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REVIEW ARTICLE

Application of nanotechnology in novel nano-based compounds development for metal poisoning treatment

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ABSTRACT

Metal toxicity or metal poisoning is one of the major global health problems. Application of metals in different industries causes their widespread release in the environment. As a result, the chances of encountering them have increased. These toxicants induce multiple organ abnormalities, though the severity of their damage is related to various factors such as exposure route, exposure time, and dose of toxicant. Supportive treatment, chelation therapy, and specific antidotes are the main approaches to metal poisoning. However, this treatment protocol is not completely effective for curing many severely intoxicated patients with metals, and on some occasions, it has adverse effects, particularly chelators, which are potential agents to induce side effects in patients. Therefore, it is urgent that alternative treatments which are safer and more effective are introduced as soon as possible to save severe cases. Recently, with the help of nanotechnology using different strategies such as solid lipid nanoparticles (SLNs), polymeric nanoparticles, liposomes, microemulsions liquid crystal (LC) systems, nanoemulsions, nanogels, polymeric micelles, phytosomes, dendrimers, inclusion complexes, and precursors systems for liquid crystals (PSLCs), new, safer and more efficient compounds have been discovered, and they are at the testing process for the treatment of metal poisonings. Therefore, this review article introduces the state of the art of novel nano-based compounds for metal poisonings.

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INTRODUCTION

Poisonings are one of the most common causes of morbidity and mortality in the globe. There are various types of exposures which cause poisoning, such as metals, medicines, chemicals, toxins and so forth. Poisoning may be intentional or unintentional following exposures [1, 2]. A chemical substance or a particular mixture of substances can damage an organism or a substructure of the organism, such as a cell or a whole organism including a human, animal, plant or bacterium, and induce toxicity. The most important approach for reducing mortality is quick diagnosis and appropriate treatment, which is a very complicated subject, particularly in severely intoxicated patients. However, treatment of poisoning has not improved significantly over the past few years. Supportive care and administration of specific antidote are the most important approaches to treatment [2-4]. With regard to the high rate of mortality in severe intoxicated cases and lack of efficient specific antidotes for different types of poisoning, the development of new and targeted antidotes for intoxicated complex cases is so urgent. Metal poisonings are one of the major health threats to humans, animals and ecosystem throughout the globe. Metals including arsenic, lead, mercury, cadmium, chromium, aluminum, iron, nickel, copper, zinc, lithium, platinum and so forth induce disorder, poisoning and toxicity in humans, animals, plants and other biological systems (Figure 1). Severity of complications

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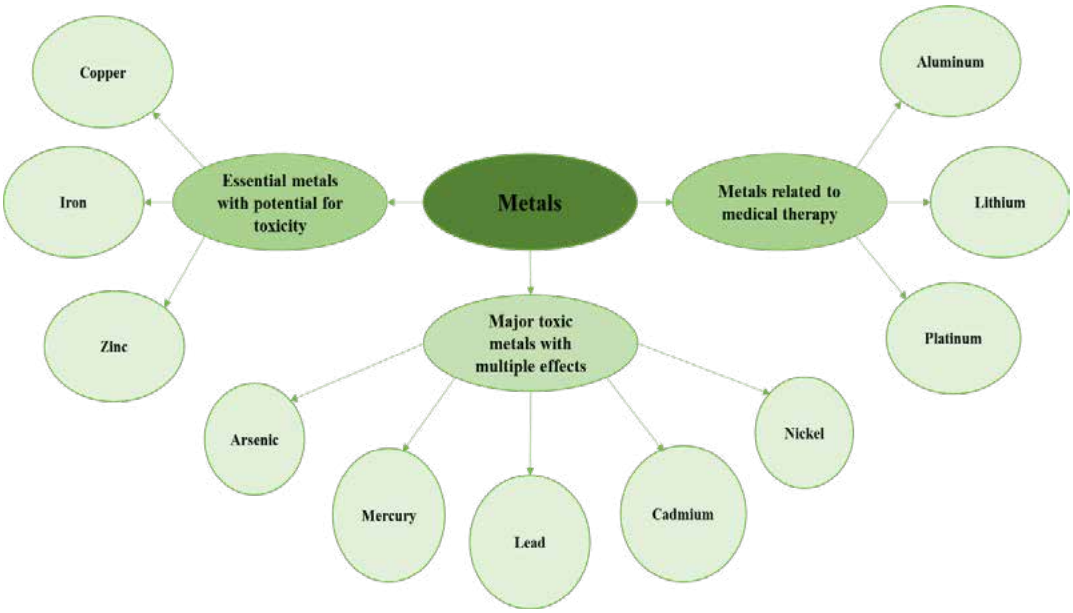

