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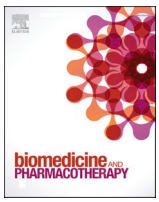

Review

Hesperidin and hesperetin against heavy metal toxicity: Insight on the molecular mechanism of mitigation

Ademola C. Famurewa [a,*,1,2], Kaviyarasi Renu [b,c,2], Mohamed Ahmed Eladl [d], Rituraj Chakraborty [b,2], Haritha Myakala [b,2], Mohamed El-Sherbiny [e], Dalia Mahmoud Abdelmonem Elsherbini [f,g], Balachandar Vellingiri [h], Harishkumar Madhyastha [i], Uddesh Ramesh Wanjari [b], Anirban Goutam Mukherjee [b], Abilash Valsala Gopalakrishnan [b,*,1,2]

[a] Department of Medical Biochemistry, Faculty of Basic Medical Sciences, College of Medicine, Alex Ekwueme Federal University, Ndufu-Alike Ikwo, Nigeria
[b] Department of Biomedical Sciences, School of Biosciences and Technology, VIT, Vellore, Tamil Nadu 632014, India
[c] Centre of Molecular Medicine and Diagnostics (COMManD), Department of Biochemistry, Saveetha Dental College & Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, 600077 Tamil Nadu, India
[d] Department of Basic Medical Sciences, College of Medicine, University of Sharjah, Sharjah 27272, United Arab Emirates
[e] Department of Basic Medical Sciences, College of Medicine, AlMaarefa University, Riyadh 71666, Saudi Arabia
[f] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, P.O.Box 2014, Sakaka, Saudi Arabia
[g] Department of Anatomy, Faculty of Medicine, Mansoura University, Mansoura, Egypt
[h] Human Molecular Cytogenetics and Stem Cell Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India
[i] Department of Cardiovascular Physiology, Faculty of Medicine, University of Miyazaki, Miyazaki 889 1692, Japan

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ABSTRACT

Toxic heavy metals (THMs) are non-essential hazardous environmental pollutants with intractable health challenges in humans and animals. Exposure to lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), nickel (Ni), and chromium (Cr) are ubiquitous and unavoidable due to food contamination, mining, and industrial mobilization. They are triggers of tissue impairment and aberrant signaling pathways that cascade into several toxicities and pathologies. Each of Pb, Cd, Hg, As, Ni, and Cr aggravate oxidative inflammation, protein dysregulation, apoptotic induction, DNA damage, endocrine deficits, and mitochondrial dysfunction contributing to the pathophysiology of diseases. Hesperidin (HSD) and hesperetin (HST) are flavonoids from citrus fruits, and systematic investigations suggest their potential to combat the molecular alterations and toxicities induced by THMs. They mitigate heavy metal toxicity via antioxidant, anti-inflammatory, and anti-apoptotic effects via scavenging free radicals and modulation of ATPases, cell cycle proteins, and various cellular signaling pathways, including Nrf2/HO-1/ARE, PI3K/mTOR/Akt, MAPK/caspase-3/Bax/Bcl-2, iNOS/NF-κB/TNF-α/COX-2. This review summarized the mechanistic effects of heavy metal toxicity and the insights on molecular mechanisms underlying mitigation of heavy metal toxicity by HSD and HST. Hesperidin and hesperetin are potential flavonoids for the modulation of pathological signaling networks associated with THMs. Therefore, HSD and HST can be suggested as natural dietary agents and blockers of harmful effects of THMs.

1. Introduction

The earth's crust is a significant reservoir of components and elements for diverse discoveries and utilization of humans for industrial and economic purposes. Heavy metals with specific density above 5 g/cm^{3}are released from the earth's crust to the top-soil environment due to ongoing human activities and remain in the background and consequently contaminate the food chains [1,2]. Some heavy metals are

* Corresponding authors.
E-mail addresses: ademola.famurewa@funai.edu.ng (A.C. Famurewa), abilash.vg@vit.ac.in (A. Valsala Gopalakrishnan).
[1] Equal Contribution for corresponding authors.
[2] Equal Contribution for first authors.

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essential and have clear biological roles, such as zinc, selenium, copper, and manganese. However, they may be toxic when present in excessive levels or if their homeostasis is disturbed by some factors. However, heavy metals classified as harmful (THMs), including Pb, Cd, Hg, As, Ni, and Cr, are non-essential devoid of biological function. THMs are known for their human toxicity and bioaccumulation potential, and they are considered critical pollutants by regulatory authorities [3,4]. Exposure to THMs is one of the significant environmental factors contributing markedly to human assimilation and bioaccumulation. They exert potential health threats emanating from toxicity and leading to genetic instability, epigenetic changes, congenital malformation, reproductive deficits, inflammation, organ damage, and pathogenesis [5–8]. Humans are exposed via occupation and environment by smoking, soil, air, water, and foods. However, food is the primary source of exposure to THMs among non-smokers. The potential of these THMs to bioaccumulate in tissues is the basis for their health hazards and pathologies even at trace amounts [5].

