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Therapeutic Strategies to Mitigate Cardiovascular Effects of Heavy Metals: A Toxicological and Pharmacological Approach

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ABSTRACT
Exposure to heavy metals, such as lead, mercury, and cadmium, poses a significant risk to cardiovascular health due to their ability to induce oxidative stress, inflammation, and endothelial dysfunction. This article discusses therapeutic strategies based on toxicological and pharmacological approaches to mitigate these adverse effects. Interventions such as the use of chelators, antioxidants and dietary modifications are reviewed, as well as emerging therapies such as biomimetic compounds and pharmacogenomics. Research demonstrates that combined strategies have a positive impact on reducing cardiovascular toxicity of heavy metals, with an emphasis on personalized and multidisciplinary management.

Keywords: heavy metals, cardiovascular health, therapeutic strategies, toxicology, pharmacology, oxidative stress.

INTRODUCTION

Exposure to heavy metals, such as lead, mercury, arsenic, and cadmium, has been recognized as a global public health problem due to its persistence in the environment and its ability to bioaccumulate in living organisms (Tchounwou et al., 2021). These metals, present in sources such as polluted water, food, and industrial emissions, exert significant toxic effects on the human body, affecting various systems, including nervous, renal, and cardiovascular systems (Guzmán-Morales et al., 2022). Among these, the effects on cardiovascular health are particularly worrying, given their relationship with chronic diseases such as hypertension, atherosclerosis, heart failure, and stroke (Yang et al., 2021).

The cardiovascular impact of heavy metals occurs mainly through mechanisms such as oxidative stress, chronic inflammation, endothelial dysfunction, and alteration of ion channels in the myocardium (Singh et al., 2022). These alterations lead to a cascade of molecular and cellular events that increase the risk of irreversible cardiovascular damage. For example, cadmium, by interfering with calcium metabolism, induces dysfunction in the muscle contraction of the heart, while lead affects endothelial function by inhibiting the production of nitric oxide, a key molecule for vasodilation (Chowdhury et al., 2022).

Given the increasing prevalence of cardiovascular diseases related to heavy metal exposure, it is critical to develop and implement effective therapeutic strategies that mitigate these adverse effects. So far, the main interventions include the use of chelating agents, antioxidants, and dietary therapies, all designed to reduce the load of metals in the body and minimize oxidative damage (Renu et al., 2023). However, recent advances in pharmacogenomics and biomimetic therapies have opened up new possibilities to address this problem with a more personalized and effective approach (Alkahtani et al., 2023).

For example, the use of antioxidants such as N-acetylcysteine and polyphenolic compounds has been shown to significantly reduce inflammatory markers and improve endothelial function in experimental models and clinical studies (Chowdhury et al., 2022; Zhang et al., 2023). In addition, the integration of combination therapies, leveraging both pharmacological strategies and lifestyle modifications, has shown promise in addressing the complexity of the cardiovascular impact of heavy metals (Zhang et al., 2023).

This article reviews the most recent therapeutic strategies and their efficacy, highlighting the need for a multidisciplinary approach to mitigate the toxic effects of heavy metals on cardiovascular health. Specifically, this work seeks to analyze how the combination of toxicological and pharmacological strategies can be optimized to improve clinical outcomes and reduce the burden of cardiovascular diseases related to exposure to these pollutants. Likewise, emerging therapies and their potential to transform the management of this problem in the future are discussed.

Theoretical Framework

The impact of heavy metals on cardiovascular health has been widely documented, highlighting their ability to alter fundamental physiological processes such as endothelial function, oxidative balance, and cell signaling. This theoretical framework addresses the main mechanisms of heavy metal-induced cardiovascular toxicity and the therapeutic strategies used to mitigate these effects.

1. Mechanisms of Cardiovascular Toxicity

Oxidative Stress

Oxidative stress, resulting from the imbalance between the production of reactive oxygen species (ROS) and endogenous antioxidant mechanisms, is one of the main mechanisms by which heavy metals induce cardiovascular toxicity (Singh et al., 2022). Cadmium, for example, promotes ROS generation by interfering with key enzymes such as superoxide dismutase (SOD) and catalase (Chowdhury et al., 2022). These processes can result in damage to DNA, proteins, and lipids, contributing to endothelial dysfunction and progression of atherosclerosis.

Chronic Inflammation

Prolonged exposure to heavy metals stimulates systemic inflammatory responses. Lead, for example, activates pro-inflammatory pathways such as NF-κB signaling, leading to the production of cytokines such as IL-6 and TNF-α, exacerbating cardiovascular damage (Guzmán-Morales et al., 2022).

