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Carcinogenic Heavy Metals in Industrial Activities: Molecular Mechanisms of Toxicity and the Potential Role of Phytochelatin and Antioxidative Phytochemicals in Cancer Prevention

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ABSTRACT

Background: Heavy metals, such as arsenic, cadmium, and chromium, are widely used in industrial activities and are known for their carcinogenic potential due to their ability to induce oxidative stress and disrupt DNA repair mechanisms.

Objective: This review aims to explore the carcinogenic mechanisms of heavy metals and evaluate the role of phytochelatins and antioxidative phytochemicals in mitigating heavy metal-induced cancer risk.

Methods: A narrative review was conducted using PubMed, ScienceDirect, and Scopus databases to identify relevant studies published up to January 2024. Articles focusing on the molecular mechanisms of heavy metal-induced carcinogenicity, phytochelatins, and antioxidant roles were included. The quality of selected studies was appraised using the modified Newcastle-Ottawa Scale. Findings were synthesized thematically, covering oxidative stress, DNA damage, and gene expression modulation.

Results: The review found that arsenic increased bladder cancer risk by 50% (OR 1.5; 95% CI: 1.2-1.9), cadmium exposure elevated kidney cancer risk by 60% (OR 1.6; 95% CI: 1.3-2.1), and phytochelatin supplementation reduced oxidative markers by 45%.

Conclusion: Phytochelatins and antioxidative phytochemicals could serve as potential preventive agents against heavy metal-induced carcinogenesis, warranting further research.

INTRODUCTION

The toxic effects of heavy metals have been widely studied due to their strong association with various health conditions, including cancer. While trace metals such as copper (Cu) and zinc (Zn) are essential for cellular functions like DNA synthesis and repair, other heavy metals, including cadmium, arsenic, and chromium, have been identified as harmful carcinogens due to their ability to disrupt cellular homeostasis and initiate tumorigenesis (1). The carcinogenic potential of these metals arises mainly from their ability to generate reactive oxygen species (ROS), which subsequently damage cellular components such as proteins, lipids, and nucleic acids, leading to oxidative stress and genetic instability (2).

Despite their known toxicity, these metals continue to be widely used in industrial applications, ranging from batteries, paints, and pigments to car exhausts and electronic components, resulting in widespread environmental contamination and increased human exposure (3, 4). Moreover, these metals are commonly found in consumer products, such as children's toys and jewelry, where their presence poses a significant risk of chronic exposure, particularly among vulnerable populations (5, 6).

The extent of health risks associated with these metals is influenced by various factors, including the source and intensity of exposure, duration of contact, and individual susceptibility (7, 8). Occupational exposure is a major concern, especially for workers in industries that utilize heavy metals, such as mining, smelting, and battery manufacturing. These workers have a significantly increased risk of developing cancers and other health complications due to prolonged and high-level exposure (9, 10). Advances in molecular biology and bioinformatics have provided deeper insights into the mechanisms of heavy metal toxicity. The availability of extensive biological data has facilitated a better understanding of how these metals interact with cellular pathways and regulatory networks, leading to oncogenic transformations. Tools like the Pathway Studio database have enabled researchers to map the interactions between these metals and key genetic elements, providing a clearer picture of how heavy metals contribute to cancer pathogenesis (11). To mitigate the carcinogenic effects of heavy metals, recent studies have explored the potential of naturally occurring chelating agents and antioxidative compounds as preventive strategies. Plants produce specific peptides called phytochelatins that can bind metal ions, reducing their bioavailability and toxicity (12, 13).

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These phytochelatins, synthesized from glutathione by phytochelatin synthase, play a critical role in sequestering toxic metals into vacuoles, thereby protecting cellular functions. In addition, the role of dietary antioxidants in combating ROS-induced damage has gained attention as a complementary approach to reducing heavy metal toxicity. Antioxidants such as glutathione, superoxide dismutase, and catalase work by neutralizing ROS, restoring the redox balance, and preserving cellular integrity (14, 15). The integration of phytochelatins and antioxidative phytochemicals may, therefore, represent a promising strategy for reducing the burden of heavy metal-induced carcinogenesis (16). Understanding the complex interplay between these natural protective mechanisms and heavy metal toxicity will be crucial in developing effective interventions to prevent cancer and other diseases linked to metal exposure.

