Journal of Trace Elements in Medicine and Biology 54 (2019) 226–231

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Heavy metal toxicity: An update of chelating therapeutic strategies

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ARTICLE INFO

Keywords:
Arsenic
Cadmium
Chelating agent
Copper
Iron
Lead
Mercury
Metal toxicity

ABSTRACT

Aim: This review illustrates heavy metals toxicity, currently available therapies and the role and efficacy of chelation therapy for its management.

Summary: Heavy metals are necessary for various biological processes, but they become harmful in excess. Specifically, they induce oxidative stress by generating free radicals and reducing antioxidant levels. Heavy metals also alter the confirmation of protein and DNA and inhibit their function. Chelation therapy is commonly used to treat metals toxicity. Chelation is a chemical process that occurs when interaction between a central metal atom/ion and ligand leads to formation of a complex ring-like structure. The ligand has a donor ion/molecule, which has a lone pair of electrons and may be monodentate to polydentate. Each metal has a different reactivity with a ligand, so a specific chelation agent is required for each metal. Combination therapy with a chelating agent and an antioxidant led to improved outcome.

Conclusion: Heavy metal poisoning is a common health problem because of mining, smelting, industrial, agricultural and sewage waste. Heavy metals can be efficiently excreted from the body following treatment with proper chelation agents.

1. Introduction

1.1. Heavy metals

These are inorganic elements that have a density greater than 5 g/cm^3 [1]. Examples of common heavy metals are chromium (Cr), lead (Pb), cadmium (Cd), mercury (Hg), copper (Cu) and zinc (Zn). Arsenic (As) is also included in this group because of similarities in physical and chemical properties. Less common heavy metals include iron (Fe), cobalt (Co) and manganese (Mn). Heavy metals were classified into two groups based on their toxicity, essential and non-essential heavy metal. (1) Essential heavy metals are harmless or relatively less harmless at low concentration (Zn, Cu, Fe, and Co). (2) Non-essential metals are highly toxic even at low concentration (such as Cd, Hg, As, and Cr).

1.2. Role of essential heavy metals in biological processes

Essential heavy metals are cofactors in a various biological process. For example, Cu, Zn, Fe, and Co play vital roles in oxygen utilization, cell growth, numerous enzymatic reactions, bimolecular synthesis and immunity of the body [2–5]. Iron is found in hemoglobin, myoglobin, cytochromes (a, b, c), catalase, aconitase, succinate dehydrogenase, aldehyde oxidase, peroxidases, tryptophan 2,3-dioxygenase and many more enzymes [4,5]. Copper is needed for tyrosinase, superoxide dismutase, cytochrome c oxidase, ceruloplasmin, and dopamine-β-hydoxylase [2,6]. Zinc is required for protein folding, conformational and configurational changes, and activity, as well as for DNA synthesis, male fertility and growth hormone [3,7]. Cobalt is essential for the synthesis of vitamin B_{12} [8].

1.3. Heavy metals homeostasis

Essential heavy metals homeostasis is carefully regulated through a system of protein transporters that are involved in uptake, distribution, storage, and excretion of metal ions inside the body [9,10]. The eukaryotic vacuolar system also plays a major role in metals homeostasis by storing metal ions and transporting them to several cellular membranes through the secretory pathway. In addition, organelles such as the peroxisome, chloroplasts, and mitochondria serve as reservoirs of metal ions and contribute to their overall homeostasis by utilizing their own transport and storage systems [9–15].

Copper is regulated by many transporter proteins, including Ctr1,

Abbreviation: Cr, Chromium; Pb, Lead; Cd, Cadmium; Hg, Mercury; Cu, Copper; Zn, Zinc; As, Arsenic; Fe, Iron; Co, Cobalt; Mn, Manganese; DMSA, Dimercaptosuccinic Acid; DMPS, 2,3-Dimercapto-Propanesulphonate; BAL, British Anti-Lewisite; Cana2-EDTA, Sodium-Calcium EDTA; DFO, Deferoxamine; BBB, Blood-Brain Barrier; WD, Wilson Disease

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https://doi.org/10.1016/j.jtemb.2019.05.003
Received 30 November 2018; Received in revised form 25 March 2019; Accepted 6 May 2019

Ctr2, Atox1, CCS, Cox1, Ceruloplasmin, ATP7A, ATP7B, and metallothioneins. Mutation in *ATP7A* and *ATP7B* gene resulted in Menkes and Wilson diseases (WD) respectively. Menkes disease shows copper deficiency while WD is characterized by the accumulation of copper in the liver brain and other organs [16,17].