Endothelial Dysfunction

Heavy metals disrupt vascular homeostasis by reducing the bioavailability of nitric oxide (NO), a key molecule for vasodilation. This occurs due to inhibition of NO synthesis and increased ROS, which degrade available NO (Renu et al., 2023). This effect contributes to the development of hypertension and arterial diseases.

Electrophysiological Alterations

Mercury and other metals can interfere with ion channels, disrupting normal heart function. These alterations include prolongation of the QT interval and arrhythmias, associated with higher cardiovascular mortality (Yang et al., 2021).

2. Therapeutic Strategies

Metal Chelation

The use of chelating agents such as ethylenediaminetetraacetic acid (EDTA) and dimercaptosuccinic acid (DMSA) is effective in reducing the body's burden of heavy metals. These molecules bind to metals, forming stable complexes that are excreted by the body (Gómez et al., 2021). However, their use should be monitored due to potential adverse effects, such as the removal of essential minerals.

Antioxidants

Supplementation with antioxidants such as vitamin E, vitamin C, and N-acetylcysteine has shown efficacy in reducing heavy metal-induced oxidative stress (Zhang et al., 2023). Polyphenols, present in foods such as green tea and fruits, have also shown antioxidant properties that improve endothelial function.

Biomimetic Therapies

Biomimetic compounds, such as nanoparticles that mimic catalase activity, represent an emerging strategy to neutralize ROS and reduce the cardiovascular toxicity of metals (Alkahtani et al., 2023).

Pharmacogenomics

Pharmacogenomics, which studies how genetic variations affect response to treatments, allows for the design of personalized strategies for patients exposed to heavy metals. This includes identifying genetic polymorphisms that predispose to increased toxicity and adjusting therapies accordingly (Chowdhury et al., 2022).

3. Comparison of Therapeutic Strategies

Below is a comparative table illustrating the effectiveness and limitations of the most common therapeutic strategies for mitigating cardiovascular toxicity from heavy metals:

Therapeutic Strategy	**Mechanism of Action**	**Proceeds**	**Limitations**
Chelation	Metal removal by excretion	Rapid reduction of metal levels	Loss of essential minerals, liver toxicity (Gómez et al., 2021)
Antioxidants	Neutralization of reactive oxygen species	Improved endo the lial function	Limited efficacy without eliminating metal exposure (Renu

			et al., 2023)
BiomimeticTherapies	Mimicking antioxidant enzymes	High efficacy in experimental models	High costs, lack of extensive clinical studies (Alkahtani et al., 2023)
Pharmacogenomics	Genetics-based personalization	Patient-specific treatments	Limited accessibility, need for genetic testing (Chowdhury et al., 2022)

Methodology

This study was conducted through a systematic review of scientific literature published between 2019 and 2024. A structured methodology was used to identify, evaluate, and synthesize relevant research on therapeutic strategies to mitigate the cardiovascular effects of heavy metals. The methodology included a detailed description of sources, selection criteria, methods of analysis, and a summary table of included studies.

1. Sources of Information

The scientific databases consulted included PubMed, Scopus, Web of Science, and ScienceDirect, due to their broad reach in biomedical and toxicological studies (Moher et al., 2020). Search terms such as 'heavy metals', 'cardiovascular toxicity', 'chelation', 'antioxidants' and 'therapeutic strategies' were used. In addition, filters were applied to include only studies published in English and Spanish during the last five years.

2. Inclusion and Exclusion Criteria

The following criteria were applied for the selection of articles:

Inclusion Criteria	**Exclusion Criteria**
Studies published between 2019 and 2024.	Studies published before 2019.
Peer-reviewed articles that analyze therapeutic strategies against heavy metals.	Studies not related to cardiovascular toxicity.
Research that includes clinical data, preclinical data or systematic reviews on therapeutic strategies.	Articles without access to the full text or that did not include specific interventions.
Publications with a focus on cardiovascular effects of heavy metals (lead, cadmium, mercury).	Research focused exclusively on other systems (nervous, immune, etc.).

3. Selection Process

The selection of articles followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations (Page et al., 2021). Theprocessincludedthefollowingstages:

1. **Initial search:** We identified 532 articles.
2. **Deduplication:** 132 duplicate studies were eliminated, leaving 400 for review.
3. **Review of titles and abstracts:** 400 articles were evaluated, excluding 250 due to lack of relevance.
4. **Full review:** 150 articles were analyzed, finally selecting 65 that met all the criteria.

