Review Article

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Hepatotoxic effect of cadmium and available therapeutic options

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ABSTRACT

Hepatoxicity, also known as toxic hepatitis, is a condition, in which the liver becomes inflamed due to exposure to such substances as chemicals, medications, herbal products, or excessive alcohol consumption. Cadmium is a major environmental pollutant from agricultural and industrial sources and has been reported to induce hepatotoxicity. Cadmium can also be found in phosphate fertilizers, detergents, and refined petroleum products as an impurity and used industrially in the production of polyvinyl chloride product stabilizers and the fabrication of nickel-cadmium batteries. Cadmium can be absorbed into the human body through the gastrointestinal tract, respiratory, and dermal routes. Cadmium-induced hepatic damage is very much associated with oxidative stress through inactivation of the antioxidant enzymes, depletion of the glutathione concentration, and increase in mitochondrial-derived reactive oxygen species production. Several processes of ameliorating cadmium-induced hepatotoxicity include the use of orthodox medicine (ethylene diamine tetraacetic acid, dimercaptosuccinic acid, and dimercaptopropane sulfonate). Furthermore, the phytomedicinal approach has served as hepatoprotective agents to averts any damage due to oxidative stress caused by cadmium in the liver. Therefore, this review seeks to understand the hepatotoxic effect of cadmium and its amelioration by orthodox medicine and selected medicinal plants.

Key words: Cadmium, liver, oxidative stress, phytomedicine, toxicity

INTRODUCTION

Hepatoxicity is also known as toxic hepatitis, it is a condition, whereby the liver becomes inflamed due to exposure to such substances as chemicals, medications, herbal products, or excessive alcohol consumption. These substances that cause liver damage are known as hepatotoxins. The liver is the main organ in the body that regulates homeostasis. It is involved in biochemical pathways that are involved in the development, disease resistance, energy provision, and nutrient supply. Chemicals can damage the liver because it plays such an important function in chemical metabolism. The liver has the specific task of handling nearly all chemicals and drugs that enter the bloodstream, as well as eliminating chemicals that are difficult to excrete by the kidneys.[1] These chemicals are converted by the liver into products that can be passed through the bile or urine system. However, unstable, highly toxic bi-products are often formed during this chemical cycle in the liver; these highly toxic bi-products can attack and damage the liver.

The following is some signs of toxic hepatitis: loss of weight, jaundice, itching, fever, rash, nausea, pain in the upper right quadrant of the abdomen, loss of appetite, fatigue, ascites, and vomiting. Toxic hepatitis is commonly caused by exposure to toxic chemicals in the workplace, such as organic chemicals and solvents.[2] Exposure can occur through ingesting a chemical, breathing it in, or coming into dermal contact with it.

Cadmium is one of such chemicals that can expose the liver to toxicity thereby resulting in hepatotoxicity.[3] Cadmium (Cd) occurs naturally as a soft and silvery-white metal. It is a significant environmental pollutant that comes from agricultural and industrial sources and is noted for its wide range of toxic effects.[4] Cadmium's toxicological properties are a result of its chemical resemblance to zinc, which is an essential micronutrient for plants, animals, and humans. Cadmium is bio-persistent as it resides in the body for a long period (decades in humans) once consumed, although it will eventually be excreted. Cadmium is mainly absorbed by the ingestion of polluted food and water, but it is also absorbed to some degree by inhalation and cigarette smoking. Several processes of ameliorating cadmium-induced hepatotoxicity include the use of orthodox medicine and the phytomedicinal

approach. Orthodox medicines however include the use of ethylene diamine tetra acetic acid (EDTA), dimercapto succinic acid (DMSA) and dimercaprol (DMPA), and phytomedicine involves the use of plants and plants products to treat various diseases.[5] This review aimed at reviewing the hepatotoxic effect of cadmium and its amelioration by orthodox medicine and selected medicinal plants.

HEPATOTOXICITY

Hepatoxicity is also known as toxic hepatitis, it is a condition, whereby the liver becomes inflamed due to exposure to such substances as chemicals, medications, herbal products, or excessive alcohol consumption. Toxic hepatitis may develop hours or days after being exposed to a toxin. In other cases, signs and symptoms may not occur for months after repeated exposure. The symptoms of this condition can be like those of other liver disease. Mild types of toxic hepatitis can go unnoticed and can only be identified by blood tests. When the liver is no longer exposed to a toxin, the signs of toxic hepatitis usually disappear. Chronic toxic hepatitis, on the other hand, can cause irreversible liver scarring (cirrhosis) and, in some cases, life-threatening liver failure.[6] There are different causes of hepatotoxicity which can either be: drug-induced, alcohol-induced, herbs-induced, chemical-induced, etc.