Homeostasis of Fe is regulated by transferrin, ceruloplasmin, hephaestin, ferroportin, and divalent metal transporter 1 (DMT1). Unpaired regulation of Fe may result in iron-deficiency anemia, hemochromatosis, Huntington's chorea, Parkinson's disease, Alzheimer's disease and Amyotrophic Lateral Sclerosis [17–19].

Zinc homeostasis is controlled by the combined activity of various zinc transporter families (ZnT and ZIP) and metallothioneins. The ZnT family decreases intracellular zinc level whereas ZIP family imports zinc ions from the extracellular space into the cytoplasm [20,21].

1.4. Heavy metals pollution

Heavy metals contamination in water and soils has swiftly increased during the last few decades because of electronic waste [22], fossil fuel burning [23], disposal of municipal wastes, mining and smelting, and application of fertilizer, pesticides, and sewage [24–26]. Heavy metals are non-biodegradable pollutants, and even low concentrations of non-essential heavy metals (As, Hg, Pb, and Cd) can be lethal to living animals. Essential metals such as Zn, Cu, and Fe may become toxic if they are present at levels above their threshold levels [14,27–29]. The United States Environmental Protection Agency (USEPA) has listed Cr, Cd, Hg, Cu, Pb, and Arsenic as priority control pollutants because of their persistence and irreversible toxic characteristics.

1.6. Heavy metals toxicity

The accumulation of heavy metals in the human body leads to severe injury to various organs, specifically the respiratory, nervous and reproductive systems and digestive tract [13,14,30,31].

1.6.1. Essential heavy metal toxicity

Heavy metals such as Zn, Cu, and Fe are required for the proper function of various enzymes and proteins. However, when the same metals accumulate at levels greater than the threshold level they become toxic. This induces the generation of reactive nitrogen and oxygen species (RNS; ROS), which results in the peroxidation of lipids in the plasma membrane. The transition metals Fe and Cu catalyzes the formation of hydroxyl radicals via Fenton-like reactions [11,32]. These metals can also react with DNA and proteins, resulting in their functional deterioration. Moreover, RNS and ROS may interfere with the electron transport system. Additionally, excesses of these metal ions in the cytoplasm may interrupt the intracellular redox equilibrium, as well as induce changes in the pH of cytoplasm and protein conformation and impede protein function, ultimately leading to cellular dysfunction and apoptosis or necrosis. These metal ions also interact with sulphur, nitrogen and oxygen atoms of functional groups such as thiol, imidazole and the carboxyl groups of proteins [28,33,34]. Metals interfere with cell growth, proliferation and development by modulating signal transduction pathways, activating/inhibiting many transcription factors, regulating cell division pathways and apoptotic/necrosis pathways and altering sodium and calcium ion homeostasis [29,35–37]. Dyshomeostasis of these biometals is also associated with the neurological disorder, and chelation therapy in these conditions may improve the outcome [38,39].

1.6.3. Non-essential heavy metal toxicity

As, Cd, and Hg are redox-inactive metals and induce oxidative stress by inhibiting the enzymatic activity of superoxide dismutase, reducing antioxidants, or binding to -SH groups of proteins. Arsenic can exist in three-valance state and induces oxidative stress by oxidation-reduction reaction. Due to multiple valance states, it also affected the methylation and acid-base reaction. Lead induces oxidative stress by the generation of free radical and reductions of antioxidant property of the cell. Prenatal exposure to As, Cd, and Hg can cause neurodevelopmental disorders and brain dysfunction [11,29,31,40,41].