For example, Pb is a non-essential element with no safe level for humans. Prevention of inhalation and ingestion of Pb, Cd, Hg, As, Ni and Cr at occupational and non-occupational environmental levels are inevitable [9]. Several research reveals that toxicity mechanisms of THMs involve the induction of oxidative stress, inflammation, apoptosis and resultant pathological alterations of signaling pathways. Studies show that natural phytochemicals, including hesperidin and hesperetin with antioxidant, anti-inflammatory and anti-apoptotic activities, could reverse aberrant effects of THMs [10]. Interestingly, accumulating evidence shows the critical role of hesperidin and hesperetin against diabetes, cancer, myocardial ischemia, neurodegeneration, cardiovascular diseases and attenuation of oxidative stress-related toxicities of heavy metals. However, there is more evidence related to heavy metals and the mitigation of their toxicity with different flavonoids. But the mechanistic link between hesperidin and hesperetin has not been established before, particularly with the heavy metals' different toxicity [10].

The use of biosafe, natural, bioactive substances like HSD and HST is a significant approach of preventing heavy toxicity. HSD increased the capability of superoxide dismutase (SOD), catalase (CAT), peroxidase (POX), glutathione S-transferase (GST), and glutathione peroxidase (GPX), which effectively eliminated ROS generation (H_2O_2) and lipid peroxidation (TBARS). In response to stress, HSD re-regulated expression of the PHT1.1 and PHT1.3 genes, reversing the negative consequences of excessive metal ion accumulation. By modulating saturated/unsaturated fatty acid composition, exogenously administered HSD efficiently preserved membrane integrity [11].

HSD has the potential to mitigate the toxic insults of heavy metal in the brain through a variety of mechanisms involving chelation of heavy metal, prevention of membrane integrity loss, and protection of thiol-containing groups, but the underlying property which supplements all of these protective actions [12]. The molecular role of HSD and HST against cancer, cardiovascular illness, and neurodegenerative disease has been extensively examined in published studies [44–46]. However, the molecular mechanisms underlying HSD and HST's roles in THM-mediated pathogenesis have yet to be investigated. This review aims to throw light on the on the toxicity of Pb, Cd, Hg, As, Ni, and Cr, as well as the molecular mechanisms behind the protective effects of HSD and HST in preventing toxicity. Additionally, this work aims to bridge the gap between the past and current research, paving the way for future scientific advancements.

1.1. Sources and exposure to THMs

Rapid industrialization and urbanization have caused contamination of the environment by THMs, and their rates of mobilization and transport in the environment have significantly escalated since the 1940 s [13]. Toxic heavy metals have harmful effects on human health, and exposure to these metals has been increased by industrial, anthropogenic activities and modern industrialization. Human activities such as quarrying and mining cause looseness of THMs in the earth's crust and are thus dischargeable to the environment. Sources of THM dispersal to the environment include natural events and anthropogenic activities [14]. Natural sources include weathering of rocks, volcanic eruption, aerosols and dust emissions [15]. Anthropogenic sources are ore-mining, smoke, coal and crude oil, gas flaring, industrial emissions, smelting, fossil fuel, and agricultural activities such as farming and agrochemical [16]. Inevitable human exposures are traceable to inhalation, ingestion and skin contact in the workplace and environment because THMs are ubiquitous; they are present in foods, drinking water, electronic wastes, electroplated metals, alloys, batteries, industrial effluent, diet supplements, paints, tobacco cosmetics, air, urban runoff, sewage discharge, soil, and dietary supplements [17–19]. Lead exposure is associated with the intake of lead-contaminated food, water, leaded gasoline, plumbing, paints and dust. Children's toys, herbal formulations, food cans, ammunition, vitrified ceramics, pottery, boat building, and the printing of books are well linked to Pb exposure [20]. Animal products and grains from contaminated seas and soils are non-industrial exposure routes to Cd [21]. Children with hand-to-mouth habits are exposed to a considerable amount of Cd from household contaminated dust and soil particles [22]. Fish, seafood, vegetables and grains are the most critical exposure routes to Hg [23]. Arsenic, a classic neurotoxicant, is a global threat to health, affecting about 200 million people from drinking water worldwide [24]. Nickel exposure is by ingesting contaminated foodstuffs or inhaling cigarette smoke. Chromium is present in several materials such as pigments, chrome-plated metals, cement and detergents [25]. Some of the heavy metals enter the cell and affect the biological growth and its function. Nickel carbonyl is fat-soluble to cross the cell membrane and undergo diffusion via calcium channels. Ni leads to entering into the intracellular space with less calcium. The entered Ni leads to cell growth, cell differentiation, apoptosis. Further, it leads to cancer. Cd mediates the immediate-early response genes (IEGs), which induce cell proliferation and carcinogenesis [26]. Some heavy metals reach into our bodies from the heavy metals contaminated site. Example: Hg, As and Pb would enter the body via various processes such as inhalation, ingestion and absorption via skin [27].