A variety of prescription and over-the-counter drugs can cause hepatotoxicity (sometimes independent of the dose of the medication), some of which may include: acetaminophen, ketoconazole, minocycline, pyrazinamide, isoniazid, diclofenac, dantrolene, methyldopa, nitrofurantoin, amoxicillin-clavulanate, and phenytoin.[7] These drugs damage the liver, especially when taken regularly with alcohol. Alcoholic hepatitis is an inflammation of the liver caused by alcohol which can lead to liver failure, it can be caused by heavy drinking over a long period. Aloe vera, chaparral, black cohosh, cascara, kava, comfrey, and ephedra are several plants that are toxic to the liver. There are many more. If children mistake vitamin supplements for candy and consume excessive amounts, they risk liver damage.

Many trace elements have also been related to cases of acute or chronic liver damage when exposed to higher concentrations. Some industries also make use of heavy metals such as lead, iron, mercury, copper, tin, cadmium, lead, zinc, in the production of electroplating, batteries, and mining. These heavy metals are toxic to cells directly and have been shown to cause hepatotoxicity *in vitro*.[8]

CADMIUM

Cadmium is sometimes found as a by-product of ores such as zinc, copper, and lead. As a result, one natural cause for a transient rise in environmental cadmium concentrations is volcanic activity. It is commonly used in industrial processes, such as polyvinyl chloride (PVC) product stabilizer, an anticorrosive agent, a neutron absorber in nuclear power plants, a color pigment, and in the fabrication of nickel-cadmium batteries. Cadmium can also be found in phosphate fertilizers, detergents, and refined petroleum products as an impurity.[3] Dumping, recycling, and incinerating of cadmium-polluted waste and cadmium-containing materials accounts for a large portion of overall cadmium emissions.[9]

Cadmium can be absorbed into the human body in three different ways: Gastrointestinal tract (GIT), respiratory, and dermal routes.

Absorption through the GIT

Iron deficiency in an individual is the most important metabolic parameter for cadmium uptake. Cadmium uptake is usually 6% higher in people with low iron supplies than in people that have a balanced iron intake.[10] This is the primary cause of increased cadmium re-absorption in people with anemia and a history of iron deficiency, such as children and women who are menstruating.

Absorption through the Respiratory System

Cigarette smoke is the most common cause of inhalation of cadmium poisoning. Cadmium is present in cigarette smoke and 40–60% of it is reabsorbed by the human lung. Acute respiratory distress syndromes (ARDSs) have been identified in workers exposed to cadmium-containing fumes. Cadmium that has been absorbed by inhalation normally enters the bloodstream as cadmium-cysteine complexes.[11]

Dermal Absorption

Cadmium absorption through the skin has received little attention, whereas some research done has shown that individuals exposed to cadmium had hyperkeratosis and scanthosis on their skin, in addition to occasional ulcerative change with a rise in the mitotic index of the skin cells.[12] Cadmium absorption by the skin is aided by two mechanisms: an induction and complexing with metallothionein, as well as binding of a free cadmium ion to cysteine's sulphydryl radicals in epidermal keratins.

The bulk of cadmium is subsequently transported to the blood by binding to proteins, namely, albumin and metallothionein (MT). After it gets into the blood, the liver is the first organ reached. Cadmium stimulates the formation of metallothionein in this case. Cd-MT complexes are then washed into sinusoidal blood after consecutive hepatocyte necrosis and apoptosis. Some parts of the absorbed cadmium are secreted into the biliary tract as cadmium-glutathione conjugates, which, then, enter the enterohepatic cycle. Cadmium enters into the small intestines again after being degraded by enzymes to cadmium-cysteine complexes in the biliary tree [Figure 1].[13]

EFFECT OF CADMIUM ON LIVER FUNCTION

Cadmium-induced Oxidative Stress

Cadmium-induced hepatic damage is very much associated with oxidative stress. The primary way by which cadmium causes toxicity is through oxidative stress, which is caused by an excess of free radicals, particularly reactive oxygen species (ROS).[14] There are three possible ways by which cadmium

