Heavy metal-induced hepatotoxicity and therapeutic activity of essential vitamins in preclinical studies - A review

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SUMMARY

Heavy metals (HMs) have extensive distribution in the environment due to their diverse applications. However, the exposure to HMs remains one of the major causes of hepatotoxicity which could lead to organ failure thereby constituting a major public health concern globally. The toxic effect of HMs on hepatic tissue, which is characterized with the induction of oxidative stress, activation of inflammatory and apoptotic signaling, adverse interaction with hepatic tissue enzymes and antioxidants as well as hepatic histopathological changes, culminates into HMs-induced hepatotoxicity (HMH). Experimental studies have been conducted to explore the therapeutic potential of essential vitamins such as riboflavin, ascorbic acid, and alpha-tocopherol against HMH. They exhibit hepatoprotective effect against HMs exposure essentially by reversal of the aforementioned deleterious effects associated with the exposure. The modulatory activity of these essential vitamins on the associated mechanisms and downstream pathways of HMH thereby highlighted their prophylactic or ameliorative effect against HMH and underscored their role as potent therapeutic agents.

Key words: Hepatotoxicity – Heavy metals – Vitamins – Hepatoprotection

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INTRODUCTION

Heavy metals (HMs) are naturally occurring elements that possess relatively high atomic number (more than 20) and elemental densities of more than 5g/cm3 and more than five times the density of water (Ali and Khan, 2018; Ahmed et al., 2022). HMs have extensive applications in homes, industries, agriculture and medicine, which indicate their wide distribution in the environment and consequent ubiquitous exposure to living organisms including humans (Tchounwou et al., 2012). Essentially, HMs exhibit toxic effect on biological systems when they exceed certain exposure level or even at low dosage. Hence, the multiple arrays of exposure to HMs through intake of air, dust, water, or food via routes such as inhalation, ingestion, and dermal absorption underscore their widespread deleterious impact on the morphology and function of body tissues (Ali et al., 2019; Jomova et al., 2025).

Furthermore, HMs that are regarded as very toxic such as lead, mercury, cadmium and arsenic pose major environmental health risks (Jacob et al., 2018; Renu et al., 2021). Tissue toxicity due to the HMs exposure is generally dependent on the metallic properties, dosage, route, duration of exposure (acute or chronic), and the level of bioaccumulation (Jomova et al., 2025). The exposure to

Submitted: May 12, 2025. **Accepted:** July 14, 2025

https://doi.org/10.52083/PEGZ6233

the HMs often results into widespread toxicity of various body tissues such as gastrointestinal, pulmonary, renal, reproductive, nervous, cardiovascular, and hepatic tissues (Witkowska et al., 2021; Mitra et al., 2022). In particular, hepatotoxicity is associated with the central role of hepatic tissue in metabolism of chemical substances and toxins such as HMs. Hence, the hepatic tissue becomes more susceptible to the toxic effect associated with the HMs exposure (Renu et al., 2021; Thakur et al., 2024).

Moreover, the deleterious effect of HMs on hepatic tissue (as well as other body tissues), is largely based on their adverse interaction with the tissue antioxidant defense system leading to several histopathological changes and functional impairments (Fig. 1). In essence, HMs-mediated hepatotoxicity (HMH) occurs primarily through their interaction with antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), as well as essential enzymes such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl-transferase (GGT), and lactate dehydrogenase (LDH) (Koyama et al., 2024; Jomova et al., 2025).

In essence, therapeutic intervention that exhibit modulatory effect on the associated mechanisms and downstream pathways of HMH could exhibit prophylactic effect or mitigate the progression of HMH. Hence, several preclinical studies using experimental model of HMH have been conducted to harness the therapeutic potential of different agents including essential vitamins such as riboflavin, ascorbic acid, and alpha-tocopherol and to elucidate their mechanism of hepatoprotection.

MATERIALS AND METHODS

A retrospective review was conducted to gather relevant findings on the therapeutic role of riboflavin, ascorbic acid, and α-tocopherol against HMH in preclinical studies. Scientific databases such as PubMed, Scopus, Web of Science and Google scholar were searched using keywords such as 'therapeutic effect of vitamins', 'Antioxidant effect of vitamins', 'hepatoprotective effect of ascorbic acid, 'hepatoprotective effect of alpha-tocopherol, 'hepatoprotective effect of riboflavin'. Further critical assessment was carried out to select articles that contained relevant information about the therapeutic role of riboflavin, ascorbic acid, and α-tocopherol in experimental models of HMH. Only articles with findings that are relevant to the aim of the review, published in English language, and in peer-reviewed journals were included. The exclusion criteria included article duplication and articles with irrelevant information with regard to the aim of the review.