4. Methods of Analysis

The data obtained from the selected studies were analyzed through a qualitative and quantitative synthesis, highlighting the results related to the following key themes:

1. Efficacy of therapeutic strategies (chelation, antioxidants, emerging therapies).
2. Molecular mechanisms involved in cardiovascular toxicity.
3. Recent clinical and preclinical studies.

To organize the information, tables were designed that summarize the main findings:

I am a student	**Therapy Analyzed**	**Population**	**Key Results**	**Reference**
Gómez et al. (2021)	Chelation (EDTA)	Patients Exposed to Lead	50% reduction in lead levels and improvement of endothelial function.	Gómez et al., 2021
Chowdhury et al. (2022)	Antioxidants (Vit. C, polyphenols)	Animal models	Improvement of oxidative stress and reduction of vascular inflammation by 40%.	Chowdhury et al., 2022
Zhang et al. (2023)	Combination therapies	Preclinical models	Synergy between chelation and antioxidants, with a 70% improvement in cardiovascular markers.	Zhang et al., 2023

Alkahtani et al. (2023)	Biomimetictherapies	In vitro experimental models	Neutralization of reactive oxygen species with high specificity, reducing cell damage.	Alkahtani et al., 2023

5. Limitations of the Methodology
Although the systematic review allowed for the collection of relevant and up-to-date evidence, the following limitations should be considered:

- **Lack of extensive clinical studies:** Most of the data comes from preclinical studies and animal models, making it difficult to generalize the findings to humans.
- **Methodological heterogeneity:** Studies used different protocols to measure the efficacy of therapies, which may limit the comparability of results.
- **Access to information:** Some relevant studies could not be included due to restrictions on access to the full text.

This methodology provides a solid basis for evaluating current and emerging therapeutic strategies against cardiovascular heavy metal toxicity, with a focus on interventions based on recent scientific evidence.

RESULTS
The analysis of the 65 selected studies allowed the identification of various therapeutic strategies used to mitigate the cardiovascular effects of heavy metals. The results highlight the benefits of chelation therapies, antioxidants, and combination approaches, as well as the potential of emerging therapies such as biomimetics and pharmacogenomics. In addition, significant variability was observed in the efficacy of these interventions depending on the heavy metal, the model studied (clinical or preclinical), and the individual characteristics of the patients.

1. Efficacy of Chelation Therapies
Chelating agents, such as EDTA and DMSA, demonstrated an effective reduction in serum levels of heavy metals such as lead and cadmium. In a clinical study, the use of EDTA reduced lead levels by 50% in patients exposed to this metal, accompanied by a 30% improvement in endothelial function markers (Gómez et al., 2021).

Chelator	**Metal Target**	**Level Reduction (%)**	**Improvement in Endothelial Function (%)**	**Reference**
EDTA	Lead	50	30	Gómez et al., 2021
DMSA	Cadmium	45	25	Renu et al., 2023

Although these therapies are effective, their prolonged use can cause side effects such as loss of essential minerals, which limits their application (Gómez et al., 2021).

2. Antioxidants as Therapeutic Strategies
Antioxidants, such as vitamin C, vitamin E, and polyphenols, were shown to be effective in reducing oxidative stress and inflammation induced by heavy metals. For example, a study in animal models exposed to cadmium found that vitamin C administration reduced inflammatory markers (IL-6 and TNF-α) by 40% and improved endothelial function by 35% (Chowdhury et al., 2022).

Antioxidant	**Metal Target**	**Reduced Inflammation (%)**	**Improvement in Endothelial Function (%)**	**Reference**
Vitamin C	Cadmium	40	35	Chowdhury et al., 2022
Polyphenols	Mercury	30	25	Zhang et al., 2023

The protective effect of antioxidants suggests that these therapies are particularly useful as part of combined approaches to maximize therapeutic benefits.

3. Combination Therapies

The combined chelation and antioxidant strategies demonstrated significant synergy, achieving better results than the individual use of each intervention. For example, in preclinical models, the combination of EDTA and vitamin E improved cardiovascular markers by 70% compared to 50% for EDTA alone (Zhang et al., 2023).

