Original Research Article

NUTRITION AS A THERAPEUTIC INTERVENTION FOR METAL TOXICITY

Abstract

Exposure to toxic metals poses serious health risks, leading to conditions like inflammation and cancer in humans. Traditional treatments, such as chelation therapy, face safety and efficacy challenges, prompting research into nutritional interventions. A well-balanced diet proves instrumental in reducing the body's susceptibility to environmental stressors. Edible plants, notably vegetables and fruits, offer essential nutrients that mitigate the absorption of toxic metals, enhance excretion, and modulate their effects. Recent studies highlight the preventive potential of bioactive nutrients, natural phenolics, microalgae, and milk in combating diseases associated with toxic metals. While nutritional strategies are beneficial, adopting positive lifestyle changes and minimizing exposure remains the most effective approach to prevent heavy metal toxicity. For occupationally exposed individuals, embracing antioxidant-rich diets becomes a key element in mitigating the risks associated with toxicants.

Keywords: Toxic metals, Heavy metal toxicity, Milk intervention, Edible plants, Environmental stressors, Antioxidant-rich diets, and Health risks

1.0 Introduction

Technological advancements have caused a massive increase in the utilization of heavy metals to sustain the demands of modern living. As such, human exposure to heavy metals such as chromium, cadmium, mercury, uranium, nickel, vanadium, lead, and arsenic is on the increase. Heavy metals are found naturally in the environment and are part of many consumer products and industrial materials, from where human exposure to toxic concentrations is likely [1,2]. Metal toxicity is an insidious health issue that is gaining serious attention today because of the increasing awareness of the environmental health impact of heavy metals. There is a burgeoning interest in the health assessment of exposure to heavy metals because it has come to be known that they may initiate an adverse health effect on man even at low concentrations and have the potential to induce multiple organ damage, as they are known to be systemic toxicants [3].

Heavy metals can potentially cause, epigenetic alteration, and disrupt cellular activities such as differentiation, growth, proliferation, apoptosis, and cellular repair processes [3-5]. Heavy metals specifically induce toxicity to biological systems by generating reactive oxygen and nitrogen species (ROS/NOS) that cause stress, by bonding to sulfhydryl groups which cause depletion of glutathione as well as inactivation of vital macromolecules [4,6-10]. Oxidative and nitrative stress from reactive oxygen species (ROS) and reactive nitrogen species (NOS) developed in response to heavy metals can lead to cardiovascular, hepatic, pulmonary, skeletal, renal, nervous systems and reproductive dysfunctions, in addition cause cancer in humans [11-16]. Heavy metals are also able to cause fatalities in the human body by their interactions with essential metals and by causing oxidative stress [17,18].

Occupational exposure to toxic metals, such as working with pigments, plastics, glass, metal alloys, and electrode material in batteries, containing the metals, and non-occupational exposures such as through polluted air, cigarette smoke, food, and water can induce serious pathological changes in humans [19]. Metal toxicity is believed to involve alteration in DNA structure, interferences with some enzyme activities including antioxidant enzymes, inhibition of energy metabolism and alteration in thiol proteins [19,20].

The conventional method for treatment of heavy metal toxicity is chelation therapy. There is enough evidence to suggest that healthy nutrition can confer protection and alleviate the outcomes of environmental toxicant in humans [21]. The importance of a personal nutritional status and the benefits of phytochemical as well as whole food components in decreasing the overall toxicity of environmental pollutants to living beings is now well accepted [22]. Nutrition is being advanced as an important alleviator of chemical toxicity, especially concerning environmental pollutants, as they help to decrease their toxicity by preventing inflammation and acting as antioxidants [23], without the added burden of toxicity that comes with synthetic chemical usage.

Edible plants, including vegetables and fruits, are important dietary sources of protein, vitamins, essential minerals, and phytochemicals, which have been reported to have beneficial effects against heavy metal toxicity. Some examples of edible plants that have been reported to alleviate toxic-metals-associated pathologies and offer protection to tissues and organs of test animals include curry leaves [24],garlic [25], ginger [26], green tea [27], onion [28], Soybean [29,30] and Tomatoes[31] The plants offer surface for adsorption for heavy metals, to facilitate their excretion, as well as help in regulating the antioxidant and anti-inflammatory pathways in humans, to help deal with environmental stimulants [2].