2. Metal chelating agents

Chelation therapy is the primary treatment for heavy metals intoxication. Chelation is a process in which ions/molecules of a ligand bind to the central metal atom/ions via a coordination bond in a cyclic or ring-like structure. A ligand is an ion or molecule that has two or more atoms capable of donating a pair of electrons to form a covalent bond with a metal atom/ion. Based on the nature of the bond between the ligand and covalent atom, ligands can be classified into three types: [A] Unidentate (one donor atom; e.g., Cl^-, NH_3, H_2O), [B] Bidentate (two donor atoms; e.g., $C_2O_4^{2-}$) and [C] Polydentate (more than two donor atoms; e.g., EDTA). Ligands that are capable of binding to a central atom through two different atoms, but can only bond with one at a time are known as ambidentate ligands (e.g., SCN^-). Polydentate ligands form five to six-membered ring complexes, which are more stable than monodentate ligand-metal complexes. The stability of these complexes varies with the ligand and metal ion interactions. Mercury and lead metal ions have higher affinities for nitrogen and sulfur than for oxygen ligands, while the reverse is true for calcium atoms. These differences in affinity are the basic principle for the selection of chelating agents [31,39,41,42].

2.1. Characteristics of a good chelating agent

Good chelating agents form chemically inert and non-toxic complexes with metal atoms/ions. In addition, good chelating agents can easily be excreted from the body without any further interaction with the vital organs. They also have the ability to enter the cell membrane to remove intracellular toxic metals. These agents can be administered orally, intravenously, or intramuscularly and have a greater affinity for metals than for normal body ligands. A good chelating agent also has a relatively higher affinity for toxic metals than for desired body metals and can compete with endogenous ligands. Finally, good chelating agents retain their chelating properties at the pH of body fluids and their distribution in the body is the same as that of toxic metals. In the case of neurotoxicity, a chelating agent with high lipophilicity and low molecular size is preferred because it can easily cross BBB [31,39,41,43–45].

2.2. Common chelating agent

2.2.1. Dimercaprol

This compound, which is also known as British anti-Lewisite (BAL), contains two –SH (sulfhydryl) and one hydroxyl groups and is commonly used for arsenic, mercury, lead, and gold. Chelation using this compound occurs via metal atom/ion binding with a thiol group to form a stable metal-ligand complex, which is later excreted via the kidney. BAL reacts with As(III) and Pb(II) to form a stable 5-membered ring complex [39,41]. (Table 1).

2.2.2. ,3-Dimercapto-Propanesulphonate (DMPS)

This compound is a water-soluble analogue of the BAL that is generally used in the management of arsenic and mercury toxicity [46–48]. DMPS contains one sulfonic group and two thiol groups. Due to water solubility nature, it has difficulties to cross the Blood-Brain Barrier (BBB) hence fails to redistribute mercury and lead from brain tissue of rats. However, DMPS compound removes deposited mercury from the kidneys [41]. DMPS causes less side effects than dimercaprol [39,49].

2.2.3. Sodium-calcium EDTA (CaNa2-EDTA)

This compound is primarily used to treat lead poisoning. The

Table 1
List of common chelating agents with generic name and chemical formula.

Sl. No.	Chelating agent	Metals	Brand name	Generic name	Chemical formula
1	BAL	Arsenic, Mercury, Lead, Gold	BAL in Oil	Dimercaprol; British Anti-Lewisite (BAL); 2,3-Dimercaptopropanol	$C_3H_8OS_2$
2	DMSA	Arsenic, Mercury, Lead	Chemet	meso-2,3-Dimercaptosuccinic acid; succimer	$C_4H_6O_4S_2$
3	DMPS	Arsenic, Mercury		2,3-Dimercaptopropane-1-sulfonic acid	$C_3H_8O_3S_3$
4	CaNa2EDTA	Lead	Calcium disodium versenate	Edetate calcium disodium; sodium calcium edetate	$C_{10}H_{12}CaN_2Na_2O_8$
5	Deferoxamine	Iron, Aluminum	Desferal	Desferrioxamine	$C_{25}H_{48}N_6O_8$
6	Penicillamine	Copper	Cuprimine, Cuprenyl, Depen	D-penicillamine	$C_5H_{11}NO_2S$

calcium atom of this compound can be replaced by metal ions to form a water-soluble complex that is eliminated via the kidney [41,50]. In animals, $CaNa_2EDTA$ does not effectively reduce the total brain lead level [51]. Rather, it removes lead from soft tissue stores and, to a lesser extent, increases the excretion of endogenous metals such as zinc, copper, and iron [39,50].