Fig. 1. Schematics of different metals categorization

which are induced by metals depends upon the dose, the route and duration of exposure to them. Unfortunately, there are no efficient specific antidotes or specific approaches for treatment of many types of poisonings. Cure is limited to general symptomatic signs, complexation and chelation therapy [5-8]. One of the sciences which is very valuable for this purpose is nanotechnology. Nanoscience has an effective role in developing different fields of science and helps to make life more convenient than before. Therefore, this branch of science is so valuable and practical, and it will be able to create more beneficial effects on the globe in the future. Nanoscience is an era of science which studies the structures and molecules on the nanometer scale ranging between 1 and 100 nm, and the technology which employs it in practical applications has been introduced as nanotechnology [9, 10]. Nanotechnology has various uses in medicine, such as diagnosis, treatment and monitoring. This branch of nanotechnology has been called nanomedicine. Drug delivery is one of the most essential fields that nanotechnology could improve for treatment purposes. It is a targeted system that introduces a therapeutic substance into the body using a special device or formulation in order to boost efficacy, potency and safety of the medication [11-14]. The nanocarriers are produced from safe materials, such as synthetic biodegradable polymers, lipids, and polysaccharides. There are different nano-based strategies which are applied in drug delivery systems including solid lipid nanoparticles (SLNs), polymeric nanoparticles, liposomes, microemulsions, liquid crystal (LC) systems, nanoemulsions, nanogels, polymeric micelles, phytosomes, dendrimers, inclusion complesxes, and precursors systems for liquid crystals (PSLCs). In addition, different nanoparticles with different sizes have remarkable applications in treating toxicities (Figure 2) [15-21]. These strategies are able to improve the bioavailability, biodistribution, of medications such as chelation agents and specific antidotes, and they act as stability boosters. These nano-based systems can deliver curing agents to target sites to improve therapeutic efficiency, decrease toxicity, and side effects. They also can protect medications from biological degradation and boost the ability of therapeutic agents to penetrate in impenetrable barriers such as the Blood-brain barrier (BBB) [18, 20, 22, 23]. This review study will discuss recent investigations in the field of application of nanotechnology in improving treatment of metal poisoning to introduce new nano-based medications.

Arsenic (As)

Arsenic poisoning is an important health problem which is widespread throughout the globe. Many humans are exposed to arsenic