Intervention	**Improvement in cardiovascular markers (%)**	**Reference**
EDTA only	50	Gómez et al., 2021
Vitamin E alone	40	Chowdhury et al., 2022
EDTA + Vitamin E	70	Zhang et al., 2023

These results highlight the importance of integrating multiple therapeutic approaches to more effectively address cardiovascular toxicity.

4. Emerging Therapies

Biomimetic and pharmacogenomic therapies represent promising advances. Biomimetic compounds mimicking catalase activity reduced reactive oxygen species by 60% in in vitro studies, demonstrating significant potential to prevent cell damage caused by heavy metals (Alkahtani et al., 2023). In addition, pharmacogenomic therapies, based on the identification of genetic polymorphisms, made it possible to design specific treatments for individuals with increased susceptibility to lead and cadmium toxicity (Chowdhury et al., 2022).

EmergentTherapy	**Mechanism**	**ROS reduction (%)**	**Reference**
Biomimetics	ROS Neutralization	60	Alkahtani et al., 2023
Pharmacogenomics	Personalization based on polymorphisms	N/A	Chowdhury et al., 2022

5. Limitations and Considerations

Despite the positive results, limitations were identified in the studies analysed:

1. **Lack of extensive clinical trials:** Most research comes from preclinical models, limiting extrapolation to humans (Renu et al., 2023).
2. **Methodological heterogeneity:** The studies used different protocols, making comparability between them difficult (Gómez et al., 2021).
3. **Limited accessibility to emerging therapies:** Biomimetic and pharmacogenomic therapies are not yet widely available due to their high cost and technological complexity (Alkahtani et al., 2023).

CONCLUSIONS

Exposure to heavy metals poses a significant challenge to cardiovascular health, given its ability to induce oxidative stress, chronic inflammation, and endothelial dysfunction. This study highlights that current therapeutic strategies, while effective in certain contexts, need to be integrated and optimized to more effectively address the multiple mechanisms of toxicity associated with these metals.

1. Importance of Combined Therapeutic Strategies

Combination therapies, such as chelation along with antioxidants, have shown promising results in addressing both the removal of metals and the mitigation of oxidative damage. For example, the combination of EDTA with vitamin E achieved a 70% improvement in cardiovascular markers, significantly exceeding the efficacy of individual therapies (Zhang et al., 2023). This finding reinforces the need to design therapeutic approaches that maximize synergy between different interventions.

In addition, combination therapies offer a model for personalizing the treatment of patients exposed to different levels and types of heavy metals. Integrating these strategies into clinical practice can provide substantial benefits, especially for patients with chronic exposure to multiple metals.

2. Potential of Emerging Therapies

Biomimetic therapies and pharmacogenomics represent emerging approaches that could transform the management of cardiovascular toxicity. Biomimetic compounds that mimic the activity of antioxidant enzymes, such as catalase, have shown a significant reduction in reactive oxygen species in experimental models

(Alkahtani et al., 2023). Pharmacogenomics also allows treatments to be personalized by identifying genetic variants that influence susceptibility to heavy metal toxicity (Chowdhury et al., 2022).
However, the implementation of these therapies still faces barriers, such as high cost and lack of access in clinical settings. Overcoming these limitations requires concerted efforts in research and development, as well as public health policies that prioritize the availability of these technologies in vulnerable regions.

3. Limitations and Future Directions

Although the findings of this study are encouraging, important limitations were identified in the literature reviewed. Most studies are based on preclinical models, which makes it difficult to generalize the results to human populations (Renu et al., 2023). In addition, there is a lack of standardization in research protocols, which limits comparability between studies (Gómez et al., 2021).
In the future, it is essential to conduct multicenter clinical trials that evaluate the effectiveness of therapeutic strategies in different population groups. It is also necessary to develop specific biomarkers that allow early detection of cardiovascular toxicity associated with heavy metals, which would facilitate more timely and effective interventions (Chowdhury et al., 2022).

4. Clinical and Public Health Implications

This analysis emphasizes the need for multidisciplinary approaches that combine toxicology, pharmacology, and personalized medicine to address the cardiovascular impact of heavy metals. Therapeutic strategies should be integrated into public health programs that include:

- **Education and prevention:** Raising awareness of the sources of exposure to heavy metals and measures to reduce contact.
- **Surveillance and monitoring:** Implementation of early detection programs in vulnerable communities.
- **Access to advanced therapies:** Ensure that emerging interventions are available in regions with a high burden of heavy metal exposure.

Ultimately, success in mitigating the cardiovascular effects of heavy metals will depend on a comprehensive approach that combines scientific research with effective public health policies.

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