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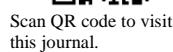
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Evaluating the Protective and Detoxifying Role of Zeolite in Heavy Metal Exposure in Animal Models

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Abstract:

Research on detoxifying living things from toxic compounds is gaining importance since many toxins have negative effects that might either directly or indirectly jeopardize human health through the environment or the food chain. The issue becomes more significant when it comes to inexpensive and plentiful elements like heavy metals and their compounds, which primarily contaminate surface, ground, subsurface, and drinking water sources. Several methods have been suggested for the cleaning of sites inaccessible to microbiological methods. Nevertheless, these methods are usually accompanied by their own side effects and inevitably contaminate the environment again or have residual toxic effects on human health during or after application. In recent years it has been observed that the minerals of the group of zeolites, which are hydrated aluminosilicates of alkali and alkaline earth metals, have the ability to detoxify soils and subsoil polluted with heavy metals. The aim of the present review is to explore the international bibliography for research on the application of zeolites in the toxicology of heavy metals. This research will hopefully contribute to a better understanding of the application of zeolites in general toxicology. Furthermore, it is suggested that the methods and the results of the studies that are described should be taken into account when experiments are carried out to investigate the effect of zeolites on the health of exposed animals.

INTRODUCTION

Heavy metals are widely spread on earth and their high toxicities cause serious harm to human beings and animals because of their accumulative bioavailability and non-biodegradable properties (Iqbal and Ashraf, 2022; Singh *et al.*, 2023). Over the past few decades, thousands of scientific reports and research investigations showed that heavy metals are the most dangerous pollutants and harmful to environmental ecology and human health (Alkhatib, and Alalawneh, 2020; Iqbal and Ashraf, 2018; 2023; Peng *et al.*, 2022).

Zeolite is a family of hydrated aluminosilicate minerals with well-defined open structures on a molecular scale containing pores of rigid dimensions (Pérez-Botella *et al.*, 2022). Among different compositions of zeolite, clinoptilolite is the most prevalent and commercially important (Rodríguez-Iznaga *et al.*, 2022). Ion selectivity is a feature typical of all zeolites, whose exchange is based on the stoichiometric substitution of one or more exchangeable ions in the zeolite structure (Morante-Carballo *et al.*, 2021). A considerable amount of information on the principal applications of zeolites has recently been summarized (Cataldo *et al.*, 2021). Their potential use in: chemical and petrochemical industries, agriculture, environment, domestic and medical applications, purification of water, and as adsorption media, is also documented (Islam *et al.*, 2022). Past reports on the effect of dietary zeolites and aluminosilicate substances on physiological conditions, reproduction, immunity response, and prevention of common diseases of farm animals are relatively rare and specialized (Fajdek-Bieda *et al.*, 2021). Most of the works are summaries without detailed information on the mode of action or the potential of their use in the feed formula so extensive study was a necessity to be undertaken (Pavlović *et al.*, 2024). The pure and hydrated forms of clinoptilolite were applied in this experiment to study their effect on the prevention and treatment of common diseases (Kordala and Wyszkowski, 2024).

Background and Rationale

The potential hazards of heavy metal exposure have attracted mounting public attention (Hadyait *et al.*, 2018). The detrimental effects of heavy metals on human and animal health have been conclusively established, even at low exposure levels (Iqbal and Ashraf, 2022). Industrialization has led to widespread heavy metal contamination from mining, agriculture, metallurgy, and other sectors (Al-Kharraz *et al.*, 2021; Ashraf and Iqbal, 2021; Ma *et al.*, 2022; Zia, 2019). Moreover, many additives in everyday commodities and materials can release heavy metals (Iqbal, 2023; Zhang *et al.*, 2021). In particular, traditional medicines may be contaminated during cultivation, production, and storage (Zhang *et al.*, 2021). Modern toxicological, biochemical, and molecular methods have been developed to assess the prevalence, toxicology, and mechanisms of heavy metal exposure (Liu *et al.*, 2021). Interest in using plants to solve environmental contamination has been growing rapidly in recent years (Ashraf *et al.*, 2021; Iqbal *et al.*, 2023; Sattar *et al.*, 2018; Sultana *et al.*, 2019a,b). Approaches to detoxifying heavy metals using natural and treated agents remain under investigation (Wangi *et al.*, 2023). Among man-made aluminosilicate adsorbents, natural zeolite stands out as a superior alternative for heavy metal uptake (Hannan *et al.*, 2024). Recent studies have shown that the administration of natural or treated zeolite can adsorb heavy metals and ameliorate toxicity effects in the blood, kidney, lung, and liver, providing a cost-effective approach for heavy metal exposure cases (Thatikayala *et al.*, 2023). Plentiful studies remain to explore methods to reduce heavy metal absorption or enhance detoxification (Senila and Cadar, 2024).