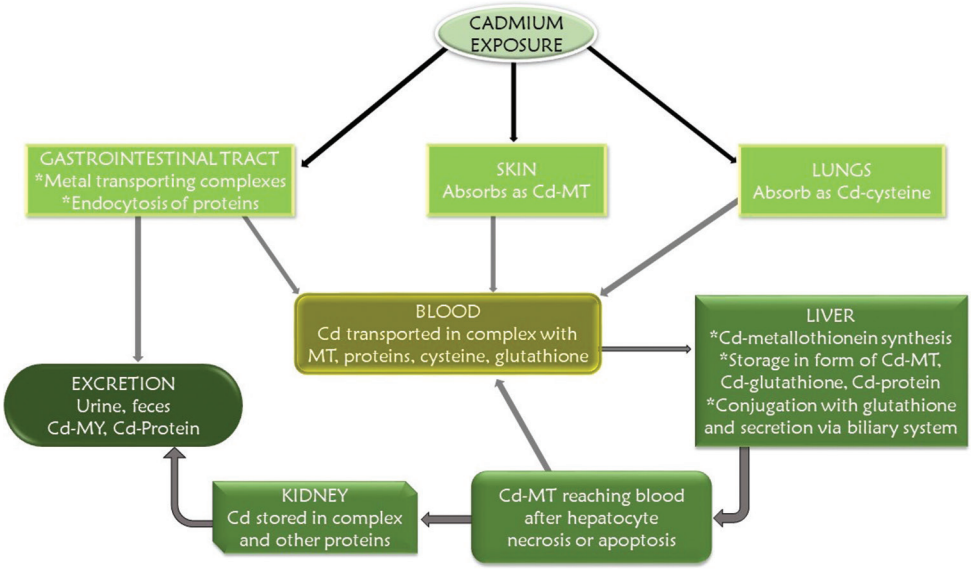

Figure 1: A schematic diagram on the absorption of cadmium and its circulating pathway.

induces hepatic oxidative stress since cadmium is unable to induce ROS generation directly because it is a non-Fenton metal.[15] Cadmium inactivates antioxidant enzymes, depletes glutathione concentration, and enhances mitochondria-derived ROS production, these three activities result in oxidative stress, this could also lead to oxidation of lipids, DNA, and proteins in the liver cells, resulting in hepatocellular damage.

ANTIOXIDANT ENZYME INACTIVATION

A complex antioxidant protection system is present within an organism to protect against the excess production of ROS. It involves a variety of components, both endogenous and exogenous in origin that function interactively and synergistically to neutralize free radicals. However, cadmium has been implicated in the production of free radicals due to its ability to mimic divalent metals such as zinc, calcium, manganese, copper, and selenium. It displaces essential metals, necessitating the inactivation of enzymes by direct displacement from their binding site. This increased lipid peroxidation (LPO), followed by a decrease in superoxide dismutase (SOD) activity, catalase (CAT) activity, and glutathione peroxidase (GPx) activity, as well as an increase in free radicals.[16]

GSH DEPLETION

Cadmium has a high affinity toward sulfhydryl groups of protein and binds to them through covalent bonding. Glutamate, cysteine (a sulfhydryl group), and glycine make up GSH (reduced glutathione). It is a sulfhydryl peptide that is used in almost every biological system. It can be used as a coenzyme or cofactor in the enzymatic detoxification of ROS, or it can serve as a non-enzymatic antioxidant by direct interaction with ROS through its sulfhydryl group. Cadmium binds to the sulfhydryl groups present in GSH, rendering it inactive. Thiols' inability to function might also cause toxicity by changing intracellular redox status, thereby leading to negative effects on some major biochemical processes.[17]

MITOCHONDRIA-DERIVED ROS PRODUCTION

Mitochondria are regarded as the powerhouse of the cell as they convert nutrients and oxygen into chemical energy. The formation of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate requires the transfer of an electrochemical proton gradient from the mitochondrial matrix to the intermembrane space. The proton gradient depends on the electrons that are transferred down the electron transport chain (ETC) through complexes, such as Complex I (NADH–coenzyme Q reductase), Complex II (succinate–coenzyme Q reductase), Complex III (coenzyme Q–cytochrome c reductase), and Complex IV (cytochrome c oxidase).[18]