2.2.4. Deferoxamine (DFO)

It is an organic compound, which contains 25 carbon atoms and three-hydroxamic acid group. It forms a strong bond with trivalent ion and shows less affinity to other metals. This property of DFO makes it more specific chelating drug for iron and aluminum. It binds to iron and aluminum ion and form ferrioxamine and aluminoxamine compound, respectively, which are stable complexes that are eliminated via the kidneys. Multiple blood transfusions and genetic diseases such as thalassemia can result in iron overload, and DFO is used as medicine [18,39,41,52].

2.2.5. Penicillamine

This compound is primarily used to remove excess Cu from the body. Wilson disease (WD) is a rare autosomal recessive disease of Cu metabolism. In this disease, Cu accumulates in the liver, brain, and tissue of other organs. Penicillamine is commonly used to treat WD; however, it leads to worsening neurological conditions in 20–30% of WD patients. In such cases, trientine hydrochloride and tetrathiomolybdate are used [53–55]. Penicillamine is also used as a second or third line agent for the treatment of lead and arsenic toxicity [39,43,44].

2.2.6. Dimercaptosuccinic acid (DMSA)

This compound, which is also known as succimer, is an analogue of BAL. DMSA contains two carboxylic group and two thiol groups, with the thiol groups participating in the metal-ligand reaction. This compound is used to treat lead, mercury and arsenic toxicity. FDA approved DMSA for the treatment of lead poisoning in pediatric patients [39,41,56,57]. (Table 1).

2.2.7. DMSA analogue

New synthetic analogue compound of DMSA have been developed and tested for their metal binding properties. Common DMSA analogues are monoisoamyl DMSA (MiADMSA), monocyclohexyl DMSA (MchDMSA), and monomethyl DMSA (MmDMSA). These analogues showed better excretory efficacy than DMSA [39].

2.2.7.1. MiADMSA. It is a C_5-branched chain alkyl monoester of DMSA and is water-soluble and lipophilic in nature. Because of its lipophilic nature, it can cross the plasma membrane and enter intracellular space to remove heavy metals [58,59]. Recent studies have shown MiADMSA efficiently chelate out arsenic [58,60], lead [61], cadmium and mercury [41].

2.2.7.2. MchDMSA and MmDMSA. MchDMSA has a cyclic carbon chain analogue of DMSA, and MmDMSA has a straight and branched chain methyl group analogue. Both are lipophilic compounds and have the ability to penetrate into cells. Both of these chelating agents are can be given orally. In vivo studies showed that co-administration of MiADMSA and MchDMSA produced significant reductions in cadmium and arsenic levels cadmium [39,41,62].

3. Metal poisoning and chelation therapy

3.1. Mercury poisoning and chelation therapy

Food is the main source of mercury poising in the common population. Fish and dental amalgam are the primary sources of methylmercury exposure. People with high fish consumption may have an increased risk of methylmercury exposure. The BBB of fetuses is less tight than of adults and therefore circulating methylmercury in mother´s blood may enter fetus´s brain. Therefore, pregnant females must avoid the intake of such fish taken from polluted waters [63–65]. Mercury toxicity may cause headache, hypertension, tremor, insomnia, change in nerve response, impaired cognitive function, muscle atrophy and weakness, and cardiac and renal dysfunction. [39,44,66–68].

Chelating agents such as DMSA and DMPS can efficiently remove mercury through the kidney. These drugs can be administered orally and have comparatively less toxicity than dimercaprol. Additionally, DMSA appears to be better at the removal of methylmercury, including from the brain region. Although DMPS is unable to recover methylmercury levels in the brain, it can efficiently remove it from the kidney. [9,39,44,66–68] (Table 1).

3.2. Lead poisoning and chelation therapy

The common people are exposed to lead and its compounds by lead related industries such as automotive and battery manufacturing, refining, and smelting. Lead inhibits several biological processes and is hazardous to the nervous system, heart, kidneys, and gastrointestinal tract, with the nervous system being the most affected. Lead also disrupts the development of the brain in children, causing cognitive impairments. Children are more sensitive to lead exposure even at low levels because of high absorption in the gastrointestinal tract and permeability of the BBB. Lead affects neurotransmission by altering Ca^{2+} associated activity, which leads to excitotoxicity [69,70]. Lead also affects glial cell (astrocyte, and oligodendrocyte) activity, resulting in demyelination [40,71]. Clinical manifestation of lead toxicity symptoms includes headache, anemia, abdominal distress, and in severe conditions, convulsions, coma, and death [27,39,72,73].