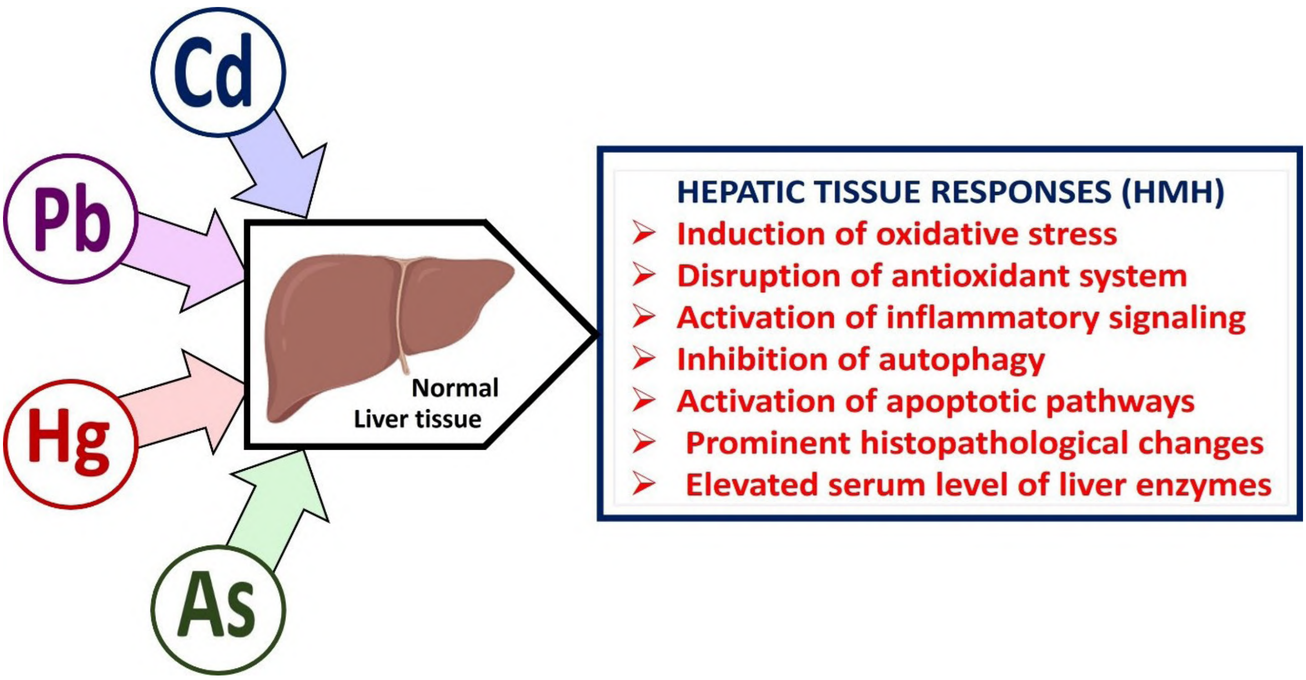

Fig. 1.- Summary of mechanisms of heavy metal-induced hepatotoxicity.