The formation of mitochondrial ROS is preferred when mitochondria are no longer producing ATP (due to lack of ADP or O_2) which leads to an excessive NADH/NAD+ ratio in the matrix. The mitochondrion is under oxidative stress in this situation.[19] One of the primary ROS contributors in most cells in the mitochondrial ETC. The transfer of an electron from reduced ubiquinone (ubiquinol, QH_2) to Complex III and the flow of electrons from Complexes I and II to QH_2 includes the semi-ubiquinone $Q^{\bullet -}$ as an intermediate that can transfer an electron to O_2, producing $O_2^{\bullet -}$.[18]

It is believed that the potential Cadmium targets site is the Fe-S clusters of the ETC complexes,[20] ensuing in the inhibition of electron transfer and the dissipation of proton electrochemical gradient essential for ATP generation.[21] These findings have been confirmed by Adiele *et al.,*[22] that tested the sensibility to Cadmium of Complexes I, II, and III, whereas the non-response to Complex IV is suspected to be triggered the absence of Fe-S clusters in Complex IV.[22] Furthermore, the overproduction of ROS and the possible alteration of the mitochondrial membrane caused by Cadmium can lead to apoptotic cell death pathways.[23]

Cadmium has additionally been proven to generate ROS by the transition pore opening of mitochondrial permeability

resulting in the release of cytochrome c.[18] Since cytochrome c is accountable for the transfer of an electron from Complex III to Complex IV, the release of cytochrome c will disrupt the mitochondrial ETC,[24] which will lead to more ROS generation. Altogether, these records indicate that the mitochondria represent the major target of Cadmium toxicity but also potential targets for new therapeutic approaches to modulate mitochondrial function.

Cadmium cytotoxic effects might result in apoptotic or necrotic processes. Cadmium-induced apoptosis is caused by the production of ROS, the accumulation of Ca2+, the overexpression of caspase-3, the downregulation of bcl-2, and the lack of p-53. Metallothionein is a zinc-binding protein that may also serve as a scavenger of free radicals. Cadmium toxicity is resistant in cells that contain metallothioneins, whereas cadmium toxicity is susceptible in cells that cannot produce metallothioneins. The decision between apoptosis and necrosis in Cd-induced toxicity is determined by metallothionein expression.

CADMIUM-INDUCED HEPATOTOXICITY

The liver is the major site for the biotransformation of toxic compounds. The liver is also the main target for cadmium-acute toxicity resulting in oxidative stress. The antioxidant system of the liver is highly influenced by cadmium. Cadmium may decrease the levels of antioxidant activities by the decrease in SOD, CAT and GPx, and intracellular GSH content as it combines with thiol groups of enzymes which indicate an increase in ROS production. Cadmium has been shown to decrease enzyme activity by forming cadmium-selenium complexes in the active core of GPx. Cadmium has also been shown to block Complex III of the mitochondrial electrical transport chain, which promotes the generation of ROS and damages the mitochondrial membrane. In some biochemical functions, cadmium can take the place of magnesium and calcium. Cadmium-induced oxidative stress causes DNA damage and mutations, as well as LPO and protein oxidation. Cadmium has the potential to harm mitochondria by interfering with Ca^{2+} signaling and increasing mitochondrial ROS production.

Zinc-binding proteins may have a role in cadmium toxicity as well. Cadmium and zinc have the same oxidation state (+2) and are almost identical in size. Cadmium may replace zinc, magnesium, and calcium in some biological systems, as well as iron and copper from cytoplasmic and membrane proteins such as ferritin and apoferritin, increasing the pool of free metal ions in many biological systems. Cadmium binds up to 10 times stronger than zinc in biological systems, making it difficult to eliminate. Cadmium's genotoxic potential has also been investigated, and it has been identified as a clastogenic agent. Cadmium is known to cause its deleterious effect by deactivating DNA repair activity.