1.2. Toxicity of THMs, hesperidin and hesperetin

Exposure and cellular assimilation of THMs provoke tissue toxicity and pathophysiology. Studies have shown that toxicity depends on the age of the exposed, dose, duration and route of exposure [28,29]. However, THM toxicity is associated with bioaccumulation, oxidative membrane degradation, protein integrity perturbation, mitochondrial and DNA damage [30]. These toxicities are related to Cd, Hg, and As, sulfhydryl-reactive metals that bind to sulfhydryl-rich proteins and enzymes, thioredoxin reductase and glutathione reductase to deplete glutathione homeostasis and exacerbate oxidative stress [24]. THMs bind to other functional groups to catalyze the oxidation of amino acid side chains, perturbing protein folding and displacing essential metal ions in enzymes. For example, zinc is an antioxidant element in signaling proteins and redox enzymes like superoxide dismutase that detoxifies superoxide radicals to sustain redox homeostasis [31]. However, studies suggest that Cd competes with zinc, iron and selenium in antioxidant enzymes to down-regulate antioxidant defense mechanisms [32,33]. A recent study shows that Pb interacts with specific amino acids in superoxide dismutase and catalase to compromise their antioxidant activities [34]. Lead also binds to the major grooves of DNA and interacts with phosphate oxygen atoms to cause DNA damage [34].

Interestingly, THMs have the potential to trigger free radical generation directly or indirectly to decrease cellular antioxidant milieu and aggravate oxidative stress and inflammatory cascades. Oxidative stress causes membrane lipid peroxidation; it destroys proteins and DNA molecules and supports carcinogenesis [30,35]. THMs alter regulatory proteins of apoptosis, cell cycle, DNA repair, cell growth and

differentiation, causing aberrant molecular signaling leading to several pathologies. Thus, abundant evidence implicates THMs in gastrointestinal, respiratory, cardiovascular, reproductive, renal, hemopoietic, neoplastic, metabolic and neurological diseases [30,34,36–38].

Citrus fruits (*Rutaceae* family) such as sweet oranges, grapes, lemon, mandarins and pomelos are sources of bioactive phytochemical polyphenols, including flavonoids, anthocyanins, terpenoids, triterpenes, and phenolic acids with immense benefits to human health. The most important and diverse group of polyphenols is flavonoids [39]. Hesperidin and hesperetin are flavonoids from citrus fruits with numerous biological effects [40]. The flavanone glycoside hesperidin is the glycosylated form of aglycone hesperetin and is the most abundant in citrus fruits. Hesperidin (HSD) and hesperetin (HST) possess abundant pharmacological efficacies that include antioxidant and anti-inflammatory activities and the potential to mitigate aberrant underlying mechanisms to prevent the onset of chronic diseases. Studies reveal the protective capacities of HSD and HST against THM-induced tissue damage, oxidative stress, inflammation, caspase-dependent apoptosis and mitochondrial dysfunction [41–44]. Moreover, HSD beneficially regulates oxidative stress, inflammation, p53 protein, p62/Keap1/Nrf2 signaling, and DNA damage to mitigate arsenic cardiotoxicity, hepatotoxicity, and nephrotoxicity animal models [45,46].

Published papers have widely reviewed the mechanistic role of HSD and HST against cancer, cardiovascular and neurodegenerative diseases [47–49]. However, to date, the molecular mechanisms that underlie the role of HSD and HST in THMs-mediated pathogenesis remain to be reviewed. Therefore, the present review will focus on the toxicity of Pb, Cd, Hg, As, Ni and Cr and molecular mechanisms underlying the beneficial effects of HSD and HST to prevent toxicity of these metals.