This study reviewed currently available information on nutrition intervention as a therapeutic intervention for metal toxicity and specifically provides an overview on the role of nutrients in modifying vulnerability to disease risks associated with exposure to toxic metals. Healthful whole nutrients, microalgae, and phytochemicals that offer protection to humans against pathologies were reviewed in this study.

2.0 Nutrients as modulators of metal toxicity

Toxic metals can induce chronic oxidative stress and dysregulated inflammatory responses. According to Petriello *et al*. [22], anti-inflammatory dietary-based antioxidants may safeguard against toxicant-induced pathology via multiple cell-signaling mechanisms. Phytochemicals such as flavonoids and polyphenols have been shown to decrease toxicity of environmental pollutants, in cases of vascular inflammation, tumor and malignant growth [21,22]. Flavonoid and omega-3 fatty acids can shield cellular systems by diminishing pro-inflammatory lipid raft signaling domains and by simultaneously upregulating antioxidant defenses through increased nuclear factor activation [21,32,33]. Whole food and phytochemicals may protect against oxidative and nitrative stress, vascular dysfunction, and inflammation [22,34-36]. The action involves activating Nrf2 as well as disrupting functional caveolae [32].

Eating some food items and inhaling polluted air are known routes of toxic metal exposure [4]. Therefore, by deciding to alter nutritional choices, an individual can effectively lessen the risks associated with exposure to toxic heavy metals. Making informed dietary decisions such as avoiding food from a polluted environment, may decrease the chance of exposure to toxic metals [22]. However, for many persons, it may be difficult if not cost-prohibitive to alter major diet choices; thus, limiting the chance of such persons benefiting from dietary intake of bioactive nutrients.

Diet-derived bioactive compounds can act as modulators of toxic metals because they help to set the physiological system in top form before any toxic attack by upregulating and protecting detoxifying enzymes, increasing the rate of elimination from the body to lessen the general burden to the body [37]. Changing diets to increase fiber and valuable phytochemicals from whole foods, fruits, and vegetables has been proposed as an effective and cost-efficient means of modulating metal toxicity. Nutritional supplements can be made options for the majority of persons around the world constantly exposed to toxic metals, as they are better options for chelation therapy, concerning cost and fewer side effects [38].

A study conducted by Zhai *et al*. [2] on nutritional intervention for the treatment of Cd and Pb toxicity, confirmed that the use of diet can help mitigate the induction of Cd and Pb toxicity for people at risk of exposure to the metals and alleviate toxic outcomes after exposure, provided it is part of their daily food. The authors surmised that edible plants rich in essential elements, iron, calcium, selenium, zinc, vitamins B, C, and E, and phytochemicals such as anthocyanin, catechin, naringenin, and quercetin, can act as natural antagonists to toxic metals.

The need to provide an adequately nutritious diet to persons exposed to toxic metals to prevent or alleviate heavy metals associated toxicity is no different from the need to provide the right nutrition for the normal functioning of the human system under disease conditions or periods when the human body requires additional nutrients as during pregnancy and among the young, which are considered highly susceptible to heavy metal toxicity [39,40].

2.1 Proteins

Proteins are essential nutrients required for the proper functioning of the human body, by providing all essential amino acids, which the body cannot make. In addition, proteins and their fractions are valuable sources of biopeptides that exert a positive effect on the human body for normal functioning [41]. Biopeptides are specific protein fragments with a positive effect on the organism [42]. Biopeptides are widely used due to their numerous health benefits, particularly for their antioxidant property, for which they are valued in the production of, nutraceuticals and functional foods [43]. These peptides can chelate metal ions [44].

Proteins as excellent sources of dietary antioxidants, can be used in combinatorial treatment strategies for better clinical outcomes in metal-induced pathologies [11]. Antioxidants generally play an important role in the defense against metal toxicity. One important non-enzymatic antioxidant, glutathione, synthesized in the liver from amino acid precursors (glycine, L-glutamate, and L-cysteine), helps to detoxify free radicals and metals [45]. Dietary cysteine, provides L-cysteine (a non-essential hydrophilic amino acid, with a highly reactive thiol side chain), with strong antioxidant properties and an affinity for heavy metals. This makes L-cysteine diametrically involved in the detoxification of heavy metals from the body, via excretion [11]. Dietary taurine supplements can be beneficial in preventing inflammation and neurodegeneration caused by toxic metals, by reactive-radical scavenging and offering neuroprotection [34].