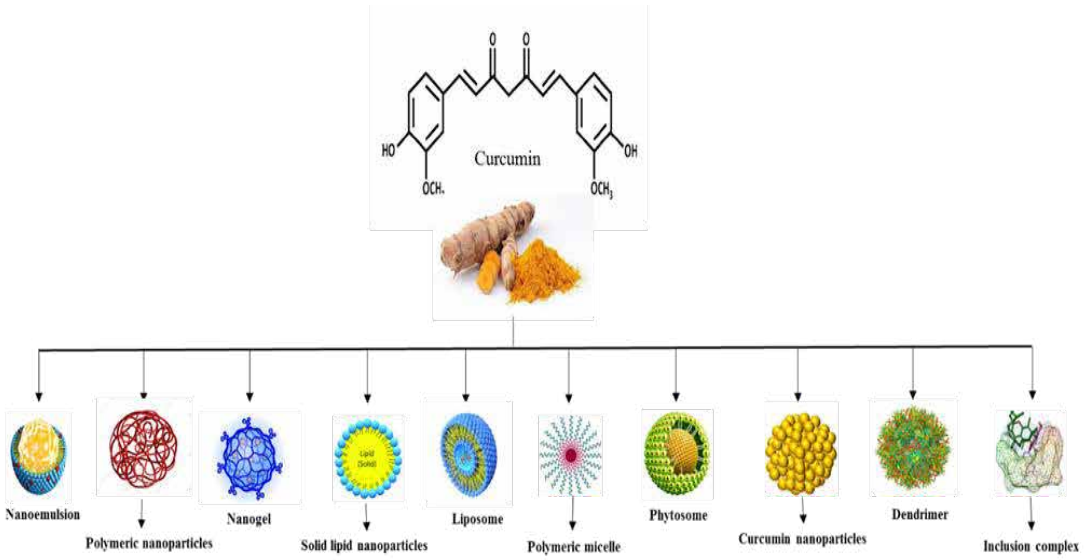

Fig. 2. Schematic illustration of different nano-based strategies which are used for metal poisoning treatment

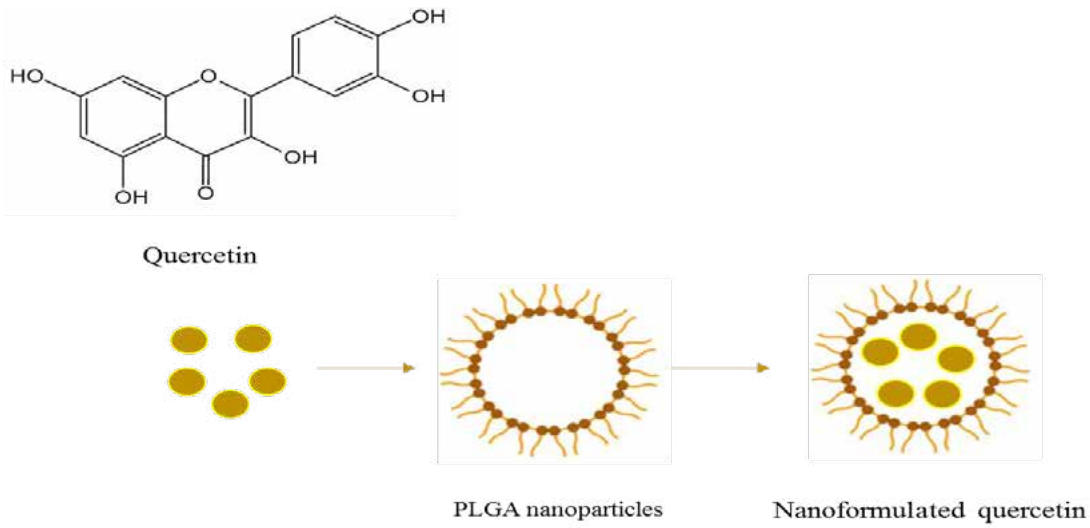

Fig. 3. Schematic illustration of nanoformulated quercetin

through environmental pathways, occupational routes, and intentional suicide attempts. However, the most common source of arsenic toxicity is contaminated water, soil and food. Cancer is one of the major health problems which is induced by long-term exposure to arsenic. High doses of arsenic induce clinical signs such as skin lesions, cardiovascular disorders, and sometimes, multi-organ failure (24-28). The classic antidote against acute arsenic poisoning is BAL (British anti-Lewite, dimercaptopropanol). Less toxic derivatives of BAL such as DMSA (dimercaptosuccinic acid) and DMPS (dimercaptopropane sulfonate) are other antidotes (24, 29). According to the side effects of the mentioned antidotes, attempts to discover new safer treatments have been performed. Nanotechnology could introduce new safer medications for treatment of arsenic toxicity. In one study, the therapeutic effect of the nanoformulated quercetin (nano-qc) to treat arsenic toxicity was