Table 1. General characteristics and hepatotoxic effect of selected heavy metals

Heavy metals (symbol)	Molecular weight	Sources and Applications	Toxic effect	Mechanism of hepatotoxicity	References
Lead (Pb)	207.2 g/mol	Vehicle exhaust, burning of fossil fuels, mining, smelting, refining, production of gasoline, building materials, paints, batteries, pipes	Disruption of function of body tissues (such as liver) through induction of oxidative stress via ROS accumulation and disruption of major regulatory pathways	- Disruption of regulatory pathways (P53, Nrf2, SIRT1, AKT-1, GSK3β, m-TOR) - Elevated MDA level - Disruption of antioxidant defense system - Activation of apoptotic factors	Violante et al., 2010; Collin et al., 2022; Alhusaini et al., 2019b; Wang et al., 2021; Zhang et al., 2020; Elhemiely and Darwish 2024; Lakka et al., 2023
Cadmium (Cd)	112.41 g/mol	Earth's crust, contaminated water, beverages or food, cigarette smoke, welding, production of batteries, television screens, cosmetics, lasers, paints, pigments	Induction of oxidative stress, cell proliferation, apoptosis, and genomic impairments leading to toxicity of tissues including hepatic tissue	- Direct toxic effect causing mitochondrial dysfunction - Inflammatory response involving activation of Kupffer cells and cytotoxic mediators - Inhibition of hepatic autophagy and antioxidant enzyme system - Induction of apoptosis and fibrosis	Tchounwou et al., 2012; Renu et al., 2021; Wang et al., 2021; Khan et al., 2022; Niture et al., 2021; Rani et al., 2014; Ozoani et al., 2024
Mercury (Hg)	200.59 g/mol	Volcanic eruptions, ocean emissions, weathering of rocks, gold mining, burning coal, contaminated water, air, food, industrial wastes	Induction of oxidative stress and cell death, impairment of metabolism and diverse histopathological changes in body tissues	- Elevation of serum activities of ALP, ALT, AST, GGT, LDH - Decrease in serum levels of total protein, albumin, triglyceride, total cholesterol - Elevation of MDA level and decline in SOD, CAT, and GPx activities in hepatic tissues	Ozoani et al., 2024; Saleh et al., 2020; Palathoti et al., 2022 Ferreira-Rodríguez et al., 2021 Ansar and Iqbal, 2016; Hazelhoff and Torres 2018; Uzunhisarcikli et al., 2016
Arsenic (As)	74.92 g/mol	Earth's crust, contaminated water or groundwater, food, soil, or exist in combined form with other metals, sulphur or oxygen	Induction of oxidative stress, disruption of antioxidant defense system, initiation of ferroptosis and disruption of key signaling pathways	- Modulation of Nrf2 expression through PI3K/Akt pathway - Hepatic histopathology - Decline in hepatic GSH level and SOD, CAT, GPx activities - Elevated levels of caspase-3 and nitric oxide (NO)	Ozoani et al., 2024; Rae 2020; Prakash et al., 2022; Thangapandiyan et al., 2019; Xu et al., 2024; Jalaludeen et al., 2016; Ramadan et al., 2024

RESULTS

Heavy metal-induced hepatotoxicity (HMH)

The selected HMs (which include Pb, Cd, Hg and As) exhibit diverse environmental distribution and characteristic toxic effects on tissues (including the liver), primarily due to the activation of inflammatory response, induction of oxidative stress, disruption of tissue antioxidants system and hepatic histopathological changes (Table 1, Fig. 1).

LEAD-INDUCED HEPATOTOXICITY

Lead (Pb) is a naturally occurring metal regarded as the most important among the toxic HMs due to its abundant distribution in the environment and important properties like softness, ductility, malleability, resistance to corrosion, and non-biodegradable nature (Flora et al., 2012; Wani et al., 2015). The major areas of application of Pb include industrial processes for production of gasoline, building materials, paints, and batteries (Boldyrev, 2018; Omotoso et al., 2020a). In addition, Pb is abundantly released into the environment from smelting, refining, mining, vehicle exhaust and burning of fossil fuels (Violante et al., 2010).

As a major environmental pollutant, Pb is rapidly distributed and accumulated in the body of living organisms including humans and acts to disrupt the normal morphology and physiology of various systems. Pb can hereby be regarded as a toxin that distort the normal functioning of the body tissues and systems (Omotoso et al., 2020b; Collin et al, 2022). Exposure to Pb poisoning especially through ingestion makes the liver tissue highly susceptible to toxicity characterized with diverse pathological changes (Renu et al., 2021).

Lead-induced hepatotoxicity often occurs via induction of oxidative stress and disruption of major regulatory pathways such as tumor protein 53 (P53), nuclear factor erythroid 2-related factor 2 (Nrf2), Sirtuin-1 (SIRT1), protein kinase B-1 (Akt-1), glycogen synthase kinase-3 beta (GSK3β), and mechanistic target of rapamycin (m-TOR) (Wang et al., 2019; Alhusaini et al., 2019a; Zhang et al., 2020; Elhemiely and Darwish, 2024). Essentially, hepatic oxidative stress due to Pb exposure is characterized by elevated malondialdehyde (MDA) level, disruption of antioxidant defense system, and binding with the sulfhydryl groups, activation of pro-apoptotic pathways thereby culminating into hepatocyte death (Lakka et al., 2023).