EFFECT OF CADMIUM ON LIVER INTERMEDIARY METABOLISM

One of the effects of cadmium on intermediary metabolism is heme. Cadmium has the potential to affect intracellular heme levels as well as to increase gluconeogenesis since it is a strong HO^- inducer.[25] Cadmium increases the expression of gluconeogenesis enzymes such as pyruvate carboxylase (PC), fructose-1,6-biphosphatase, phosphoenolpyruvate carboxykinase, and glucose-6-phosphatase. Cadmium promotes glycogenolysis, which leads to the depletion of liver glycogen. As a result, cadmium could cause hyperglycemia in the fasting state. However, fed-state hyperglycemia in cadmium-induced diabetes is triggered by constant hepatic gluconeogenesis or an impaired ability to inhibit hepatic gluconeogenesis after a meal degradation.[26]

Cadmium also has an impact on GSH recycling. Due to cadmium induction of HO^-, the need for NADPH utilization in GSH regeneration and heme catabolism increases in cadmium-exposed liver cells. As a result, glucose is metabolized for NADPH production through the pentose phosphate pathway instead of through mitochondrial oxidative phosphorylation for ATP production. Cadmium-exposed cells may have a limited capability to produce and sustain optimal cellular ATP levels due to less ATP production,[27] based on the results that cadmium affects mitochondrial oxidative phosphorylation in human proximal tubular cells. Ellis *et al.*[28] found that cadmium exposure was correlated with irregular mitochondrial activity, as evidenced by unusual urinary emission of mitochondria markers such as 3-hydroxyisovalerate, citrate, and 4-deoxyerythronic acid.

TREATMENT OF CADMIUM-INDUCED HEPATOTOXICITY

Orthodox Treatment of Cadmium-induced Hepatotoxicity

Orthodox drugs used in the treatment of cadmium-induced hepatotoxicity act as chelators by binding the heavy metal in the blood and transporting them to the excretory system for safe removal of the toxic substance. Some of these chelators include; 2,3-dimercaptopropanesulfonic acid (DMPS), Dimercaptosuccinic acid (DMSA), and Calcium disodium ethylene diamine tetraacetic acid (EDTA) are all used in this method. When carried out according to proven guidelines, intravenous EDTA chelation is considered the most effective method for clinical detoxification of cadmium.[3]

EDTA

In current clinical practice, it is available in the form of sodium edetate (Na_2EDTA) and calcium disodium edetate ($CaNa_2EDTA$). However, the use of calcium disodium edetate ($CaNa_2EDTA$) is more preferable than sodium edetate (Na_2EDTA).[2] Calcium EDTA must be administered through intravenous infusion because it cannot be absorbed in the digestive tract adequately. In the pharmacological mechanism of the calcium EDTA given intravenously, calcium (Ca) is displaced by toxic metals like cadmium to form stable EDTA complexes, which are excreted in the urine. The chelator is quickly excreted by glomerular filtration, with approximately half of it appearing in the urine within 1 h.[29]

Sodium 2,3-dimercapto-1-propanesulfonate (DMPS)

DMPS can form complexes with a wide range of metals and metalloids. DMPS has been used to treat heavy metal

Table 1: Plants that possess ameliorative effect on cadmium-induced liver toxicity

No.	Botanical name	Plant part used	General biochemical effect on the liver	References
1.	*Monodora myristica*	Seed	Increase in GSH concentration, SOD and CAT activities	Oyinloye *et al.*[14]
2.	*Physalis peruviana*	Fruit	Reduced LPO and nitric oxide.	Dkhil *et al.*,[34]
			Enhanced activities of SOD, CAT, GPx and GSH concentration	
3.	*Salvia rosmarinus*	Leaf	Reduced MDA concentration.	Sakr *et al.*,[35]
			Increased SOD, CAT activities and GSH concentration	
4.	*Aframomum melegueta*	Seed	Reduced LPO and reversal of deleterious effect on CAT, GPx, SOD, ALT, AST activities	Oyinloye *et al.*,[36]
5.	*Allium hirtifolium*	Leaf	Significant improvement in functional and oxidative stress indices (ALT, AST, LPO, total thiol Molecule)	Omidifar *et al.*,[37]
6.	*Telfaria occidentalis*	Leaf	Restoration of activities of AST, ALT, ACP, ALP, GST, SOD, CAT, and concentrations of MDA and GSH	Oladele *et al.*,[16]
7.	*Tinospora cordifolia*	Stem	Enhanced activities of SOD, CAT, GPx, GST, membrane ATPases, and GSH concentration	Baskaran *et al.*,[38]
8.	*Polyalthia longifolia*	Leaf	Decreased hepatic MDA concentration.	Oyeyemi *et al.*,[39]
			Improved SOD, GPx, CAT, GST activities and GSH concentration	
9.	*Murraya koenigii*	Leaf	Restoration of the activities of mitochondrial Kreb's cycle and respiratory chain enzymes.	Mitra *et al.*,[40]
10.	*Trema orientalis*	Leaf	Reversal of adverse effect on ALT activities, total protein, albumin and bilirubin concentration	Olajide *et al.*,[41]
11.	*Cinnamomum verum*	Bark	Improvement of oxidative profile by increasing total antioxidant capacity and CAT activity and reduction of MDA concentration	Ghonim *et al.*,[42]
12.	*Gingko biloba*	Leaf	Restoration of ALP, AST, and ALT activities and preservation of liver histoarchitecture	Olubunmi *et al.*,[43]