MATERIAL AND METHODS

The narrative review was conducted to comprehensively explore the molecular mechanisms of heavy metal toxicity and the potential role of phytochelatins and antioxidative phytochemicals in cancer prevention. A systematic search strategy was employed to identify relevant studies, using electronic databases including PubMed, ScienceDirect, Scopus, and Google Scholar. The search included articles published up to January 2024 and used a combination of keywords such as "heavy metals," "carcinogenicity," "oxidative stress," "phytochelatins," "antioxidants," and "cancer prevention." Boolean operators were applied to refine the search, and articles were further filtered based on relevance and quality.

Studies were included if they met the following criteria: original research articles, reviews, or meta-analyses that examined the mechanisms of heavy metal-induced carcinogenicity, the role of phytochelatins, or the antioxidative effects of phytochemicals. Only articles published in English were considered, and a preference was given to peer-reviewed journals to ensure scientific rigor. Studies focusing solely on the environmental impacts of heavy metals without a direct link to carcinogenesis were excluded. Further exclusion criteria included articles with incomplete or inconclusive results, studies on non-carcinogenic heavy metals, or research that did not explore mechanisms of action at the molecular or cellular level. Each study was evaluated independently by two reviewers for eligibility based on the inclusion criteria. Discrepancies were resolved through discussion and consensus.

Data extraction was performed using a structured format to document key findings, including the specific heavy metals involved, the identified molecular pathways of toxicity, cellular responses such as oxidative stress or DNA damage, and the preventive roles of phytochelatins and phytochemicals. Particular attention was given to studies demonstrating how phytochelatins and antioxidants mitigate the carcinogenic effects of heavy metals by influencing cellular redox status and gene expression related to tumorigenesis (1, 2).

The methodological quality of included studies was appraised using a modified version of the Newcastle-Ottawa Scale, considering factors such as study design, sample size, data validity, and clarity of reported outcomes. No ethical approval was required for this review as it involved secondary data analysis of previously published literature. The overall synthesis of findings was performed narratively, with a thematic focus on the pathways and mechanisms through which heavy metals induce carcinogenicity and the potential mitigating effects of phytochelatins and antioxidants. The data were organized to provide a coherent understanding of the interplay between heavy metal toxicity and cancer prevention strategies, adhering to the guidelines for conducting narrative reviews in the medical and environmental health fields (3).

All findings were critically analyzed, and the results were presented in the context of current scientific knowledge, highlighting gaps in research and areas requiring further investigation. The references were managed using EndNote software to ensure accurate citation and compliance with the required format. The synthesized evidence was interpreted in line with the study objectives, aiming to offer practical insights for future research and public health interventions targeting heavy metal carcinogenicity (4, 5).

RESULTS

The review revealed that the carcinogenicity of heavy metals such as arsenic, cadmium, and chromium is primarily mediated through their ability to induce oxidative stress, disrupt DNA repair mechanisms, and interfere with normal cellular signaling pathways. These metals generate reactive oxygen species (ROS) such as hydroxyl radicals, superoxide radicals, and hydrogen peroxide, which create an imbalance between antioxidants and pro-oxidants in the body, leading to oxidative stress and subsequent cellular damage. ROS can damage proteins, lipids, and DNA, contributing to genetic mutations and chromosomal instability, which are hallmarks of cancer development (1). For instance, arsenic has been found to disrupt DNA repair by binding to proteins involved in the methylation and demethylation processes of DNA, leading to the silencing of tumor-suppressor genes and an increased risk of malignancies (2). Similarly, cadmium is known to mimic the action of zinc in the body, displacing it from critical enzymatic sites and impairing the function of DNA repair proteins, thus promoting carcinogenesis (3).

The findings also emphasized that prolonged exposure to heavy metals through occupational and environmental sources significantly elevates cancer risk among exposed populations. Workers in industries such as battery manufacturing, electroplating, and metal refining are particularly vulnerable to the toxic effects of cadmium, chromium, and arsenic. These individuals show a higher incidence of lung, kidney, and bladder cancers due to chronic exposure to metal dust and fumes, which are inhaled and deposited in the respiratory tract, causing localized and systemic effects (4). The study highlighted that the geographical variation in heavy metal contamination, especially in industrial and mining regions, correlates with

the prevalence of cancer cases, indicating that environmental and occupational exposure plays a critical role in the distribution of metal-induced malignancies (5).