A great deal of literature has investigated the protective and detoxifying role of zeolite in heavy metal exposure in animal models. Nonetheless, the quantity and quality of studies focusing on this subject remain limited (Verma *et al.*, 2023). The hypotheses and methods adopted to evaluate the protective and detoxifying function of zeolite in heavy metal exposure were uneven (Szerement *et al.*, 2021). Consequently, a

comprehensive knowledge-based study was conducted to assess the protective and detoxifying effect of zeolite in animal models for preventing heavy metal-associated diseases (Liaquat *et al.*, 2024).

Heavy metal toxicity in animals

Every day, the presence of heavy metals continues to be a serious problem in the environment (Zaynab *et al.*, 2022). These metals include lead, cadmium, mercury, iron, copper, zinc, aluminum, and selenium (Mitra *et al.*, 2022). The most toxic heavy metals among these are lead, cadmium, and mercury (Sun *et al.*, 2021). They are regarded as highly hazardous due to their biological impact at even a very low concentration and to contamination problems. In general, heavy metal concentrations in the environment are getting increased (Balali-Mood *et al.*, 2021). Most heavy metals are not easily biodegradable in the natural environment. Heavy metals are of serious concern because of their toxic effect on the growth of animals, plants, and human beings (Zhai *et al.*, 2014).

Considering the toxic elements, heavy metals like lead, mercury, and cadmium are listed as toxic even at very low doses (Balali-Mood *et al.*, 2021). Given rapid progress in industrialization and urbanization, widespread use of chemical substances, and the need for high productivity in agricultural practices, the current heavy metal pollution scenario appears to be a serious global environmental issue (Khatun *et al.*, 2022). In animals, heavy metals affect the physiological, biochemical, and behavioral systems (Satarug *et al.*, 2022). Exposure to high levels of heavy metals can cause severe health implications (Charkiewicz *et al.*, 2023; Iqbal and Ashraf, 2022). Due to an increase in pollution, grazing animals come into direct/internal contact with heavy metals (Glicklich and Frishman, 2021). The risk factors associated with heavy metal toxicity are the species variation, stage of life, and duration and amount of toxic exposure metals, and include effects on physiology, biochemistry, behavior, reproduction, and growth performance (Wang *et al.*, 2021). There is variation in the ability of species to counteract

the ill effects of harmful agents, including heavy metals (Ungureanu and Mustatea, 2022). The need for urgent attention on this issue due to potential human health implications is highlighted (Mitra *et al.*, 2022). In order to secure and maintain the health of consumers scientific data is necessary to create awareness concerning sources of heavy metal contamination in the ecosystem (Martinez-Finley and Aschner, 2011).