SOD: Superoxide dismutase, CAT: Catalase, LPO: Lipid peroxidation, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GPx: Glutathione peroxidase

poisonings, especially arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg).[30] It's unable to get through the blood-brain barrier. DMPS and its metabolites are excreted relatively easily.[31] The highest concentrations of DMPS enter plasma and kidneys after intravenous administration and are visible in urine within 2 h. In humans, the plasma half-life after intravenous administration is 30–45 min. After 3 h of oral administration, the highest concentration of DMPS is detected. Around 80% of the drug is excreted in the urine within 5–6 h.

Meso-2,3-dimercapto-succinic Acid (DMSA)

DMSA is normally given to humans orally at a therapeutic dose ranging from 8 to 50 mg/kg/day. DMSA has a significantly lower oral absorption rate than DMPS.[32] Intravenous, rectal, and transdermal administrations of the antidote are also used in clinical practice. The bulk of DMSA is found in extracellular fluid. In humans, DMSA has a half-life of around 4 h and it is covalently bound to proteins in plasma. The urine excretes 10–25% of an orally administered dose of DMSA, with the majority excreted within 24 h.[33] The rest is mostly removed by feces.

PHYTOMEDICINAL TREATMENT OF CADMIUM-INDUCED HEPATOTOXICTY

Medicinal plants are becoming more widely used to treat a broad range of diseases, and they are a potential source of hepatoprotective and antioxidant compounds that could be useful in the treatment of liver disease as well as the prevention of poisoning from chemical and environmental toxins.[34] Many of these plants which are phytotherapeutic agents play an important role in the removal of cadmium from the liver by mitigating cadmium-induced oxidative stress. They bind to the heavy metal to chelate it and reduce its absorption in the intestine, support to release of the body's excretion mechanisms (in cases of excessive poisoning) and facilitate its excretion from the body. These agents showed an increase in the enzymatic antioxidant activities which averts any damage as a result of oxidative stress. The following plants have been reported for their ameliorative effect on cadmium-induced liver toxicity [Table 1].

CONCLUSION AND FUTURE STUDIES

Although cadmium has deleterious effects on the liver resulting in hepatotoxicity or toxic hepatitis, its detrimental effects can be treated either by the use of orthodox drugs (including EDTA, DMSA, and DMPA) or the use of phytomedicine. Both methods are beneficial and are currently being explored in ameliorating the toxic effects of cadmium on the liver.More research is needed to determine the mechanism of action of these phytomedicinal plants in preventing Cd toxicity.Isolating the most active chemicals in these plants will be a promising field for cadmium treatment research.In pre-clinical and clinical investigations, it will also be indicated that co-administration

of phytomedicine with traditional medicine may be beneficial in the treatment of cadmium toxicities.