Succimer, BAL and $CaNa_2EDTA$ and are primarily used for chelation of lead. $CaNa_2EDTA$ only removes extracellular lead, and its effectiveness increases when used in combination with BAL. Co-treatment with $CaNa_2EDTA$ and MiADMSA showed better biochemical and clinical outcome than monotherapy against subacute lead toxicity in the rat model. Treatment with α-lipoic acid in combination with a thiol chelator reduces the oxidative stress and brain lead concentration in rat [39,40,50,72–75]. (Table 1).

3.3. Cadmium poisoning and chelation therapy

Cadmium exposure to human populations is mainly because of the use of rechargeable nickel-cadmium batteries and cigarettes. Food is the

key route of cadmium exposure in non-smokers. Exposure to cadmium even at low levels damages kidneys and may also affect bones and fractures [76,77]. The chronic effects of cadmium exposure may include lung damage, bone fractures, liver, and kidney dysfunction and reproductive defects. Cadmium affects the nervous system by inhibiting acetylcholinesterase activity [39,71]. Moreover, acute inhalation exposure can result in flu-like symptoms (fever, chills, body aches, muscle, and joint pain) and lung damage.

Cadmium toxicity is treated with EDTA, DMPS, and DMSA. Of these, three chelating agent EDTA is the drug of choice. In an animal study, DMSA removed cadmium more effectively than DMPS. Studies in vitro and in vivo suggest that EDTA has better efficacy to DMSA in mobilizing intracellular cadmium. [39,49,78,79]. Moreover, the effectiveness of EDTA is improved with the adjunctive use of antioxidants such as glutathione [80], which also protects against nephrotoxicity. The effectiveness of EDTA may also be enhanced by the concomitant use of vitamin E and C and antioxidants [31] including methionine, mannitol [81], thiamine [82], and zinc [83].

3.4. Arsenic poisoning and chelation therapy

Food and drinking water are the main sources of arsenic exposure in most populations. Chronic exposure can result in dermal lesions such as hyperkeratosis and pigmentation changes, as well as increased risks of skin and other cancer. Chronic exposure to arsenic dust results in peripheral neuropathy and peripheral vascular disease and lung cancer [39,40,67,84–86].

Chelating agents such as DMSA, DMPS, and penicillamine are commonly used in chronic arsenic toxicity. The concomitant use of DMSA with long carbon chain analogue such as monocyclohexyl and monoisoamyl DMSA together showed an improved efficiency at reducing the arsenic load when compared to DMSA alone [40,67,87]. However, a recent randomized placebo-controlled clinical study showed satisfactory results in response to the use of DMPS in chronic arsenic poisoning [46].

3.5. Iron poisoning and chelation therapy

Iron exposure to the environment mainly occurs through mining, manufacturing units, and municipal or industrial wastewater. Iron pollution also occurs in response to corrosion of pipes, water supply from groundwater systems and from the atmosphere via rainwater. Soils and groundwater are contaminated through human agricultural and industrial wastes containing iron. Air pollution from the steel sector contains particulate iron and iron oxide. The common symptoms of iron toxicity are vomiting, diarrhea, nausea, abdominal pain, dehydration and lethargy [39,88,89]. Iron is usually well regulated, but in some condition, its poisoning can be caused by (a) accidental overdose, (b) repeated blood transfusion in anemic patients, (c) excessive iron therapy, (d) genetic condition (such as hemochromatosis or thalassemia).

Deferoxamine, deferasirox, deferiprone, and clioquinol are common iron chelating agents. Deferoxamine, deferasirox, and deferiprone are hexadentate, tridentate, and bidentate, respectively. Clioquinol is a small lipophilic molecule that can cross the BBB. It exhibits neuroprotective property by chelating metallic ions such as Fe, Cu, and Zn [39,90–92]. Clioquinol is toxic because of its ambiguous selectivity to iron. Deferoxamine treatment is recommended for β-thalassemia patients who are receiving regular transfusions [18,93] (Table 1).