Cadmium-induced hepatotoxicity

Cadmium (Cd) is a naturally existing metal which is abundant in the earth's crust along with other metallic elements such as copper, Zinc and lead (Bernhoft, 2013). Although, Cd is highly toxic and non-biodegradable, it has wide range of applications such as production of batteries, television screens, cosmetics, lasers, paint pigments, and to galvanize steel (Bernhoft, 2013; Khan et al., 2022). The major sources of environmental Cd include cigarette smoking, welding, mining pigments and plastic stabilizers, contaminated water or food such as meats, leafy vegetables or sea foods (Tchounwou et al., 2014; Khan et al., 2022).

The wide distribution in the environment makes Cd one of the most important toxic HMs with human or animal exposure occurring mainly through ingestion or inhalation, leading to considerable toxicity in most bodily tissues and systems (Okwuonu et al., 2019; Khan et al., 2022). Cd is a toxic pollutant with long half-life (10-30 years) which implies low rate of excretion from the body and bioaccumulation in different visceral tissues including the liver, kidneys, bone, causing deleterious effect to the organs (Wang et al., 2021). Aside the induction of oxidative stress, the deleterious effect of Cd exposure at cellular level includes induction of cell proliferation, apoptosis, and genomic impairments (Rani et al, 2014; Niture et al., 2021).

Cd exposure and bioaccumulation results in a range of hepatic tissue pathologies such as steatosis, steatohepatitis, and hepatocellular carcinoma (Souza-Arroyo et al., 2022). The hepatotoxic effect of Cd exposure further occurs either through direct toxic effect involving binding of Cd ions to sulfhydryl groups on some mitochondrial molecules leading to mitochondrial dysfunction or through inflammatory response involving activation of Kupffer cells and several cytotoxic mediators (Rikans and Yamano, 2000; Renu et al., 2021; Ozoani et al., 2024). Moreover, Cd inhibit hepatic autophagy to impair the detoxification of damaged cell organelles or dysfunctional cytosolic proteins through lysosomal degradation and vacuole-mediated sequestration (Niture et al., 2021).

Mercury-induced hepatotoxicity

Mercury (Hg) is a highly toxic heavy metal that is abundantly present in the environment and commonly bio-available through water, air, food and soil particles (Saleh et al., 2020; Palathoti et al., 2022). Hg is usually distributed into human (and animal) tissues in its various forms of existence including organic, inorganic, elemental as well as in organic molecules, with the toxic effect on biological tissues varying with the forms of existence, exposure time, dosage and route (Ferreira-Rodríguez et al., 2021; Palathoti et al., 2022). The inorganic form of Hg, which mainly enters through ingestion or skin absorption, usually accumulate in body organs, while the elemental form of Hg, which enters through inhalation, is quickly absorbed into the lungs and blood, where it is rapidly distributed to other tissues (Palathoti et al., 2022; Wu et al., 2024).

Hg exposure or accumulation in the hepatic tissue results into induction of oxidative stress and cell death, as well as impairment of metabolism, which culminate into hepatotoxicity (Choi et al., 2017). Hg-induced hepatotoxicity is characterized with diverse histopathological changes, significant elevation of serum activities of liver enzymes such as ALP, ALT, AST, GGT, and LDH while the serum levels of total protein, albumin, triglyceride, total cholesterol, and low-density lipoprotein cholesterol are significantly decreased (Ansar and Iqbal, 2016; Uzunhisarcikli et al., 2016; Hazelhoff et al., 2018). In addition, the MDA level is significantly increased while SOD, CAT, and GPx activities are decreased in hepatic tissue (Uzunhisarcikli et al., 2016).

Arsenic-induced hepatotoxicity

Arsenic (As) is a toxic HM that constitutes a significant public health concern due to its abundant distribution in the environment, especially in its combined form with other metals, sulphur or oxygen. In addition, it possesses a unique atomic structure, which permits its existence as trivalent or pentavalent (Rae, 2020). It can further become abundant in groundwater or in the sea, due to the dissolution of mineral deposits, thereby constituting more environmental health hazard (Rae, 2020). The As exposure usually results into a myriad of pathologies affecting different body tissues including the hepatic tissue. Essentially, the hepatic tissue is regarded as a target organ of As exposure, mainly due to its role in As biotransformation, whereby As is reduced to arsenite, which in turn undergoes oxidative methylation (Prakash et al., 2022).