2. Molecular mechanisms of heavy metal toxicity

2.1. Mechanisms of lead toxicity

Lead (Pb) is amongst some of the toxic heavy metals which have caused significant environmental pollution, with its non-biodegradable attribute being the reason for its environmental persistence. Its exposure to drinking water is one of the primary reasons for its intake into the body [50]. The heavy metal Pb has been found to have toxic effects on kidneys, liver, the nervous system and the hematopoietic system, along with a carcinogenic risk. These harmful effects have been seen to occur upon induction of oxidative stress and a subsequent rise in reactive oxygen species (ROS), and a decline in the levels of antioxidants [51]. Pb has also been seen to affect events regulated by calcium and the generation of genotoxic compounds, an effective Pb-toxicity mechanism. Other effects of Pb-toxicity involve alteration of cellular processes like transportation of ions, folding of the protein and their maturation, regulation of an enzyme. Pb-treatment has also been seen to cause endoplasmic reticulum (ER) stress and UPR stress [52]. Studies have shown Pb exposure causes autonomic dysregulation and significantly affects a parasympathetic part of the nervous system [53]. Activation of phosphoinositide 3-kinase, Akt, p38 MAP kinases has been involved in Pb-toxicity. Pb has been found to affect the synthesis of heme significantly. Impairment of cellular differentiation and their maturation occurs too upon Pb-exposure [54].

Studies have shown the association of apoptosis with oxidative stress occurrence upon lead treatment. Exposure to Lead nitrate has been shown to cause phosphatidylserine externalization, cellular death induction and caspase-3 activation [55]. Studies on *Channa punctatus* have shown a decline in TNF-α level upon Pb-exposure, indicating the involvement of MAPK and NF κβ pathways of signaling. Pb has also been found to cause damage to DNA. *Oreochromis niloticus* based studies have shown that Pb can influence macrophage phagocytic activity. Studies have also demonstrated Pb exposure causing a decline in NO levels and NOS2 expression inhibition leading to a negative effect on macrophage antimicrobial activity [56]. Exposure of lead acetate in rats showed Pb functioning as an endocrine disruptor. It has been seen to cause alteration in the metabolism of hormones like FSH and LH in terms of their synthesis or alteration in testosterone breakdown and impairing Sertoli cells' function [57]. Pb has been found to interact covalently with glutathione's -SH group and of other antioxidant enzymes as well and inactivate them.

Furthermore, Pb has been found to substitute various monovalent cations and divalent cations, which affect major biological processes. Studies demonstrated that Pb alters the calcium regulatory actions on the functions of a cell. Oxidative damage to DNA due to ROS generation is another form of Pb exhibiting its toxicity [58]. Pb has also enhanced cyclooxygenase-2 gene transcription and prostaglandin E2 production, resulting in oxidative stress and inflammation [59]. Epigenetics mechanism has also been implicated in Pb mediated toxicity. Hypomethylation of LINE-1 upon Pb-exposure was observed. PLAGL1 has also shown a positive interaction between its status of methylation and exposure to Pb [60]. Exposure of lead acetate in the mice model showed alteration in DNA methylation. Changes were observed in the expression of MeCP2, Dnmt3a and Dnmt1 upon Pb-exposure. Association of IAP loci with alteration in DNA methylation was also observed [61]. Studies have also shown those Pb-exposure upregulated levels of long non-coding RNA and circular RNA in mice hippocampus and their cerebral cortex. The same was observed in lead acetate treated N2a cells. They have been shown to cause apoptosis in the neuronal region via an interaction with miR-671 [62] (represented in Table 1).

2.2. Mechanism of Cadmium toxicity

Cadmium (Cd) toxicity is among one of the significant health concerns, and long-term exposure to it via water, air, soil or food can lead to toxicity in multiple organ systems such as the cardiovascular system, the respiratory systems, urinary system, skeletal system and central as well as peripheral nervous system. It can also lead to cancer [63]. Cd-induced oxidative stress is an important mechanism causing kidney and liver diseases. Cd has also been found to cause damage to the mitochondria as they are responsible for the formation of ROS [64]. GSH has been observed as a significant target of Cd, and a depletion of the reduced GSH is seen to occur upon Cd-toxicity, causing a disturbance in the redox balance.