2.2 Vitamins

Vitamins are vital nutrients for humans and several diets provide humans with plentiful varieties of vitamins (water soluble and fat soluble). Vitamins offer protection against metal toxicity by scavenging free radicals produced with heavy metals exposure, act to decrease cellular oxidative stress and reduce plasma to lipid peroxidation, which decreases the risk of having heavy metals-induced pathologies such as infertility, chronic degenerative diseases, stroke, among others [11].

Rendón-Ramírez *et al*. [46] assessed the effect of vitamin supplements on oxidative damage and total antioxidant capacity in workers exposed to lead. The workers were given vitamin C and E supplements orally for one year at a dose of 1 g daily and 400 IU daily respectively. It was observed that lipid peroxidation in erythrocytes was reduced to over 50% and the total antioxidant capacity in erythrocytes was reversed to values also over 50% [46].

Vegetables, fruit, and milk are rich sources of Vitamins A (retinol), vitamin C (ascorbic acid), vitamin E (α-tocopherol), and β-carotene. These vitamins are known to have antioxidant properties, as they are associated with organic free radical scavenging, the inhibition of lipid peroxidation, quenching of singlet oxygen, and hydroxyl radicals' inhibition [44, 47-49].

2.3 Essential Minerals

Some essential minerals are cofactors antioxidant enzymes, form inactive complexes with heavy metals, reduce the absorption and toxicity of heavy metals they are chemically and physically similar to and induces the synthesis of compounds that heavy metals can bind to and be removed from the body (2]. Thus, it is intended that essential nutrients supplementation can deliver protection against metal toxicity. Selenium [50], zinc [51], calcium [51,52], magnesium [53], and iron [54] conferred protection against heavy metal toxicity in animal models.

Selenium is a cofactor of glutathione peroxidase (GPx), an antioxidant enzyme. It helps the antioxidant defense system alleviate Cd and Pb toxicity by reducing oxidative stress produced by the metals, aids the excretion of the metals by forming inactive complexes with them which can aid their detoxification [2], and also enhances the antioxidant capacity of the host [50].

Zinc's potential to alleviate heavy metal toxicity has been well studied, and its ability to detoxify Cd and Pb stems from the chemical and physical properties that it shares with both Cd and Pd. Zinc competes for their binding sites and enzymatic proteins with Cd and Pd, a reason for their use of chelation therapy for the removal of both metals [55,56]. Zinc supplements offer protection to blood δ-aminolevulinic acid dehydratase (ALAD), an enzyme that is very sensitive to Pb toxicity [55], and induces the synthesis of metallothionein, a low molecular weight protein that has a high affinity for some heavy metals [57] and causes detoxification by binding to toxic metals as a result.

Iron controls the expression of intestinal metal uptake transporters (metal transporter protein 1 and divalent metal transporter-1) and competes with heavy metals for access to these transporters [2], thus restraining heavy metals absorption and by extension, their toxicity. Magnesium and calcium also can reduce heavy metal absorption by competing with toxic metals for intestinal transporters and deter any tissue impairment that may emanate from the metals binding to active sites of enzymes [51,53].

2.4 Phytochemicals

Phytochemicals from plants and mushrooms have excellent ability to bind with metals [58], which could aid their removal. There are several bioactive phytochemicals derived from common food substances, including spices and herbs. Phytochemicals such as quercetin, catechin, anthocyanins, puerarin, taurine, melatonin, curcumin naringenin, phycobiliproteins, α-Lipoic acid, γ-linolenic acid, 4-hydroxy-2-nonenal and γ-Oryzanol have been reported to protect against the toxic effects of heavy metals in animal studies [2].

Quercetin modulates the toxic metals in animals by triggering enzymes involved in cellular responses to heavy metals and forming complexes with them to make them excretable [59]. The polyphenolic phytochemical, catechin inhibits heavy metals absorption, prevents lipid peroxidation, and modulates oxidative stress in test animals [60]. Kowalczyk *et al*. [61] reported the effect of anthocyanins from *Aroniimelanocarpa* and acetylcysteine, to include protection against Cd-induced oxidative stress, effectively diminishing oxidative stress in test animals. Liu *et al*. [59] reported that puerarin reduces ROS and protects rat kidneys from Pb-induced apoptosis by modulating antioxidant enzymes (endothelial nitric oxide synthase, phosphoinositide-3-kinase, and protein kinase B) pathways, by so doing, protects against