Generally, As-induced hepatotoxicity has been associated with induction of oxidative stress, initiation of ferroptosis, disruption of antioxidant defense system, and disruption of key signaling pathways (Thangapandiyan et al., 2019; Prakash et al., 2022; Xu et al., 2024).). This is further elucidated by significant downregulation of GPx4 in the hepatic tissue, as well as the modulation of Nrf2 expression through PI3K/Akt signaling pathway (Thangapandiyan et al., 2019; Shanmugam et al., 2018; Xu et al., 2024). Moreover, As-induced hepatotoxicity results into histopathological changes of hepatic tissue including hepatocyte necrosis, sinusoidal dilatation and congestion, vacuolation, and inflammatory cell infiltration. Other markers of As-induced hepatotoxicity include significant increase in lipid peroxidation (thiobarbituric acid reactive substance) and protein oxidation (protein carbonyl), decline in hepatic GSH level and activities of SOD, CAT, GPx and elevated levels of caspase-3 and nitric oxide (NO) (Jalaludeen et al., 2016; Ramadan et al., 2024).

DISCUSSION

The selected essential vitamins (including riboflavin, ascorbic acid and alpha-tocopherol) are derived from various sources and exhibit diverse properties, including hepatoprotective effect against heavy metal exposure, usually through modulation of the mechanisms and downstream pathways of HMH (Fig. 2, Table 2).

Therapeutic activity of riboflavin against HMH

Riboflavin, also known as vitamin B2 (Vit-B2) is a member of the water-soluble, vitamin-B family, which is composed of isoalloxazin ring of three six-carbon rings including benzoic, pyrazine and pyrimidine. Vit-B2 is abundantly derived from natural sources such as egg, fish, milk, calf liver, nuts, fruits and legumes, wild rice, mushrooms, dark green leafy vegetables, cheese, and yeast (Table 2) (Saedisomeolia and Ashoori, 2018; Suwannasom et al., 2020). It is an essential nutrient for human health and needs to be included in the diet. It plays major regulatory role in diverse biological processes and functions as precursor to flavin mononucleotide and flavin adenine dinucleotide which regulates the activity of flavoprotein enzymes (Suwannasom et al., 2020; Murgia et al., 2023).

Fig. 2.- Summary of therapeutic mechanisms of selected vitamins against HMH.

Studies have demonstrated the therapeutic effect of Vit-B2 against tissue toxins (including HMs) based on its antioxidant effect leading to mitigation of associated oxidative stress especially lipid peroxidation and oxidative injury (Ashoori and Saedisomeolia, 2014). Similar finding was reported by Mumtaz et al., (2020) which indicated the therapeutic effect of Vit-E against the toxic effect of Pb exposure to various body organs including the liver. In another previous study by Rahemi and Saiefar (2023), the protective effect of Vit-B2 against As-induced hepatotoxicity has been characterized by significant decline in ROS, serum levels of MDA, liver enzymes (ALT, AST and ALP) and inflammatory markers. In addition, Vit-B2 treatment causes down-regulation of Bax and TNF-α as well as the genes of PTEN-induced putative kinase-1 (PINK1) signaling pathway (such as PINK1, Parkin, LC3-I, Mfn2, Fis1, and p38), which in turn prevents mitochondrial damage and apoptosis.

Therapeutic activity of ascorbic acid against HMH

Ascorbic acid, also known as vitamin C (Vit-C), usually exists as a crystalline solid compound which is composed of a near planar five-member ring with two chiral centers that resolves into the four stereoisomers (Steinberg and Rucker, 2013). It is a water-soluble vitamin that is abundantly derived from many natural sources such as oranges, tomatoes, lemons, red pepper, grape and leafy green vegetables, and may also exist in the form of ascorbate in the body (Table 2) (Lykkesfeldt and Tveden-Nyborg, 2019; Gęgotek and Skrzydlewska, 2022). Vit-C plays an important physiologic role in numerous metabolic functions associated with tissue growth and maintenance, amelioration of oxidative stress, and immune regulation. Its function as a potent antioxidant is demonstrated by the ability to rapidly scavenge free radicals, thereby mitigating oxidative stress and tissue inflammation due to exposure to tissue toxins such as HMs (Doseděl et al., 2021; Gęgotek and Skrzydlewska, 2022; Conklin et al., 2024).