compared with the native form of quercetin in brain cells (30). Quercetin is a polyphenolic compound with antioxidant properties which is an option to ameliorate arsenic-induced oxidative stress (31). Finally, it was proved that nano-qc completely inhibited stress oxidative, while native quercetin was not effective like nano-qc (Figure 3). Curcumin (CMN) is another potential medication to metal poisoning with robust antioxidant, radical-scavenging and metal-chelating characteristics [32]. With regard to its unique chemical properties, it has low bioavailability which declines its therapeutic potential, significantly [33]. Therefore, its bioavailability should be higher to be more efficient. One of the best approaches to enhance this property is to encapsulate it into different nanoparticles [34, 35]. For instance, in a study, the effect of nano-encapsulated CMN was analyzed in rats which were poisoned by arsenic, in comparison to native CMN. The findings of this study demonstrated that nano formulated CMN was more effective in recovering brain oxidative stress and lipid peroxidation markers compared to the native CMN. In this study, native CMN was unable to chelate arsenic in the brain, while the nano-formulated CMN chelated and cleared a significant amount of the arsenic from the brain. Findings of this study showed that nano-formulated CMN could evade from reticuloendothelial system (RES) uptake and, as a result, spend a longer time in the blood circulation. Also, it could get the ability to cross the BBB (Figure 4) [36].

Mercury (Hg)

Mercury is the only toxic metal that is in liquid form. The major source of mercury is emission from different industrial activities. Of course, it also occurs naturally through natural degassing of the earth's crust. This metal has various forms, such as Mercury vapor, Mercuric salts, Mercurous mercury and methyl Mercury. Different forms of mercury induce various health problems such as acute bronchitis, interstitial pneumonitis, severe abdominal cramps, bloody diarrhea, and neurotoxicity [37-43]. Chelating agents are common for treating mercury poisoning. Also, selenomethionine is an antidote for this poisoning, though it has low bioavailability [44]. In this field, nanotechnology introduced recipes for mercury poisoning. Aptamers are the best alternative for detoxification of mercury due to their high affinity and selectivity. However, they are sensitive to serum degradation. However, biocompatible NPs are the compounds that protect aptamers against degradation [45, 46]. In this regard, the efficacy of nano aptamer was evaluated in rats which were poisoned with mercury in comparison to free aptamer. Findings from this study demonstrated that nano aptamer could alleviate neurotoxic effects of mercury, while free aptamer had no protective role against neurotoxicity [47]. Rahayu at al. reported that nano calcium supplementation