Different heavy metals can exert toxicity through several complex mechanisms (Balali-Mood *et al.*, 2021). Metal causes toxicity due to a toxic derivative produced during metal metabolism or exposure. These can include enzyme activities, hormone concentration, and other biochemical measures (Mitra *et al.*, 2022). Changes in biochemical compounds may precede changes in physiological or behavioral phenomena indicators of animal heavy metal toxicity (Alotaibi *et al.*, 2021). Commonly measured parameters in the studies include serum biochemical compounds such as protein, cholesterol, urea, creatinine, glucose, enzymes, and minerals (Cao *et al.*, 2021). Blood, urine, and some tissues are frequently analyzed for heavy metal residue and the health status of animals (Ungureanu and Mustatea, 2022). Behavioral effects are caused by changes in the way animals interact with their environment such as changes in feeding behavior, drinking behavior, motion, or locomotion activity in animals (Aslam *et al.*, 2021). At the cellular level, some animal behavior may be due to changes in the enzyme system or neurotransmitter system in the brain of exposed animals (Peana *et al.*, 2021). Broad behavioral assessments are typically used to investigate abnormalities in animals exposed to heavy metals. Such an approach provides a potential for developing behaviorally related biomarkers of heavy metal exposure and toxicity (Alengebawy *et al.*, 2021). Long-term effects of heavy metals include non-carcinogenic risks to systemic toxicity (pharmaceutical, reproductive, cardiovascular, endocrine, or central nervous system effects). Hormonal changes influence the growth performance of exposed animals (growth rate, conversion efficiency, distribution of lean and fat tissue, etc.) (Peana *et al.*, 2021). Additionally, deficiencies in trace minerals may

add to the effects of heavy metals (Alengebawy *et al.*, 2021).

Sources of heavy metal exposure

Various abiotic and biotic factors contribute to metal exposure in animals (Martinez-Finley and Aschner, 2011). Abiotic factors include natural sources such as weathering of metal ores, parent rocks, forest fire, and volcanic eruption, which also contribute to an increase in soil metal concentration that can subsequently be colonized by nearby plants and bio-accumulated in their cells, being ingested by animals (Liu *et al.*, 2024). Anthropogenic factors play a greater role in increasing the environmental heavy metal concentration worldwide and are considered a major concern (Petrlik *et al.*, 2024). Particular to these issues are the industrial discharge activities which inadvertently dispose of metal waste to the nearest water ponds, rivers, or land crops (Guan *et al.*, 2023; Iqbal, 2024; Iqbal and Khalid, 2024). In the same way, the polluted irrigated water also additionally contaminates the plant's metabolites and serves as a significant medium for metal transmission to animals (Pathak *et al.*, 2023). Before reaching the human body, these metals would be bio-accumulated in the food chain, potentially increasing several thousand to million folds depending on the bio-accumulation behavior of each metal (Oginawati *et al.*, 2024). Geographical variation also plays a significant role in the heavy metal distribution and concentration attributed to differential indigenous physicochemical and ecological factors, differences in habitats, water quality, soil quality, monsoon, industrial distribution, farming, and industrial practices, type of ore, mining activities, etc. (Abd Elnabi *et al.*, 2023). The attention of health and natural sciences is also particularly drawn to understand the health effects of metal-contaminated water, and crop soil on animals, and by analogy to humans, providing possible methods of treatment and prevention by occupational or therapeutic means for metal exposure. In developing countries like Indonesia, with a high majority of rural areas, heavy metal contamination is largely overlooked. The risk of absorption from exposure to all sources of a group in the environment, reference dose, and health-based standard set by the

corresponding health-based guidance value of each source of exposure results in about 20-95% of the source of exposure occurring throughout the population, and that 50% of the population exposure is exceeded (Kurniawan *et al.*, 2024).