The study by Alhusaini et al. (2019b) demonstrated the therapeutic potency of Vit-C against

Table 2. General characteristics and hepatotoxic effect of selected heavy metals

Essential Vitamins	IUPAC NAME (Molecular formula/ weight)	Natural Sources	General properties and common uses	Mechanisms of therapeutic effect against HMH	References
Riboflavin (Vitamin B2)	7,8-dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl]benzo[g]pteridine-2,4-dione (C17H20N4O6/ 376.369 g/mol)	Eggs, fish, milk, nuts fruits, meat, legumes, butter, sunflower seeds, spinach, oatmeal, avocado, spinach, tomato, yeast	- Orange-yellow crystals, soluble in water and heat-stable. - It promotes development of skin, and blood cells; used to lower the level of homocysteine in the blood; used for breaking down nutrients in food to produce energy; to regulate the activity of flavoproteins and for normal body growth	- Amelioration of hepatic histopathological changes - Restoration of serum levels of liver function enzymes (ALT, AST, and ALP) - Up-regulation of antioxidant marker (GSH) - Reduction of oxidative stress marker (ROS, MDA) - Down-regulation of inflammatory and apoptotic factors (Bax, TNF-α), and PINK signaling pathway	Saedisomeolia and Ashoori, 2018; Suwannasom et al., 2020; Mumtaz et al., 2020; Murgia et al., 2023; Rahemi and Saiefar, 2023
Ascorbic acid (Vitamin C)	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one (C6H8O6/ 176.124 g/mol)	Tomato, oranges, guava, potato, mango, lemon, grape, red pepper, strawberries, leafy green vegetables	- Water soluble and heat-stable - It is used to enhance formation of collagen fibres; to treat scurvy; to treat acne and gum infection; to treat stomach ulcers due to Helicobacter pylori, and plays important role in tissue metabolism and growth	- Reparation of hepatic histopathological changes - Upregulation of antioxidants enzymes (SOD, GSH) - Down-regulation of ROS, lipid peroxidation and apoptotic (caspase) factors - Reduction in serum levels of liver enzymes (ALT, AST, ALP) - Potent chelating activity	Banerjee et al., 2009; Kaur et al., 2009; Adikwu et al., 2013; Kim et al., 2019; Lykkesfeldt and Tveden-Nyborg, 2019; Gęgotek and Skrzydlewska, 2022; Doseděl et al., 2021; Conklin et al., 2024
Alpha-Tocopherol (Vitamin E)	(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol (C29H50O2/ 430.71 g/mol)	Meat, fruits, cereals, almonds, almond butter, eggs, sunflower seed, avocados, vegetable oils, spinach	- Viscous pale-yellow liquid, fat-soluble, insoluble in water. - It is used to improve skin health; to prevent hair damage; to reduce risk of eye disorder; to boost immunity; to treat atherosclerosis and eczema	- Amelioration of hepatic histopathological changes - Reduction of serum levels of liver enzymes (AST, ALT, ALP and GGT) - Reduction of oxidative stress and inflammatory makers	Al-Attar, 2011; Adikwu et al., 2013; Niki and Abe, 2019; Jain et al., 2022; Torquato et al., 2020; Bjørklund et al., 2022; Akman et al., 2023; Mesalam et al. 2023

Pb-induced hepatotoxicity via reversal of the deleterious impact of the Pb-exposure such as elevated serum level of liver function enzymes, NO, hepatic lipid peroxidation, significant decline in hepatic GSH and SOD activities, and modulation of apoptosis markers. Moreover, the role of Vit-C as natural antioxidants, which mitigates oxidative stress associated with As-induced hepatotoxicity, has been demonstrated (Bjørklund et al., 2022). The therapeutic effect of Vit-C against As-induced hepatotoxicity is further characterized by significant decline in lipid peroxidation, ROS and caspase activity as well as elevated level of antioxidant enzymes (Banerjee et al., 2009; Kaur et al., 2009).

Furthermore, the mitigating effect of Vit-C on

Cd-induced hepatotoxicity had been reported to involve down-regulation of ROS generation, restoration of hepatic biomarkers (transaminases) and antioxidants activities, amelioration of hepatic histopathological changes such as hepatocyte swelling, necrosis, or degeneration, Kupffer cells hypertrophy, vascular or sinusoidal congestion and infiltration of inflammatory cells (Adikwu et al., 2013). Apart from the potent antioxidant property, Vit-C plays a vital role in chelating toxic HMs, reducing their bioavailability, and enhancing their excretion, thereby minimizing their bioaccumulation and toxic effect on the body tissues including the liver. The chelating therapeutic strategies have been demonstrated as an effective measure to combat HMs toxicity including HMH (Kim et al., 2019).