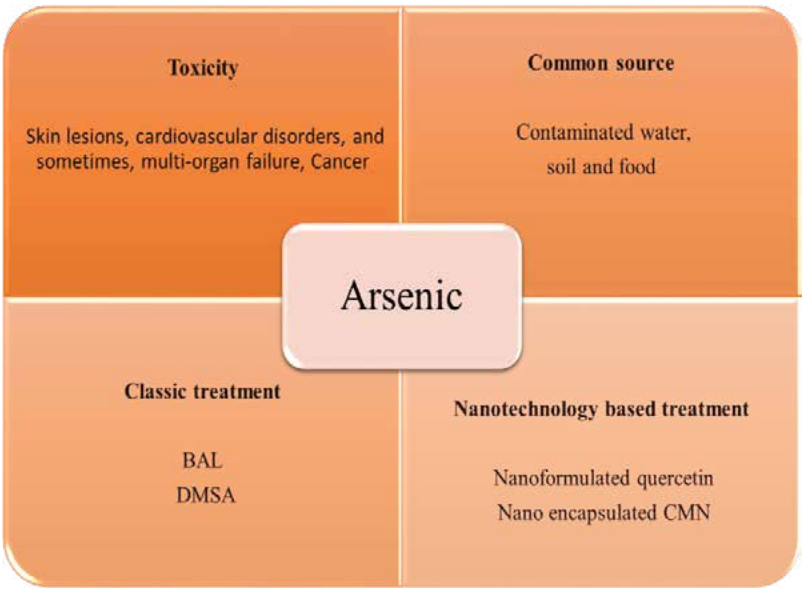

Fig. 4. Schematic illustration of arsenic toxicity, source and treatment

reduced the concentration of Hg in the blood of mice. They administered orally different doses of nano calcium (9 mg, 18 mg, and 27 mg) to the mice for three weeks and then 1300 µg mercury acetate injected intraperitoneally on the last day of treatment. Findings of this study showed that nano Ca supplementation could decline hepatotoxicity induced by mercury in mice. Therefore, nano Ca would be considered as a potential detoxifying agent in Hg poisoning cases [48]. Mahboub at al. studied the potential protective role of magnetite nano-particles (Fe3O4 NPs) against toxicity induced by mercury in the Nile tilapia (*Oreochromis niloticus*). One group of fishes received 1.0 mg/L aqueous suspension of Fe3O4 NPs, the second group received Hg ions at a concentration of 0.025 mg/L and the last group received a mixture of Hg ions and Fe3O4 NPs. Findings of this investigation demonstrated that Hg ions induced toxicity in fishes. Low appetite, reduced growth, microcytic hypochromic anemia, lymphopenia, neutrophilia, leukocytosis, higher concentrations of hepatotoxicity factors such as ALT, AST, and renal toxicity including urea, creatinine, pathological abnormalities of some important tissues and a higher bioaccumulation of Hg ions in the muscles. On the other hand, in the last group of fishes, Fe3O4 NPs could ameliorate all of the mentioned toxicity signs induced by Hg ions. Therefore, they concluded that Fe3O4 NPs is a potential strong detoxifying nanomaterial for mercury poisonings in fish (Figure 5) [49].

Lead (Pb)

Lead is an extremely toxic metal which induces many health problems and contaminates the environment throughout the globe. The main sources of lead exposure are food, drinking water, air and smoking. It has been demonstrated that lead poisoning can induce oxidative stress in various tissues [5, 50]. Lead is a systemic toxicant that induces toxicity in different organs including the liver, kidneys, and brain, and systems such as the nervous, hematopoietic, endocrine, gastrointestinal and reproductive systems [6, 51, 52]. Chelation therapy is the routine for treatment of lead poisoning. Chelating agents such as penicillamine, dimercaptosuccinic acid (DMSA), dimercaptopropane sulfonate (DMPS), dimercaprol (BAL), and CaNa2EDTA bind to lead and remove it from soft tissues. In addition to chelation therapy, antioxidants including vitamins (vitamin B6 and B1, vitamin C and vitamin E), flavonoids (quercetin and α-lipoic acid), and herbs (Garlic and curcumin) are efficient in ameliorating and treating the oxidative stress-induced toxicity of lead [53-56]. However, these chelating agents have some side effects on patients. Therefore, there is a need to discover new, safer and more effective agents to cure lead poisoning. In this regard, nanotechnology could introduce new agents to treat lead poisoning. Mohammadi at al. compared the protecting effects of silibinin and nano-silibinin against lead poisoning in rats. Results of this study demonstrated that nano-silibinin had a more ameliorating effect on weight loss and reduction of lead level in blood rats compared to silibinin. In addition, nano-silibinin was more effective than silibinin in superoxide dismutase (SOD) activity, catalase (CAT), total thiol molecules (TTM), glutathione (GSH), total antioxidant capacity (TAC), and the level of lipid peroxidation products such as (MDA) and nitric oxide (NO)

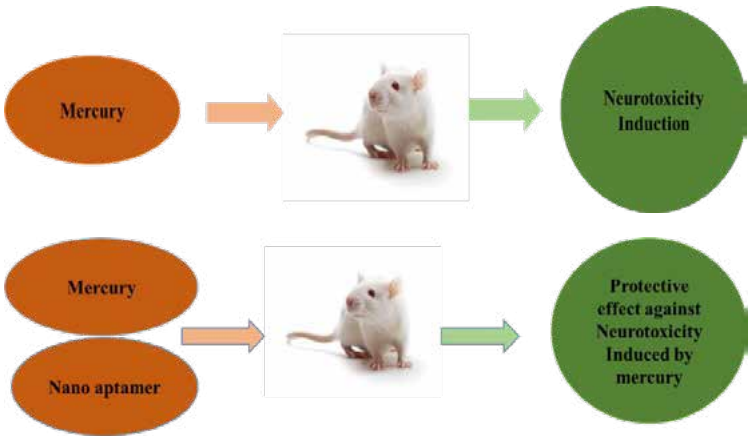

Fig. 5. Schematic illustration of nano aptamer application for mercury poisoning treatment