3.6. Copper poisoning and chelation therapy

Copper pollution mainly occurs through manufacturing operations, mining, farming, and municipal and industrial wastewater. Acute copper toxicity symptoms include vomiting, hypotension, jaundice, and abdominal pain with gastrointestinal distress. Long-term copper exposure may damage the liver, brain, and kidney [12,39].

Penicillamine therapy is commonly used to treat copper toxicity and Wilson disease [53,55], although tetrathiomolybdate and trientine have also been prescribed for the treatment of Wilson disease [44,94] (Table 1).

4. Adverse effects of chelation therapy

During the course of chelation therapy, worsening conditions are reported in some patients. Common adverse effects include fever, nausea, headache, vomiting, high/low blood pressure, gastrointestinal distress, muscle pain, pain at the site of the injection, and burning sensation. Severe adverse health effects include heart failure, breathing difficulty, respiratory failure, low blood pressure, permanent kidney damage, convulsions or seizures and low blood calcium [44,95,96]. During treatment, it is important to provide the appropriate dose of the drug according to the metal concentration at a regular interval because a high dose of the chelating drug for a longer duration may also decrease the levels of essential metals. Selection of the chelating drug must be specified according to the affinity of the metal and ligand. A high dose of a chelating drug can suddenly increase toxic metals in a body fluid, causing further worsening of patients [39,43].

5. Combination therapy with chelating agents

Adjunctive antioxidants therapy with chelation treatment is useful for the treatment of metals toxicity. Combined treatment of DMSA with α-lipoic acid in lead poising was found to improve oxidative damage [97,98]. Additionally, $CaNa_2EDTA$ in combination with zinc showed improved chelating ability. Zinc and Selenium have shown protective potential against non-essential metals [39,99,100]. Co-admission of MiADMSA with an antioxidant (preferably having a thiol moiety) show better efficiency in chelation treatment against chronic arsenic toxicity [101]. The Co-treatment of vitamin E with DMSA or MiADMSA shows better outcomes [97]. Co-admission of common chelating agent with antioxidant (such as Vitamin E and C, thiol group, zinc, and selenium) reduces oxidative stress by minimizing lipid peroxidation and increasing antioxidant activity. This treatment protocol helps to decrease the dose of the chelating agent, minimizes possible side effects and provides better clinical recoveries [39,41,102].

6. Alternate therapy to acute heavy metal poisoning

6.1. Plasma exchange/plasmapheresis

Plasma exchange treatment can be used as an alternative therapy in an emergency condition if there is high metal toxicity. Some studies have shown that plasma exchange is most efficient for inorganic mercury and could be useful when applied in association with chelation therapy during the early phase of intoxication. [103,104].

6.2. Hemodialysis

This treatment protocol has been used to treat mercury toxicity, but was found to be ineffective [104].

6.3. Induced perspiration (or sauna therapy)

Sweating is one of the natural processes to excrete toxins. The increased concentration of Cd, Ni, Pb, Al, Mn, and Co were found in sweat [105].

7. Conclusion

In the present review, we discuss heavy metal toxicity, its adverse effects and possible use of chelating drugs to treat heavy metals

exposure. Exposure to metals is common in individuals who are involved in mining, smelting, industrial and agricultural activities, as well as those who come into contact with sewage. These metals induce oxidative stress and impede enzyme and proteins activities. Moreover, long-term exposure to these metals may result in cell death via apoptosis. Heavy metals also affect signaling pathways and cause alterations in DNA, lipids, proteins, enzymes and calcium and sodium ions homeostasis.

Metal poisoning treatment with chelation agents is the standard protocol. However, the use of BAL and EDTA are now restricted because of their own toxicity. Oral administration of DMSA and DMPS effectively removes mercury and lead via the kidney with less toxicity than other chelating agents. Penicillamine is commonly used to treat copper poisoning. Deferiprone and deferasirox are recommended for the treatment of iron poisoning because they can achieve a beneficial outcome with less toxicity. A combination therapy treatment protocol helps to reduce the dose of the chelating agent, minimizes possible side effects and provides a better clinical outcome.

8. Limitations

In this review, we only discuss chelating agents in routine use; however, some new drugs currently under clinical trials have shown good results in animal studies. Additionally, we focused on arsenic, cadmium, lead, mercury, iron and copper toxicity and their treatment. This review help in selecting the proper drug and help to design potential drugs with less toxicity and high specificity for selected metal.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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