Moreover, the ROS induced by Cd have been seen to activate MAPKs and interaction with defense at the cellular level via them has been reported too [65]. *Paralichthysolivaceus exposed to Cd,* and metamorphosing larvae showed inhibition in CAT and SOD levels and enhanced lipid peroxidation. In juveniles, however, the SOD activity was increased along with the enhanced lipid peroxidation [66]. In *Cyprinus carpio var. color,* alteration in the levels of SOD, MDA and GSH upon Cd-exposure was observed as well [67]. In Jurkat T Cells, Cd exposure led to damage to the DNA and decreased GPx and SOD activities. Lipid peroxidation was also seen to be enhanced [68]. Studies have also shown an increase in the Nrf-2 levels upon Cd-exposure [69]. Cd exposure in chick models led to downregulation in DNMT3A/3B levels [70]. Studies have shown Cd exposure being associated with hypomethylation of DNA in the peripheral blood, and this association was modified by DNMT1 [71]. Cd-mediated methylation of the maternal genome and a fetal genome was reported in studies [72]. Cd-exposure led to upregulation in the levels of Il-6, IL-8 and IL-18 and NF-KB1, MYD88, as well as NF-kB-p65. Upregulation of cox-2 via the MAPK pathway has been seen as well [73]. A rise was observed in IL-11b and IL-1β levels upon Cd-exposure [74]. Studies on prostate epithelial cells of humans have shown Cd causing apoptosis in them in p53 dependent fashion [75]. More studies have shown Cd toxicity causing an extracellular influx of Ca^{2+} leading to neuronal apoptosis [76]. Cd2 + treated crabs showed a rise in caspase-3, caspase-8 and caspase-9, indicating the occurrence of apoptosis [77]. CdCl2 increased the expression of caspase-3 and Bax and decreased Bcl-2 levels in the liver and kidneys of mice models, indicating an occurrence of apoptosis [78] (represented in

Table 1
Mechanistic action, different pathways and toxic nature of the heavy metals.

Heavy metals	Mechanistic action and different pathways involved	Elevated toxic order of heavy metals	Reference
Lead (Pb) (Oxidation state +2 to +4)	1. DNA damage 2. Covalently binds with glutathione's -SH group 3. Epigenetic mechanism 4. Elevated ROS level 5. ER and UPR stress 6. PI3-kinase, Akt, p38 MAP kinases and NF κβ 7. Increased inflammatory cytokines IL-1β, TNF-α, and IL-6 8. Inhibition of heme biosynthesis 9. Reduced GSH, SOD, CAT, and GPx levels	Pb^{2+}	[48–57]
Cadmium (Cd) (Oxidation state +2 to +1)	1. Mitochondrial damage 2. ROS generation and oxidative stress 3. Reduced GSH, SOD, CAT, and GPx levels 4. Nrf-2 and MAPK activation 5. Calcium homeostasis impairment 6. Decreased DNMT3A/ 3B levels 7. Upregulation of Il-6, IL-8 and IL-18, IL-11b, IL-1β and NF-KB1, MYD88	Cd	[59–71]
Mercury (Hg) (Oxidation state +1 and +2)	1. Thiol binding (GSH conjugation) 2. Alters the protein synthesis and energy production 3. Binding with the SH group, it activates apoptosis via NF-κB, Akt/CREB, Keap1/Nrf2 and other mitochondrial pathways 4. Elevated ROS level, TrXR, LPO and MDA 5. Methylation of the DNA 6. Activation of of IL-4, IL-6, IL-17 and IFN-γ 7. Decreased level of Akt, ERK-1 and p-Akt 8. Activation of Cyt C, 9. Cas 3 and PARP.	Inorganic mercury$Hg^{\circ} < Hg^{2+} < Hg^{+} <$ CH3-HgOrganic mercury (methyl mercury (Me-Hg) and ethyl mercury (Et-Hg) are more toxic	[79–9-]
Arsenic (Oxidation state:+3, +5)	1. Thiol binding (GSH conjugation) 2. ROS generation via Nox2, mitochondrial ETC, lipooxygenases, NOS, cyclooxygenases and cyt P450 epoxygenases 3. PKCδ-Nrf2-ARE activation, 4. Reduced GSH, SOD, CAT, and GPx levels 5. Increased inflammatory cytokines IL-1β, TNF-α, and IL-6 6. Modulation of miR-22, miR-221, mir-210, miR-34a and miR-22 7. Activation of P53, Cyt C, Cas 3 and PARP.	Organic arsenicals $> As^{\circ} <$ inorganic sp (As^{5+} to As^{3+}) < Arsine	[94–104]
Nickel (Oxidation state: −2, −1, 0, +1, +2, +3, +4)	1. ROS generation and calcium-dependent signaling cascades. 2. Epigenetic actions 3. Increased inflammatory genes TNF-α, IL-1β, IL-8, IL-18, COX-2, NLRP3 and NF-κB 4. Decreased anti-inflammatory genes IL-4, IL-2 and IL-13. 5. Reduced GSH, SOD, CAT, and GPx levels 6. Upregulates genes involved in ER stress 7. Decreases anti-apoptotic genes such as NLRP3 and increased apoptotic genes such as Cas-3, Cas-9, Bax, Bak and PARP	Ni^{2+}	[112–120]
Chromium (Oxidation state: −2 to +6)	1. Damage to the 2. DNA Instability of genomes 3. Methylation of DNA 4. Cas-3, Cas-9, Bax and PARP 5. Generation of ROS and Oxidative stress 6. Reduced GSH, SOD, CAT, and GPx levels 7. Decreases ATP level	Cr (III) to Cr (IV)	[125–131]

Table 1).