in blood [57]. In another investigation, Jafari Dehkordi reported that nano-selenium particles are more effective in comparison with selenite in decreasing the toxicity of lead on antioxidant activity and immune system function in rats [58]. Sadeghian at al. compared the protective effect of sodium selenite and nanoparticles of selenium on the antioxidative activities of neutrophils and the hematological factors in sheep. Finally, they found that nanoparticles of selenium were more effective in amelioration of hematological parameters abnormalities compared to sodium selenite in sheep [59].

Cadmium (Cd)

Cadmium is known as a highly toxic heavy metal that poses health hazards to humans and animals. It is used in different industrial products, such as pigments, rechargeable batteries, special alloys, coatings, and plastic stabilizers. The most prevalent routes for human exposure to this metal are inhalation, ingestion and rarely skin absorption, which could induce acute and chronic poisoning [5, 6]. This metal induces toxicity in different organs such as the liver, kidney, lung and bones [60-62]. It could induce gastrointestinal tract erosion, pulmonary, hepatic or renal toxicity, cancer, coma, and even death, which depends on the exposure route, dose and time [5, 6, 37, 62-64]. Cadmium intoxicated cases must be treated with mixed activities such as gastrointestinal tract irrigation, chelation therapy, supportive care, and antidotes [65-67]. In addition, some new treatments have been introduced which are based on nanotechnology. Simona Ioana Vicas at al. reported that selenium nanoparticles (SeNPs) improved cadmium toxicity in mice. In this study, they exposed mice with 5 mg/kg b.w. cadmium and different doses of SeNPs or lacto-SeNPs (LSeNPs) for a month. The ameliorative role of LSeNPs was considered by the improvement of hepatic biomarkers including AST, ALT, GGT and total bilirubin, and antioxidant enzymes, including catalase (CAT) and glutathione peroxidase (GPx). In addition, the antioxidant capacity of mice plasma was improved in the 0.2 mg/kg LSeNPs group. Cadmium induced pathological abnormalities which were alleviated following the administration of SeNPs or LSeNPs [68]. In addition, Du at al. reported that nano-selenium is more effective than sodium-selenite against cadmium toxicity in mice. In this study, scientists treated mice with 126 mg/kg cadmium in the first group, 0.2 mg/kg sodium-selenite in the second group and 0.2 mg/kg nano-selenium in the third group for 14 days. Finally, on the last day of treatment, the second and third groups were treated with 126 mg/kg cadmium. The results of this investigation demonstrated that nano-selenium ameliorated Cd-induced hepatic histopathological abnormalities, decreased activities of ALT and AST and increased the activities of T-AOC, T-SOD and GSH. It also elevated mRNA expressions of Nrf2 pathway related molecules (Nrf2, HO-1, NQO-1, GST, GSH-Px, CAT and SOD) in comparison to the cadmium group [69]. In another study, saleh at al. reported CaNa2EDTA nanoparticles are more efficient chelating antidote in comparison with the macroparticles for cadmium poisoning treatment. In this study, they divided forty rats into 4 groups including control, cadmium, cadmium + CaNa2EDTA macroparticles and Cd + CaNa2EDTA nanoparticles. They added cadmium to the drinking water at a dose of 30 ppm for 70 days. Then, CaNa2EDTA macroparticles and nanoparticles (50 mg/kg) were administered during the last 28 days of the treatment period. Cadmium boosted the levels of urea and creatinine in the serum and the levels of metallothionein and cadmium in the serum and urine of animals. A reduction in bone mineralization by X-ray examination in addition to different pathological abnormalities in the kidney and femur bone of cadmium exposed rats were seen as well. Treatment with both CaNa2EDTA macroparticles and nanoparticles alleviated the adverse effects caused by cadmium on the kidney and bone [70].