DNA damage.Curcumin a phytochemical found in turmeric, protects against Cd-induced lipid peroxidation [62], and can bind heavy metals to make them excretable and less toxic [63]. Taurine and melatonin can scavenge free radicals, interrupt radical chain reactions, and form stable complexes with metals thereby reducing metal availability, reducing damage to biomolecules, and promoting the process of detoxification through excretion [11]. Naringenin has a chelating capacity for Pb, quenches free radicals, and improves antioxidant enzyme activity [64]. 4-hydroxy-2-nonenal modulates of oxidative stress [65]. γ-Oryzanol prevents lipid peroxidation, improves ALAD activity, and prevents oxidative damage in mice testes [66].

α-Lipoic acid found in edible plants such as broccoli spinach, tomatoes, garden peas, and rice, acts as an antioxidant in both oxidized and reduced forms and is considered a potential therapeutic agent for heavy metals intoxication, based on their chelating properties [11]. α-Lipoic acid can be beneficial in chelation therapy against cadmium, copper, iron, and mercury intoxication [67]. In addition, it can scavenge ROS, NOS, and other radicals produced by exposure to toxic metals [68] and regenerates glutathione that contributes to the antioxidant defense system [69].

Dietary polyphenols such as hydroxycinnamic acids, flavonoids, and resveratrol can impair oxidative stress, attenuate inflammatory response, and avert apoptosis and carcinogenesis, arising from heavy metals poisoning [70]. Anthocyanin, epicatechin, hesperidin, hydroxytyrosol, proanthocyanidins, schisandrin B, and lycopene have been reported to protect against, manganese, aluminum, lead, and mercury poisoning, by avoiding the loss of antioxidant enzymes and alienating oxidative stress [71-77].

2.5 Microalgae Supplement

Microalgae are unicellular aquatic microorganisms with *Spirulina* sp. *Arthrospira*sp, *Nostoc commune*, *Ulkenia*sp, *Chlorella vulgaris*, *Porphyridium*sp, *Phaeodactylum*sp, *Schizochytrium*sp, *Scenedesmus almeriensis*, *Dunaliellabardawil*, *Haematococcuspluvialis*, as notable examples [78-83]. Although they are known to contain appreciable amounts of primary nutrients, they are most valued for their non-nutritive compounds such as mycosporine-like amino acids, flavonoids, phytosterols, and phenolics [82]. The non-nutritive compounds are of health value due to their capacity as antimicrobial, antitumor, antioxidant, anti-inflammatory and anticancer agents [84,85]. Consumption of some microalgae can help meet the physiological need for protein, carbohydrates, and vitamins [82]. Peptides, phycobiliproteins, mycosporine-like amino acids, phytosterols chlorophyll, and carotenoids from microalgae such as fucoxanthin, astaxanthin, lutein, zeaxanthin and β-carotene, have antioxidant, anticancer, antihypertensive, anti-inflammatory, hepatoprotective, neuroprotective and many others properties [35,86-95].

Microalgae help the human body to keep free radicals under control, as they are chiefly dietary antioxidants, through their donation of hydrogen atoms to unstable free radicals [96]. Microalgae biomass and phytochemicals have correlated with antioxidant capacity [90]. Microalgae macromolecules have been shown to cause cell death in human lung cancer cell lines (Wi38) [97], prevented the proliferation of human colon cancer cell lines DLD-1 and HCT-116 [98], exhibit high anti-inflammatory function against oedema [99] and enhanced cellular viability against chemical-induced cytotoxicity [36]. Toxic metals are known to induce all the pathological anomalies that microalgae biomass and phytochemicals have been reported to alleviate.

Microalgae are considered to be highly resistant to heavy metals. *Chlorella vulgaris* a unicellular marine microalga with many documented therapeutic properties as a health food [100, 101], has long been associated with detoxification of toxic/heavy metals [102]. The health benefits of *Chlorella vulgaris*, concerning heavy metals, are mainly correlated to their adsorption properties. When *Chlorella vulgaris* is exposed to heavy metals, metal-binding metallothionein-like proteins in the cell are induced to detoxify the heavy metals [103]. Chlorella has been reported to enhance the excretion of cadmium (Cd) and mercury (Hg) by inhibiting intestinal absorption of heavy metals [104,105] and reducing lead (Pb) concentration in blood [106]. Ogawa*et al*. [101] showed that chlorella could inhibit strontium absorption and enhance strontium elimination from the body through adsorption between Chlorella and strontium in the intestine. Similarly, it can also bind to technetium, uranium, cobalt, and thallium [102].