2.3. Mechanisms of mercury toxicity

The element Mercury (Hg) is another widely present environmental pollutant. Humans are exposed to Hg by occupational means, consuming fish containing Hg (Methyl), dental amalgams, etc. [79]. Methyl mercury is the most toxic of the mercury compounds and is found in water bodies. The majority of this is absorbed in the GI tract and some in the brain and blood. [80] The primary organ of inorganic Hg accumulation is the kidneys. Hg compounds (organic) have affected the CNS, developmental processes, and immune system [81]. Exposure to Hg and its compounds has been found to affect renal functioning, cause structural bone deformity, disease of cardiovascular and reproductive systems, nervous system dysregulation, etc. [82]. Studies have shown Hg exposure leading to oxidative stress generation, glutathione depletion, a decline in proteins' sulfhydryl groups. Hg has been found to interfere with the functioning of enzymes altering the synthesis of proteins and disturbing energy production [83].

Hg-induced ROS generation and occurrence of oxidative stress are significant pathways of Hg-toxicity. Studies have also shown Hg-induction causing Glutathione (GSH) decline. It has also established a reduction in the level of antioxidants like Glutathione peroxidase (GPx) and Superoxide dismutase (SOD) [84]. Hg also caused mitochondrial damage by depletion of GSH. Hg compounds have been found to bind to thiol groups and cause a decline in the sulfhydryl proteins necessary to counteract oxidative damage. The ROS produced is responsible for oxidative insults to lipids, nucleic acids and thioredoxin reductase (XR) [85]. Selenoproteins involved in the TrXR1 and TrxR2 system and glutathione-glutaredoxin have been seen as primary targets of Hg. Binding of Hg to this and inhibition in their function resulting in redox imbalance have been observed. Selenoprotein P, Selenoprotein K, Selenoprotein T, have also been seen in studies as Hg targets. A Hg-induced

inhibition of selenoprotein generation needed to restore redox balance in a cell is also observed [86]. Toxic effects were observed when Hg was seen binding to cysteine. The binding of Hg to SH groups has been seen to mediate the apoptosis process by interfering with NF-κB, Akt/CREB, Keap1/Nrf2 and mitochondrial pathways. Oxidative stress induction by Hg may also result due to Mn-SOD inhibition, TrXR activity inhibition, among others [87]. Hg-exposure-induced ROS formation leading to lipid peroxidation was also observed [88]. Hg exposure was associated with epigenetic disruption of the PON1 gene. DNA methylation of cord blood at the PON1 locus was observed upon Hg-exposure [89]. Studies have shown that exposure to methyl form of Hg was associated with the SEPP1 promoter region [90]. Hg exposure has also resulted in DNA lesions induced by oxidative stress generation. An increase in the concentration of 8-OHdG in Hg-exposed groups was observed [91]. A study on Hg-exposed American alligators showed an association of global DNA methylation with Hg exposure [92]. Studies have shown Hg exposure increases the TNF-α and IL-6 levels, which are inflammatory, in the duodenum and colon regions [82]. Upon Hg-exposure in fish consumers in the Amazonian region of Brazil, upregulation in IL-4, IL-6, IL-17 and IFN-γ was observed [93]. Hg-treatment in PC12 type cells showed a decline in Akt and p-Akt. The expression levels of ERK-1 were down-regulated upon Hg-exposure as well. An increase in the levels of cytochrome-C was observed, and deregulation in levels of caspase-3 was seen upon Hg-treatment, contributing to apoptosis induction [94]. HgCl2 treatment in HIT-T15 cell type cells also showed disruption of the membrane potential of mitochondria, PARP (poly ADP-ribose polymerase activation), caspase-3 activation, cytochrome c release increase, all of which are indicators of apoptosis [95] (represented in Table 1).

2.4. Mechanisms of arsenic toxicity

Arsenic (As) is another toxic metal found in the environment, seriously detrimental to global health. Its exposure caused cancers of the skin, lungs, liver, and diseases related to the cardiovascular system, the GI tract, reproductive system, nervous system, and the developmental processes of the body that are dysregulated [96]. As-contaminated water and food have been seen as the primary As-exposure routes in humans. Its contamination leads to outbreaks in India, the Republic of China, and Taiwan [97]. The solubility of arsenites and the solubility of arsenates have been seen to be high in water. The trivalent form of As has been seen in studies to be more toxic than the pentavalent As-form by 2–10 folds approximately [98].