Nickel (Ni)

Nickel is a respiratory tract carcinogen (lung fibrosis, lung and nasal cancer) in nickel-refining industry workers. Nickel induces a variety of adverse effects on human health, including allergic reaction, dermatitis, cardiovascular and kidney disorders. Nickel exposure can occur through inhalation, ingestion, and dermal contact in humans and animals. For humans, exposure may result from food or from contact with everyday items including nickel-containing jewelry, cooking utensils, and clothing fasteners [71-73]. Chelation therapy is the suggestive protocol for nickel poisoning. Diethyldithiocarbamate (DDC) has been considered as an antidote and could be administered parentally at a dose of 12.5 mg/kg IV and should be injected into patients as soon as possible [74, 75].

However, a new nanotechnology based treatment has been reported for nickel poisoning. Wang at al. studied protective effects of Nano-Se against nickel (Ni)-induced toxicity in rats. For this purpose, they exposed Sprague-Dawley rats to 5.0 mg/kg nickel sulfate with or without Nano-Se (0.5, 1, and 2 mg/kg, oral gavage) co-administration for two weeks, and HepG2 cells were exposed to 1500 μM nickel sulfate with or without 20 μM Nano-Se for 24 h. Results of this study demonstrated that Nano-Se apparently prevented Ni-induced hepatotoxicity indicated by improving pathological abnormalities and reducing Ni accumulation in rat livers. Nickel elevated hepatic activities of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH-Px), and malondialdehyde (MDA) level, reduced the glutathione (GSH) content and finally, Nano-Se could improve these enzyme changes. Nano-Se reduced the cell mortality, and alleviated morphological abnormalities of nuclear structures in Ni-treated HepG2 cells. Thus, they concluded that Nano-Se is a protective agent against Ni-induced hepatotoxicity [76].

Iron (Fe)

Acute iron poisoning is one of the most common lethal poisonings for children. It can be so hazardous for health if diagnosis and treatment are inappropriate. As a result, patients would face different types of serious consequences such as multi-organ failure and death. Acute iron toxicity in adults is usually associated with intentional ingestion [77, 78]. Oral intake of 20 mg/kg to 60 mg/kg iron induces moderate adverse clinical signs. While over 60 mg/kg can be lethal and induces severe clinical symptoms [79-81]. The specific antidotes for iron poisoning are, deferoxamine (DFO), deferiprone (L1) and desferasirox (ICL-670) chelating agents which are able to remove iron from tissues and blood [77, 80, 82]. However, deferoxamine can induce some adverse effects in patients including infection, gastrointestinal bleeding, kidney failure, and liver fibrosis [83]. As a result, for declining side effects, some nano-based compounds have been introduced for iron toxicity. In one study, kang at al. compared the efficacy and safety of a nanochelator in mice and rats intoxicated with iron. They demonstrated that this nanochelator was much more efficient and safer compared to the native defroxamine. It could boost kidney-specific biodistribution, rapid renal excretion and reduce liver and serum iron concentration, significantly. It also reduced nephrotoxicity induced by iron [83]. In 2003, Imran at al. conjugated defroxamine with hyperbranched polyglycerols (HPG) which is a class of versatile, biocompatible nano polymers. Safety assays of this nano polymer demonstrated that it is biocompatible, and it would be potentially effective for patients suffering from iron overload [84]. In 2023, Zhu at al. developed a series of carrier-free, high defroxamine -loading, uniform spherical nanoparticles (NPs) assisted by polyphenols. Then, they tested the ability of this nano-antidote to cure an iron-intoxicated animal. They observed this nano-chelator was efficient at scavenging iron and protecting the brain in poisoned animals [85].