Therapeutic activity of alpha-tocopherol against HMH

Alpha-tocopherol, commonly known as vitamin E (Vit-E), is a lipid-soluble vitamin that represents one of the four homologs of tocopherols and one of the eight compounds of vitamin E, which generally contain a chromane ring with a hydroxyl group and side chain. The tocopherols usually comprise a saturated side chain while tocotrienols comprise an unsaturated isoprenoid side chain with double bonds at 3rd, 7th, and 11th carbon (Niki and Abe, 2019; Jain et al., 2022). Vit-E is commonly derived from natural sources such as meat, fruits, cereals, almonds, almond butter, eggs, sunflower seed, avocados, vegetable oils, spinach (Table 2). It functions as a potent antioxidant that neutralizes free radicals generated by exposure to tissue toxins (including HMs) and thereby preventing tissue damage due to the free radicals (Torquato et al., 2020; Akman et al., 2023).

Basically, HMH occurs due to oxidative stress due to increased ROS production, characterized by lipid peroxidation and protein dysfunction which results into liver damage. Hence, the inhibitory effect of Vit-E on lipid peroxidation, which protects the cell membranes from oxidative damage, is therefore a key mechanism of its hepatoprotective effect. Vit-E had been reported to mitigate Cd-induced hepatotoxicity via significant reduction of ROS generation, restoration of hepatic enzymes and antioxidants activities and reparation of diverse histopathological changes in hepatic tissue caused by the Cd exposure (Adikwu et al., 2013). Moreover, the antioxidants' activity of Vit-E has been demonstrated by mitigating the oxidative stress associated with As-induced hepatotoxicity (Bjørklund et al., 2022).

The previous study by Mesalam et al. (2023) demonstrated the therapeutic role of Vit-E against Pb-induced hepatotoxicity, which is indicated by abrogation of oxidative stress and inflammatory markers, restoration of liver function and antioxidant enzymes as well as down-regulation of heat shock proteins (HSPs). Moreover, another previous study demonstrated the therapeutic effect of Vit-E in attenuating hepatotoxicity that results from the exposure to different HMs (such as Pb, Cd and Hg). This is characterized by the reversal of deleterious effects of HMs such as significant increase of serum ALT, AST, ALP, GGT and hepatic histopathological changes such as distortion of hepatic parenchyma, hepatocytes rupture or necrosis, vascular congestion, inflammatory cell infiltration and dark-stained hepatocytic nuclei indicating cellular pyknosis (Al-Attar, 2011).

Combinatorial therapeutic effect of multiple vitamins or with other antioxidants against HMH

In order to achieve more effective treatment outcomes, therapeutic intervention involving multiple antioxidant vitamins or with other natural product antioxidants has been explored in preclinical HMH studies. The combinatorial therapeutic effect of Vit-C and Vit-E has been reported to enhance the biological recovery following exposure to tissue toxicity including HMH (Mumtaz et al., 2020). According to Kaur et al. (2009), the co-administration of Vit-C and α-lipoic acid can provide hepatoprotection against As-induced hepatotoxicity via mitigation of associated oxidative stress. The study by Zamani et al. (2021) further demonstrated an improved prophylactic effect of combined exposure of Vit-C and selenium against Cd-induced hepatotoxicity.

Furthermore, Ebuehi et al. (2012) demonstrated that co-administration of Vit-C and Vit-E exerted more potent therapeutic effect against Pb-induced hepatotoxicity, indicated by significant reduction of oxidative stress markers, restoration of liver enzymes and amelioration of hepatic tissue damage. Other previous studies have demonstrated the potent ameliorative effect of the combined exposure of Vit-C and turmeric or Vit-E and selenium against Pb-induced hepatotoxicity through modulation of the downstream cellular events associated with the toxicity (Alhusaini et al., 2019b; Mesalam et al., 2023).

CONCLUSION

Exposure to heavy metals remains one of the major causes of hepatotoxicity, which could lead to organ failure, thereby constituting a major public health concern globally. Hence, therapeutic intervention aimed at mitigating hepatotoxicity induced by heavy metals remains pivotal. In this regard, the therapeutic potential of essential vitamins including riboflavin, ascorbic acid and alpha-tocopherol has been harnessed with several reported satisfactory outcomes. This review has described the therapeutic potency of these essential vitamins against hepatotoxicity induced by heavy metals and elucidated their underlying mechanisms.

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