Studies have shown that As binds to tissue proteins' thiol groups and subsequently dysregulates their function and affects the mitochondrial enzymes [99]. As exposure caused an upsurge in ROS generation leading to oxidative stress-mediated by Nox2, mitochondrial ETC, lipooxygenases, NOS, cyclooxygenases and cyt. P450 epoxygenases [100]. This As-mediated ROS generation-induced oxidative stress occurs due to an imbalance in the pro-and antioxidant levels in the body. Studies have shown alterations in levels of GST (glutathione-S-transferase), GSH and SOD upon As-treatment [101]. Sodium arsenite treated rats showed an elevation in the levels of Malondialdehyde (MDA) and a decrease in the levels of catalase (CAT), SOD and glutathione peroxidase (GPx) [102]. Studies have shown As-exposure leading to an increase in the expression levels of SOD1 mRNA, GPx1 mRNA and Nrf2 mRNA. The expression of pPKCδ, pNrf2 and Nrf2 proteins was also increased. Reports thereby have suggested the PKCδ-Nrf2-ARE pathway being involved in As-induced oxidative stress-mediated damage upon As-exposure [103]. As-intoxicated rats showed a rise in the TNFα levels and the levels of NFκB. Activation of PARP1 was observed as well. IL-1β and IL-6 also seemed to be activated upon As-exposure [99]. As-treated kidneys of rats showed upregulation in TNFα and NO levels. Increased expression of iNOS and NFκB was observed too upon As-treatment [104]. As exposure led to H4K16Ac decrease leading to urothelial cell toxicity in humans. As-induced reduction in H4k16 has been observed, leading to carcinogenesis in the bladder region. Moreover, As-exposure led to H3K9 dimethylation increase and H3K27 trimethylation decrease. Modulation of miR-22, miR-221, mir-210, miR-34a and miR-22 have been seen in studies upon As-exposure in lymphoblasts of humans [105]. The heavy metal, As, influenced the activity and mRNA levels of DNMTs (DNA methyltransferases) like DNMT3A, DNMT3B and DNMT1 and reduced their activities/levels. It has been shown to cause DNA hypomethylation (Global) too. By altering SAM (S-adenosyl methionine) levels and its insufficiency and a reduction in DNMTs expression [106]. As-induced damage to DNA in liver cells also led to activation of p53 and increased expression of Bax and miR-34a [107]. Apoptosis was seen to occur in the event of As-exposure with the release of cyt C in the cytosol, increase in caspase-9 and caspase-3 activities [108]. PLHC-1 cells treated with arsenic trioxide showed apoptotic cell death occurring with a rise in caspase 3 activity. An increase in expression of Bax and p53 was also seen, highlighting the role of p53 in As-induced apoptosis [109] (represented in Table 1).

2.5. Mechanisms of nickel toxicity

Nickel (Ni) is a transition metal and occurs in combination with As, Sulphur, etc. It is used in the electroplating process of alloy in Nickel-Cadmium batteries [110]. Ni is present in the soil, in the air and the water, and in various forms. Various other activities like metal mining, burning of fossil fuels, emission from vehicles, smelting release Ni into the environment. Exposure to Ni has been seen to cause cancers of the lung, prostate, kidneys, etc. Occurrences of contact dermatitis have been seen as well [111]. Ni-exposure has been found to cause the generation of ROS as well as activating calcium-dependent signaling cascades. It has also been found to deplete ascorbate levels present intracellularly and cause the inactivation of prolyl hydroxylases. This led to HIF-1α induction and induction of genes inducing hypoxia [112]. Studies have shown that Ni exposure in the form of nanoparticles led to ROS generation. This increased ROS production led to lipid peroxidation, and the level of MDA was also increased. This Ni-exposure also caused GSH depletion [113]. DNA damage is also observed upon Ni-exposure. This has been linked to the binding of Ni to DNA and nuclear proteins. It has also been found to interfere and impair nucleotide-excision repair and base-excision repair processes [114]. Dysfunction of mitochondria and oxidative stress induction have been two significant pathways of Ni-toxicity. The dysfunction of mitochondria results in ROS increase. Activities of CAT and SOD have been seen to decline in studies on Ni-toxicity. Also, MDA levels, lipid peroxidation and levels of NO (nitric oxide) have been seen to increase upon Ni-exposure [115]. Ni-exposure has been associated with impairment of average homeostatic balance of metal ions essential in nature. A decrease in calcium levels and levels of manganese, magnesium, and zinc have also been seen upon Ni-exposure. Also, interference with iron cofactor binding ability to proteins has been observed [116]. Ni-exposure has been linked to histone H2B-ubiquitination dysregulation and histone H3 methylation. Dysregulation of acetylation of Histone H4 was attended to. Ni-exposure has been found to inhibit histone H2A, histone H2B, histone H3 and histone H4 acetylation and alter DNA methylation status [117]. Recent studies have shown Ni (II) having an inhibitory effect on DNA 5-methylcytosine mediated by oxidation of Tet proteins. It has also been found to cause a reduction of global level DNA demethylation [118]. NiCl2-treated broilers showed an increase in expressional mRNA levels of TNF-α, IL-1β, IL-8, IL-18 and COX-2 inflammatory in nature via NF- κB activation. A decline in IL-4, IL-2 and IL-13, mRNA expression anti-inflammatory in nature was also seen [119]. Mice treated with Ni showed an increase in the levels of p38 phosphorylation and STAT1 phosphorylation in the liver tissue. Ni also increased NF-κB p65 (nuclear) expression in Ni-treated mice livers [120]. Studies have also shown NiCl2 treatment led to inflammatory activation of macrophages derived from bone marrow via MAPk, IRF3 (interferon regulatory factor 3), NF-κB and NLRP3 (Nod-like receptor 3) inflammasome pathway [121]. Ni-nanoparticle-induced apoptosis induction via inhibition of