REFERENCES

1. Godt J, Scheidig F, Grosse-Siestrup C, Esche V, Brandenburg P, Reich A, *et al*. The toxicity of cadmium and resulting hazards for human health. J Occup Med Toxicol 2006;1:22.
2. Gerhardsson L, Kazantzis G. Diagnosis and treatment of metal poisoning: General aspects. In: Handbook on the Toxicology of Metals. Cambridge: Academic Press; 2015. p. 487-505.
3. Bernhoft RA. Cadmium toxicity and treatment. ScientificWorldJournal 2013;2013:394652.
4. Renugadevi J, Prabu SM. Cadmium-induced hepatotoxicity in rats and the protective effect of naringenin. Exp Toxicol Pathol 2010;62:171-81.
5. Houghton PJ. Synergy and polyvalence: Paradigms to explain the activity of herbal products. In: Evaluation of Herbal Medicinal Products. London: Pharmaceutical Press; 2009. p. 85-94.
6. Rifai N. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics-E-Book. 8th ed. Netherlands: Elsevier; 2019.
7. Nathwani RA, Kaplowitz N. Drug hepatotoxicity. Clin Liver Dis 2006;10:207-17.
8. Suh JI. Drug-induced liver injury. Yeungnam Univ J Med 2020;37:2-12.
9. Järup L. Hazards of heavy metal contamination. Br Med Bull 2003;68:167-82.
10. Flanagan PR, McLellan JS, Haist J, Cherian G, Chamberlain MJ, Valberg LS. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology 1978;74:841-6.
11. Zalups RK, Ahmad S. Molecular handling of cadmium in transporting epithelia. Toxicol Appl Pharmacol 2003;186:163-88.
12. Lansdown AB, Sampson B. Dermal toxicity and percutaneous absorption of cadmium in rats and mice. Lab Anim Sci 1996;46:549-54.
13. Orłowski C, Piotrowski JK. Biological levels of cadmium and zinc in the small intestine of non-occupationally exposed human subjects. Hum Exp Toxicol 2003;22:57-63.
14. Oyinloye BE, Adenowo AF, Osunsanmi FO, Ogunyinka BI, Nwozo SO, Kappo AP. Aqueous extract of *Monodora myristica* ameliorates cadmium-induced hepatotoxicity in male rats. Springerplus 2016a;5:641.
15. Haidry MT, Malik A. Hepatoprotective and antioxidative effects of *Terminalia arjuna* against cadmium provoked toxicity in albino rats (*Ratus norvigicus*). Biochem Pharmacol 2014;3:1-4. Arroyo VS, Flores KM, Ortiz LB, Gómez-Quiroz LE, Gutiérrez-Ruiz MC. Liver and cadmium toxicity. J Drug Metab Toxicol 2012;S5-001.
16. Oladele JO, Oyewole OI, Bello OK, Oladele OT. Hepatoprotective effect of aqueous extract of *Telfairia occidentalis* on cadmium chloride-induced oxidative stress and hepatotoxicity in rats. J Drug Des Med Chem 2017;3:32-6.
17. Milton Prabu S, Muthumani M, Shagirtha K. Protective effect of *Piper betle* leaf extract against cadmium-induced oxidative stress and hepatic dysfunction in rats. Saudi J Biol Sci 2012;19:229-39.
18. Branca JJ, Fiorillo C, Carrino D, Paternostro F, Taddei N, Gulisano M, *et al*. Cadmium-induced oxidative stress: Focus on the central nervous system. Antioxidants (Basel) 2020;9:492.
19. Brand MD. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. Free Radic Biol Med 2016;100:14-31.
20. Dorta DJ, Leite S, DeMarco KC, Prado IM, Rodrigues T, Mingatto FE, *et al*. A proposed sequence of events for cadmium-induced mitochondrial impairment. J Inorg Biochem 2003;97:251-7.
21. Kurochkin IO, Etzkorn M, Buchwalter D, Leamy L, Sokolova IM. Top-down control analysis of the cadmium effects on molluscan mitochondria and the mechanisms of cadmium-induced mitochondrial dysfunction. Am J Physiol Regul Integr Comp Physiol 2011;300:R21-31.
22. Adiele RC, Stevens D, Kamunde C. Differential inhibition of electron transport chain enzyme complexes by cadmium and calcium in isolated rainbow trout (*Oncorhynchus mykiss*) hepatic mitochondria. Toxicol Sci 2012;127:110-9.
23. Chatterjee S, Kundu S, Bhattacharyya A. Mechanism of cadmium induced apoptosis in the immunocyte. Toxicol Lett 2008;177:83-9.
24. Nemmiche S. Oxidative signaling response to cadmium exposure. Toxicol Sci 2017;156:4-10.