Health effects

Exposure to heavy metals has numerous deleterious health effects on exposed animals (Mitra *et al.*, 2022). These can manifest rapidly as symptoms of acute poisoning or after chronic exposure and may include loss of appetite, colic, aspiration of stomach contents in the lungs, diarrhea, constipation, fever, bloody stool, shock, hepatotoxicity, and increased blood levels of metals, among many others (Sun *et al.*, 2021). Chronic diseases related to chronic metal exposure occur in systems such as anemia, bladder cancer, diabetes, gastrointestinal disorders, hemochromatosis, hepatotoxicity, kidney disease and kidney stones, lung cancer through occupational exposure, neurodegenerative diseases, dermatoses, peripheral neuropathy, and encephalopathy, osteomalacia, and osteoporosis, including examples like lead poisoning from exposure through water pipes, mercury poisoning while tanning hides, and zinc, iron and copper poisoning in patients with hemochromatosis, Wilson's diseases and Menke's kinky hair syndrome, among many others (Martinez-Finley and Aschner, 2011). The health effects of heavy metals are broad and complex, depending on the exact composition of the metal-containing soil (Munir *et al.*, 2021). Through metal exposure, a broad range of physiological responses can be triggered, from organ damage or loss of function to changes in behavior, adaptations to reduce the accumulation of metal, and damage to the central nervous system, which may involve gender differences (Budi *et al.*, 2024). On a larger level metal can affect ecosystems by modulating nutrient availability, affecting soil organisms, or killing plant species, hence reducing overall biodiversity (Parida and Patel, 2023). Since many elements exhibit toxic metals at relatively low levels of exposure, this constitutes a major concern in agriculture and food safety (Naz *et al.*, 2021). Metal toxicity is

found in all species, and numerous researchers have been involved in trying to elucidate the effects of excess metal on the biological processes of a particular organism and the possible solutions, especially in the recent development of cost-effective methods (Garai *et al.*, 2021). The finding of the acute and chronic effects of heavy metal poisoning across species is of paramount importance (Mansoor *et al.*, 2023).

Zeolite: Properties and Applications

According to the UNEP, diverse types of fast urbanization, different industrial activities, combustion of fossil fuels, and others, have rolled out the quick increase of ecological pollution with heavy metals, contamination of groundwater, soil, and all living organisms formed in them consistently (Grifasi *et al.*, 2024). Developing and testing effective nutrients for safeguarding the ecological media versus the heavy metals needs to be materialized very large concern and engage in looking for alternative solutions (Gorimbo *et al.*, 2021). Zeolites occur in nature, predominantly in sedimentary rocks and as a result of atypical secondary minerals (Prisa, 2023). Natural zeolites have been located in almost all nations, with explicit amount in Greece, Korea, Italy, Russia, Japan, Turkey, and as a component of the Carpathian Mountains region; in the north-eastern area of Romania (Jarosz *et al.*, 2022). Zeolites require mechanical processing to be actuated, which allows for cutting, washing, drying, grinding, and sizing (Mytiglaki *et al.*, 2024).

Therefore, zeolites have been applied widely in detergents; pet stock feed adsorption agents, dietary supplements, soil conditioners, slow catalysts, and fertilizers, as well as ion exchangers in nuclear, mining, and hydrometallurgical industries (Zhang *et al.*, 2022). With relation to the heavy metal blooming of the ecological environment, it is very exploitable property of their high affinity (Velarde *et al.*, 2023). Zeolites have high selectivity and affinity for heavy metals and are well in concord with their serious environmental concerns (Pérez-Botella *et al.*, 2022). Numerous

researches found high efficiency of zeolite to remove heavy metals from environmental media (Li and Yu, 2021). The use of zeolites for the adsorption of ions and pollutants has a pivotal in the last few decades. Due to the structure and physical and chemical properties, zeolites have been commonly applied for adsorption in a multitude of applications, including e.g., environmental remediation, agriculture, and wastewater treatment. Efforts have been made for their application in order to reduce pollutants like phosphorus and ammonium (Sun *et al.*, 2021). Zeolites can be applied in deterging and dispersing laundry. Zeolites present a wide adsorption area (Fan *et al.*, 2021). Zeolites are widely employed in environmental and industrial processes, including the adsorption and removal of substances like heavy metals that are both solid and gaseous. They are good adsorbents for a variety of pollutants due to their high surface area and special porous structure (Tufail *et al.*, 2024).