Copper (Cu)

Copper is toxic and has the potential to damage many organs. Food and drinking water are potential sources of excess copper exposure for humans. However, miners and industrial workers who have more exposures to copper fumes are more in danger of being poisoned [86, 87]. Copper toxicity (Copperiedus) can be induced by drinking water with excess copper, eating foods with high amounts of copper or other environmental sources. Ingestion of more than 1 g of copper sulfate induces clinical signs of copper toxicity. Copper toxicity induces oxidative stress, DNA damage and reduced cell proliferation. In mild copper toxicity, gastrointestinal symptoms such as vomiting, nausea and diarrhea are observed, but severe toxicity causes intravascular haemolysis, hepatic necrosis, renal failure and death [87-90]. D-Penicillamine is the classic antidote used for copper toxicity. EDTA (Ethylenediaminetetraacetic acid) and DMPS (dimercaptopropanesulfonic acid) are also administered in some patients [91-94]. However, according to the side effects of classic antidotes, there is still the need for new, safer and more efficient antidotes. Recently, nanotechlogy introduced a new nano-based treatment for copper toxicity. In 2021, 2022 and 2023, Sarawi e al demonstrated that liposomal nano-curcumin had a protective role in copper toxicity. They compared the ameliorating effect of liposomal nano-curcumin with the native form of curcumin in rats. They found nano-curcumin was more effective in alleviating tissue injury, oxidative stress, inflammation, and apoptosis than the native form [95-97].

Table 1. Different classic antidotes and nano-based antidotes for metal poisoning treatment

poisoning	Classical antidote	Nanotechnology based antidote (References)
Arsenic	BAL	nanoformulated quercetin (30)
	DMSA	nano encapsulated CMN (36)
	DMPS	
Mercury	selenomethionine	nano aptamer (47)
		magnetite Nano-Particles (Fe3O4 NPs) (49)
Lead	Penicillamine	nano-silibinin (57)
	DMSA	nanoparticles of selenium (58)
	DMPS	
	BAL	
	$CaNa_2EDTA$	
Cadmium	No antidote	selenium nanoparticles (68)
		CaNa2EDTA nanoparticles (70)
Nickel	DDC	selenium nanoparticles (76)
Iron	deferoxamine (DFO)	nano polymer (84)
	deferiprone (L1)	nano chelator (85)
	desferasirox (ICL-670)	
Copper	D-Penicillamine	liposomal nano-curcumin (97)
	EDTA	
	DMPS	
Aluminum	deferoxamine (DFO)	nano-curcumin (98)

Aluminum (Al)

Aluminum is a toxic metal that induces adverse effects on the CNS, bone, spleen, liver, kidney and hepatic hematopoietic system. Aluminum poisoning has been reported in different parts of the globe. Aluminum compounds are used in different products, such as pharmaceuticals, food additives, cosmetics, drinking water, food, air, deodorants and some household products [98-103]. Chelator agents like deferoxamine (DFO) are administered for aluminum poisoning [104]. In 2019, Mohamed Ibrahim at al. reported that curcumin nanoparticles had a protective role in aluminum chloride toxicity in rats. In this study, they compared the protective effect of 15 mg of these materials in six groups of intoxicated rats with AlCl3. The findings of this investigation demonstrated that Nano-curcumin had more effective biological and antioxidant activity than curcumin in AlCl3-intoxicated rats (Table 1) [98].

CONCLUSION

The data from this literature demonstrated that new nano-based compounds had appropriate therapeutic effects for the treatment of metal poisoning. In addition to the topic of treatment, they have fewer side effects compared to classic antidotes and chelators. Due to the fact that the complications of metal poisoning in patients are very diverse and complex, the patient's body cannot tolerate the side effects of such medications. As a result, along with the patient's recovery, it can cause unwanted health problems for the patient. Therefore, it is very urgent to replace more effective and safer treatments which currently have been developed and will be discovered in the future with the help of nanomedicine. However, it is very important that these new compounds are subjected to multiple and additional tests, especially on humans, so that more reliable treatments can be performed with more knowledge of the action mechanism of these compounds.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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