25. Satarug S. Long-term exposure to cadmium in food and cigarette smoke, liver effects and hepatocellular carcinoma. Curr Drug Metab 2012;13:257-71.
26. Gobe G, Crane D. Mitochondria, reactive oxygen species and cadmium toxicity in the kidney. Toxicol Lett 2010;198:49-55.
27. Fulgenzi A, Vietti D, Ferrero ME. Aluminium involvement in neurotoxicity. Biomed Res Int 2014;2014:758323.
28. Ellis JK, Athersuch TJ, Thomas LD, Teichert F, Pérez-Trujillo M, Svendsen C, *et al*. Metabolic profiling detects early effects of environmental and lifestyle exposure to cadmium in a human population. BMC Med 2012;10:61.
29. Aposhian HV, Arroyo A, Cebrian ME, del Razo LM, Hurlbut KM, Dart RC, *et al*. DMPS-arsenic challenge test. I: Increased urinary excretion of monomethylarsonic acid in humans given dimercaptopropane sulfonate. J Pharmacol Exp Ther 1997;282:192-200.
30. Jones MM. Chemistry of chelation: Chelating agent antagonists for toxic metals. In: Toxicology of Metals. Berlin, Heidelberg: Springer; 1995. p. 279-304.
31. Sears ME. Chelation: Harnessing and enhancing heavy metal detoxification-a review. ScientificWorldJournal 2013;2013:219840.
32. Maiorino RM, Bruce DC, Aposhian HV. Determination and metabolism of dithiol chelating agents. VI. Isolation and identification of the mixed disulfides of meso-2,3-dimercaptosuccinic acid with L-cysteine in human urine. Toxicol Appl Pharmacol 1989;97:338-49.
33. Ikyembe D, Pwavodi C, Agbon AN. Hepatoprotective effect of methanolic leaf extract of *Anacardium occidentale* (cashew) on carbon-tetrachloride-induced liver toxicity in Wistar rats. Sub Saharan Afr J Med 2014;1:124-31.
34. Dkhil MA, Al-Quraishy S, Diab MM, Othman MS, Aref AM, Moneim AE. The potential protective role of *Physalis peruviana* L. fruit in cadmium-induced hepatotoxicity and nephrotoxicity. Food Chem Toxicol 2014;74:98-106.
35. Sakr SA, Bayomy MF, El-Morsy AM. Rosemary extract ameliorates cadmium-induced histological changes and oxidative damage in the liver of albino rat. J Basic Appl Zool 2015;71:1-9.
36. Oyinloye BE, Ajiboye BO, Ojo OA, Musa HM, Onikanni SA, Ojo AA. Ameliorative potential of *Aframomum melegueta* extract in cadmium-induced hepatic damage and oxidative stress in male Wistar rats. J Appl Pharm Sci 2016b;6:1-6.
37. Omidifar N, Nili-Ahmadabadi A, Gholami A, Dastan D, Ahmadimoghaddam D, Nili-Ahmadabadi H. Biochemical and histological evidence on the protective effects of *Allium hirtifolium* Boiss (Persian Shallot) as an herbal supplement in cadmium-induced hepatotoxicity. Evid Based Complement Alternat Med 2020;2020:7457504.
38. Baskaran R, Priya LB, Kumar VS, Padma VV. *Tinospora cordifolia* extract prevents cadmium-induced oxidative stress and hepatotoxicity in experimental rats. J Ayurveda Integr Med 2018;9:252-7.
39. Oyeyemi AO, Oseni OA, Babatunde AO, Molehin OR. Modulatory effect of *Polyalthia longifolia* leaves against cadmium-induced oxidative stress and hepatotoxicity in rats. J Complement Integr Med 2020;17:2019-38.

40. Mitra E, Ghosh AK, Ghosh D, Mukherjee D, Chattopadhyay A, Dutta S, *et al*. Protective effect of aqueous Curry leaf (*Murraya koenigii*) extract against cadmium-induced oxidative stress in rat heart. Food Chem Toxicol 2012;50:1340-53.
41. Olajide JE, Sanni M, Achimugu OJ, Suleiman MS, Jegede ER, Sheneni VD. Effect of methanol extract of *Trema orientalis* leaf on some biochemical and histopathological indices of Wistar albino rats with cadmium-induced-hepatotoxicity. Sci Afr 2020;10:e00568.
42. Ghonim A, Abdeen A, El-Shawarby R, Abdel-Aleem N, El-Shewy E, Abdo M, *et al*. Protective effect of cinnamon against cadmium-induced hepatorenal oxidative damage in rats. Int J Pharmacol Toxicol 2017;5:17-22.
43. Olubunmi OP, Yinka OS, Oladele OJ, Afees OJ, Ekenedilichuku EJ. *Gingko biloba* extract ameliorates cadmium-induced hepatotoxicity in experimental animals. Int J Clin Dev Anat 2017;3:16.