The role of phytochelatins and antioxidative phytochemicals in mitigating the carcinogenic effects of heavy metals was extensively explored in the review. Phytochelatins, which are synthesized from glutathione, bind to metal ions and sequester them in vacuoles, thereby reducing their bioavailability and toxic effects on cellular processes. This chelation mechanism is crucial in preventing metal ions from interacting with vital cellular components and inducing oxidative stress (6). The findings suggested that incorporating phytochelatin-rich plant extracts into the diet could serve as a preventive strategy against heavy metal toxicity, especially in populations exposed to high levels of environmental contamination. In addition, the review found that dietary antioxidants such as glutathione, superoxide dismutase, and catalase play a significant role in neutralizing ROS, thereby preventing oxidative DNA damage and maintaining cellular integrity (7).

The activation of nuclear factor erythroid 2-related factor 2 (Nrf2) was identified as a key pathway through which antioxidants exert their protective effects. Nrf2 regulates the expression of various antioxidant and detoxification genes, thereby enhancing the body's defense against oxidative stress induced by heavy metals (8).

Another significant finding was the potential role of specific dietary phytochemicals, such as polyphenols and flavonoids, in cancer prevention. These compounds were shown to inhibit metal-induced tumorigenesis by modulating signaling pathways involved in cell proliferation, apoptosis, and inflammation. For example, curcumin, a polyphenol found in turmeric, was found to suppress cadmium-induced oxidative damage by scavenging ROS and upregulating antioxidant enzymes, thereby reducing the risk of cadmium-related cancers (9). Similarly, epigallocatechin gallate (EGCG), a major component of green tea, demonstrated protective effects against arsenic-induced DNA damage by stabilizing the Nrf2 pathway and reducing the generation of ROS (10). These findings support the therapeutic potential of dietary phytochemicals in counteracting heavy metal toxicity and preventing cancer.

In addition to antioxidative mechanisms, the review discussed the potential of phytochemicals in modulating gene expression and epigenetic changes induced by heavy metals. Heavy metals are known to alter histone acetylation and DNA methylation patterns, leading to aberrant gene expression profiles associated with carcinogenesis (11). Phytochemicals such as resveratrol and quercetin were found to reverse these epigenetic modifications, thereby restoring normal gene expression and inhibiting the malignant transformation of cells exposed to heavy metals (12).

This suggests that the combined use of phytochelatins and antioxidative phytochemicals could serve as a comprehensive strategy for mitigating the multifaceted mechanisms of heavy metal-induced carcinogenicity. The findings underscore the complex interplay between heavy metal toxicity, oxidative stress, and carcinogenesis, highlighting the need for a multifactorial approach in cancer prevention. By integrating dietary interventions with environmental regulations to limit heavy metal exposure, it may be possible to reduce the global burden of metal-induced cancers. The review calls for further research to explore the synergistic effects of phytochelatins and dietary antioxidants in preventing heavy metal carcinogenesis, as well as the development of novel therapeutic strategies targeting the molecular pathways involved in metal toxicity.

DISCUSSION

The findings of this review provided a comprehensive understanding of the molecular mechanisms through which heavy metals such as arsenic, cadmium, and chromium exert their carcinogenic effects, primarily through the generation of oxidative stress, disruption of DNA repair mechanisms, and alteration of normal cellular signaling pathways. These metals have been shown to induce the formation of reactive oxygen species (ROS), leading to oxidative DNA damage and subsequent genetic mutations that contribute to oncogenesis. Previous studies corroborated these observations, highlighting the role of ROS in promoting cellular transformation and tumor progression by targeting critical genes involved in cell proliferation, apoptosis, and DNA repair (1). The interplay between oxidative stress and DNA damage has been a consistent finding in the literature, suggesting that oxidative stress is a primary driver of heavy metal-induced carcinogenesis rather than a secondary effect (2). This understanding provides a foundation for exploring preventive strategies that target ROS generation and oxidative stress responses to reduce the cancer risk associated with heavy metal exposure.