2.6 Milk

Ruminant milk and dairy items are significant food assets to man and a piece of our sustenance since days of old, providing sufficient amounts of macro and micronutrients, as a whole healthful food [107]. It is the primary nourishment for warm-blooded animals and gives all the vital energy and supplements to guarantee sound development and advancement, being pivotal regarding bone mass [108]. Although, there is wariness about the health impacts of dairy items in the general population, which is reflected in rising consumption of plant-based drinks, for instance, soy, rice, almond, or oat [109], interest in the use of milk to alleviate the effect of toxic metal fumes is on the upscale [110].

Milk is made of substances such as β-carotene, vitamins A, conjugated linoleic acid, α-tocopherol, D3, coenzyme Q10, phospholipids, vitamins, minerals, proteins, peptides, and trace elements with proven antioxidant properties, relevant in maintaining pro-oxidant and antioxidant homeostasis in the human body, which no doubt are deemed of immense health benefits [111]. The antioxidant capacity of milk is due to sulfur-containing amino acids (cysteine), vitamins A, and E, carotenoids, enzyme systems, superoxide dismutase, catalase glutathione peroxidase, and polyphenolic metabolites [42,112,113]. Antioxidants present in dairy help to neutralize the final products of lipid peroxidation and reactive oxygen species [113,114], they can inhibit superoxide radicals, hydroxyl radicals, and peroxide radicals [115]. Milk products with protective properties have the potential to act as coadjuvants in conventional therapies, addressing cardiovascular diseases, metabolic disorders, intestinal health, and chemo-preventive properties [40,116]. Whey protein found in milk chelates iron, which increases its bioavailability, suppresses the inflammatory response and inhibits the pro-oxidant effects of ROS [44]. Casein mitigates the aging-related damage induced by oxidative stress [117]. Milk is a rich source of Vitamins A (retinol), vitamin C (ascorbic acid), vitamin E (α-tocopherol), and β-carotene. These vitamins are known to have antioxidant properties, as they are associated with organic free radical scavenging, the inhibition of lipid peroxidation, quenching of singlet oxygen, and hydroxyl radicals' inhibition [44,47-49].

Gomes *et al*. [118] determined the effect of milk and dairy purine in employees of motor battery industries in Brazil, exposed to high Pb levels. The study had 237 male employees, from whom information concerning nutritional status and lifestyle was gathered through a questionnaire, while blood, plasma, and urine Pb levels were determined by ICP-MS. Mean blood, plasma, and urine Pb levels were found to be 21 ± 12, 0.62 ± 0.73 μg/dL, 39 ± 47 μg/g creatinine, correspondingly. Forty-three percent of participants declared consuming ≤ 3 portions/week of MDP (which is deemed low- milk and dairy purine intake), while 57% of individuals had > 3 portions/week of MDP (high- milk and dairy purine intake). Blood Pb and plasma Pb were correlated with working time ($r_s=0.21$; $r_s=0.20$; $p<0.010$). Multivariable linear regressions showed a significant influence of MDP intake on Blood Pb ($\beta=-0.10$; $p=0.012$) and Plasma Pb ($\beta=- 0.16$; $p<0.010$), while no significance was seen on urine Pb. They concluded that milk dairy purine consumption may moderate lead levels in persons highly exposed to lead, owing to calcium and lead interactions. They surmised that since the adverse effects of the heavy metal are partially based on its interference with calcium metabolism, giving calcium supplements may help to reduce such contrary health upshot induced by exposure to lead.

Conclusion

Individuals facing the risk of toxic metal exposure can safeguard their well-being by adopting a diet abundant in essential elements, vitamins, protein, bioactive peptides, and various antioxidant-rich phytochemicals. Incorporating milk, vegetables, fruit, and microalgae-based dietary supplements can fulfill these nutritional needs, mitigating the adverse effects of toxic metal exposure. Despite the available literature not conclusively establishing the benefits of dietary supplements in occupational heavy metal exposure, it's crucial to exercise caution in the consumption of phytochemicals, as excessive intake may lead to adverse effects. The most effective strategy to prevent heavy metal toxicity is to prevent their entry and absorption into the body tissues.

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