Structure and composition

Natural zeolites are a group of crystalline hydrated aluminosilicates, characterized by a framework structure consisting of tetrahedra of aluminum and silicon with a variety of cations and water molecules occupying the interstitial sites or occluded in the cavities. The crystalline framework is the basic structure of zeolite and determines its robustness (Velarde *et al.*, 2023). The microporous nature and uniform size of the cavities and channels allow selective ion exchanges, enabling zeolites to act as adsorbents for ammonium ions or cationic heavy metals (Kayan and Kayan, 2021). The chemical composition of zeolite also plays an important role in heavy metal detoxification (Irannajad and Haghghi, 2021). The cavities in the zeolite permit a wide range of cations to exchange, like NH_4^+ , Na^+ , and Zn^{2+} . The adsorption of heavy metals in solutions or soils by zeolite, a widely available natural mineral, is an efficient, economically feasible, and sustainable method of decontamination (Ugwu *et al.*, 2022). Land application of animal manure containing zeolites can inhibit NH_3 release and fix NH_4^+ , blocking NH_3 volatilization, and enhancing plant availability of soil-bound mineralized N to

enhance N efficiency (Lu *et al.*, 2022). Adsorption is the result of the interaction of a substance with the molecular structure or the surface of another. Adsorption on zeolites may be divided into two main categories, identified as absorption and adsorption. The latter process may be physical or chemical (Morante-Carballo *et al.*, 2021). Animal manure applications also increase crop production, waste disposal, and the need for soil remediation (Sudagar *et al.*, 2021). Although various detoxifying agents were tested and found effective, there were trade-offs to consider. The reuse potential and stability of zeolite were analyzed, advocating the use of zeolite as a detoxification agent (Zhang *et al.*, 2021). Ultimately, these analyses will aid in evaluating zeolite as an economically viable, environmentally friendly, and sustainable solution (Vishnu *et al.*, 2021).

Detoxification mechanisms

Zeolite is employed to detoxify heavy metals in biological systems in order to enhance the health of living creatures (Beltcheva *et al.*, 2022). The mode of its action is through adsorption, ion exchange, and complexation of heavy metals. The detoxification capacity of zeolite when exposed to animals was studied with special emphasis on its protective role under long-term exposure conditions, and its possible consequences in an analysis of health status (Silva *et al.*, 2023). Results indicated that the efficiency of zeolite in detoxifying heavy metals under short-term exposure conditions is proportional to the dose of zeolite and the level of metal (Young and Mansfield, 2024). Its protective role is most intensive when it is applied simultaneously with the metal but attenuates with the lifetime of the bio-adsorption of heavy metals (Mastinu *et al.*, 2019).

The importance of zeolite in the prevention of the bioavailability of different heavy metals was also assessed (GirijaVeni *et al.*, 2021). Zeolite significantly reduced the concentrations of bioavailable Cd ions in the muscle and Pb in the liver of the animals exposed to these metals (Adhikari *et al.*, 2022). The high detoxification efficiency of zeolite in normal life and other environmental conditions suggests that zeolite

can be successfully used as a detoxifying agent for living creatures in living environments (Liu *et al.*, 2023).

CONCLUSION

Heavy metal exposure represents a serious threat to humans and animals due to its influence on multiple organs and systems. Zeolites have drawn interest in toxicology and environmental assessment due to their availability and specific physiochemical properties. The current study examines the protective and detoxifying role of zeolite in combination with heavy metal exposure in animal models. The findings indicate that zeolite has the potential to reduce the biodistribution of heavy metals and decrease toxicity levels in test animals. This research contributes substantially to a better understanding of the protective effects and a broadening of the appropriate application of zeolite as a remedy. Due to increasing concerns about the accumulation of heavy metals in the environment, current research has focused on modifying natural zeolites to enhance their adsorption effect for heavy metals, including ion exchange, acid treatment, or alkali activation. At present, modifications of zeolites using organically modified reagents, surfactants, and organic polymers to augment their satisfactory adsorption properties are also under intense study. These studies have provided important hints that these modified zeolites might be an excellent and low-cost tool for detoxification and environmental remediation due to their fast adsorption rate and ability to reduce toxicity responses observed in the study of animal models.

CONFLICT OF INTEREST

The author declares that this article's content has no conflict of interest.

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