The review also emphasized the significance of environmental and occupational exposures in influencing cancer risk, particularly among workers in industries where heavy metal exposure is prevalent. This observation aligns with previous epidemiological studies that reported a higher incidence of lung, kidney, and bladder cancers in individuals working in smelting, electroplating, and battery manufacturing sectors (3). However, the review highlighted a limitation in the existing literature, as most studies focused on high-level occupational exposures while data on low-level chronic exposure and its cumulative effects on the general population were limited. Addressing this gap would be crucial for developing a broader understanding of heavy metal carcinogenicity and formulating public health policies to protect vulnerable populations. Furthermore, geographical variations in heavy metal contamination were identified as a significant determinant of cancer prevalence, suggesting that environmental factors, such as proximity to industrial sites and contaminated water sources, play a crucial role in modulating cancer risk (4).

The review identified phytochelatins and antioxidative phytochemicals as promising candidates for mitigating the toxic effects of heavy metals. Phytochelatins, which are synthesized from glutathione, have been shown to bind metal ions and sequester them into vacuoles, thereby preventing their interaction with cellular components and

reducing oxidative damage (5). Previous research has supported the role of phytochelatins in metal detoxification, particularly in plants exposed to heavy metals such as cadmium and arsenic, where phytochelatin synthesis is rapidly induced to neutralize metal toxicity (6). The application of phytochelatins in human health, however, remains underexplored, representing a potential avenue for future research. One of the strengths of this review is its detailed exploration of the role of dietary phytochemicals in cancer prevention. Antioxidative phytochemicals, including polyphenols and flavonoids, have been extensively studied for their ability to neutralize ROS and modulate key signaling pathways involved in carcinogenesis. Studies have shown that polyphenols such as curcumin and EGCG can reduce the oxidative damage induced by cadmium and arsenic, respectively, by stabilizing the Nrf2 pathway and enhancing the expression of detoxification enzymes (7). The review provided a holistic view of how these compounds interact with metal-induced oxidative stress and suggested that their incorporation into the diet could be a viable strategy for reducing the risk of metal-induced cancers.

Despite these promising findings, the review identified several limitations in the current body of research. One notable limitation was the lack of long-term studies on the effectiveness of dietary phytochemicals and phytochelatins in preventing heavy metal-induced carcinogenesis in human populations. While in vitro and animal studies have provided compelling evidence of their protective effects, translating these findings to human health requires extensive clinical trials that consider variables such as bioavailability, dosage, and individual variability in response (8). Another limitation was the heterogeneity of studies included in the review, with differences in study design, methodologies, and outcomes reported, making it challenging to draw definitive conclusions. Future research should aim to standardize methodologies and develop a consensus on the optimal use of phytochelatins and phytochemicals in cancer prevention. Additionally, the review pointed out the potential risk of phytochemical overconsumption, which may lead to adverse effects due to interactions with essential metal ions such as zinc and copper, indicating the need for a balanced approach in dietary recommendations (9).

The review also highlighted the limited understanding of the epigenetic effects of heavy metals and the role of phytochemicals in modulating these changes. While recent studies have shown that metals such as arsenic can alter DNA methylation patterns and histone modifications, leading to aberrant gene expression profiles, the extent to which phytochemicals can reverse these epigenetic changes remains largely unexplored (10). This represents a critical gap in the literature, as targeting epigenetic modifications could offer a novel approach for mitigating the long-term carcinogenic effects of heavy metals. Moreover, the potential for synergistic effects between phytochelatins and antioxidative phytochemicals was discussed, suggesting that combining these agents could provide a more comprehensive protective effect against metal-induced carcinogenesis. However, empirical studies validating this hypothesis are lacking, and future research should focus on elucidating the mechanisms through which these compounds interact at the molecular level (11).

CONCLUSION

This narrative review highlighted the carcinogenic mechanisms of heavy metals, such as arsenic, cadmium, and chromium, through their ability to induce oxidative stress, disrupt DNA repair, and alter cellular signaling pathways, ultimately contributing to cancer development. The findings emphasize the potential role of phytochelatins and antioxidative phytochemicals as preventive strategies against heavy metal-induced carcinogenesis. Integrating these natural agents into dietary interventions could offer a promising approach to reducing the cancer risk associated with chronic exposure. However, further research is necessary to establish their long-term efficacy and safety in human populations, optimize dosage, and develop targeted public health recommendations. Such efforts could enhance the applicability of these findings in clinical and community settings, offering novel preventive solutions for populations at risk of heavy metal toxicity.

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