Assessment 102(1): 159-166.

36. Haskins DL, Brown MK, Bringolf RB, Tuberville TD (2021) Brown watersnakes (Nerodia taxispilota) as bioindicators of mercury contamination in a riverine system. Science of the Total Environment 755(2): 142545.

37. Riou L, Nasser NA, Patterson RT, Gregory BR, Galloway JM, et al. (2021) Lacustrine Arcellinida (testate lobose amoebae) as bioindicators of arsenic concentration within the Yellowknife City Gold Project, Northwest Territories, Canada. Limnologica 87: 125862.

38. Samecka-Cymerman A, Kempers AJ (1994) Aquatic bryophytes as bioindicators of arsenic mineralization in Polish and Czech Sudety Mountains. Journal of Geochemical Exploration 51(3): 291-297.

39. Sabovljević M, Vukojević V, Mihajlović N, Dražić G, Vučinić Z, et al. (2005) Determination of heav metal deposition in the county of Obrenovac (Serbia) using mosses as bioindicators: I. Aluminum (Al), arsenic (As), and boron (B). Archives of Biological Sciences 57(3): 205-212.

40. Iriel A, Dundas G, Cirelli AF, Lagorio MG (2015) Effect of arsenic on reflectance spectra and chlorophyll fluorescence of aquatic plants. Chemosphere 119: 697-703.

41. Bekuzarova SA, Bekmurzov AD, Datieva IA, Lushchenko GV, Salbieva MG (2020) Clover nodule bacteria as bioindicators of soils contaminated with heavy metals. IOP Conference Series: Earth and Environmental Science IOP Publishing 421(6): 062043.

42. Macek T, Kotrba P, Svatos A, Novakova M, Demnerova K, et al. (2008) Novel roles for genetically modified plants in environmental protection. Trends in biotechnology 26(3): 146-152.

43. Hasairin A, Siregar R. (2018) The analysis of level of lead (Pb) on lichens as a bioindicator of air quality in Medan Industrial Area and Pinang Baris Integrated Terminal in Medan, Indonesia. In: IOP Conference Series: Earth and Environmental Science. IOP Publishing 187(1).

44. Agrahari P, Richa, Swati K, Rai S, Singh VK, et al. (2018) *Ficus religiosa* Tree Leaves as Bioindicators of

Heavy Metals in Gorakhpur City, Uttar Pradesh, India. Pharmacog J 10(3): 416-420.

45. Temara A, Skei JM, Gillan D, Warnau M, Jangoux M, et al. (1998) Validation of the asteroid Asterias rubens (Echinodermata) as a bioindicator of spatial and temporal trends of Pb, Cd, and Zn contamination in the field. Marine environmental research 45(4-5): 341-356.

46. Sharma B, Singh S, Siddiqi NJ (2014) Biomedical Implications of Heavy Metals Induced Imbalances in Redox Systems. Biomed Res Int.

47. Attahiru U, Birnin-Yauri UA, Muhammad C. (2015) Acacia nitolica as bioindicator of copper and cobalt pollution due to vehicular emission along the main entrance road of Usmanu Danfodiyo University, Sokoto-Nigeria. Int J Adv Res Chem Sci 2: 1-8.

48. Stojanowska A, Rybak J, Bozym M, Olszowski T, Ihalowicz JS (2020) Spider Webs and Lichens as Bioindicators of Heavy Metals: A comparison study in the vicinity of a copper smelter (Poland). Sustainability 12(19): 8066.

49. Nasirian H, Irvine KN (2017) Odonata larvae as a bioindicator of metal contamination in aquatic environments: application to ecologically important wetlands in Iran. Environmental monitoring and assessment 189(9): 1-18.

50. Aliko V, Hajdaraj G, Caci A, Faggio C (2015) Copper induced lysosomal membrane destabilisation in haemolymph cells of Mediterranean green crab (Carcinus aestuarii, Nardo, 1847) from the Narta Lagoon (Albania). Brazilian Archives of Biology and Technology 58(5): 750-756.

51. Nedelescu M, Stan M, Ciobanu AM, Balalau C, Filippini T, et al. (2022) Attention Deficit among Preschool and School-Aged Children Living near Former Metal-Processing Plants in Romania. Environ Res 208: 112689.

52. O'Callaghan-Gordo C, Fthenou E, Pedersen M, Espinosa A, Chatzi L, et al. (2015) Outdoor air pollution exposures and micronuclei frequencies in lymphocytes from pregnant women and newborns in Crete, Greece (Rhea cohort). Environ Res 143: 170-176.