PI3K/AKT/mTOR signaling pathway has been observed in studies [122]. Recent studies have also shown NiCl2 activated the apoptotic pathway mediated by mitochondria. A decrease in Mcl-1, Bcl-2, Bcl-xl levels and a rise in caspase-3, caspase-9, Bax, Bak and PARP expression of their mRNA was observed. Also, the Fas-mediated pathway saw a rise in expression of the Fas, FasL and caspase-8 mRNA. Endoplasmic reticulum(Er)-stress-mediated induction of apoptosis was also seen with NiCl2 treatment with upregulated levels of GRP94 and GRP78. The arrest of the G2/M phase by the p53-dependent pathway was seen [123]. A study on Sertoli germ cells of rats exposed to Ni also showed levels of Bax, caspase-3 and 9 and Igfbp3(Insulin-like growth factor-binding protein 3) being upregulated and occurrence of apoptosis in them as well [124]. An interplay between caspase 3 and 8, p53 and MAPK signaling has been suggested in the event of Ni-exposure induced apoptosis [125] (represented in Table 1).

2.6. Mechanisms of chromium toxicity

Chromium (Cr) is another widely distributed metal found on the earth's surface. In environment Cr in + 3 and + 6 state is the most stable. Absorption of Cr in the body occurs via oral, inhalation or dermal route [126]. The + 6 form of Cr is more toxic than the + 3 form by about 100 times owing to its higher solubility in water and ease of reduction. Exposure to Cr has been seen to cause respiratory system dysfunction and affects the liver, immune system, blood, dermal region, kidney and gastrointestinal region [127]. Studies have shown Cr in its hexavalent form entering a cell getting reduced to its trivalent form and mediating its toxic effects by oxidative stress induction. The trivalent form of Cr has also been seen to form DNA adducts, subsequently leading to mutations. Cr also form crosslinks with cysteine GSH and deplete the antioxidants causing an imbalance of the redox system leading to oxidative stress [128]. Cr-compounds have been seen in studies inflicting damage to DNA, dysregulating the gene functions, exchange of sister chromatids, aberration of chromosomes and transformation of the cell. Cr (+6) mediated genotoxic effects like DNA adducts formation leading to inhibition of DNA replication have been seen too [129]. Goldfish treated with a hexavalent form of Cr showed alteration in the levels of CAT and SOD. Alterations were also observed in the levels of GPx. Dysregulation of metallothioneins was seen too [130]. Cr-induction has been associated with the methylation of DNA of the p16 promoters and MLH1 promoters, causing a decline in the expression of their mRNA. Cr forming complexes with DNMT1 and HDAC1 (histone deacetyltransferase 1) lead to repression of the transcription of the Cyp1a1 gene. Dysregulation of methylation levels of H3K9, H3K4 and H3K27 upon Cr-exposure has been documented as well [117]. Cr exposure led to CpG methylation of genes involved in DNA repairs like XRCC1, RAD53, HOGG1, ERCC3, and MGMT. The activity of TET protein was found to be decreased. miR-143 downregulation was also observed in Cr-treated cells leading to transformation and angiogenesis. A rise in miR-21 levels led to a decrease in its target gene PDCD4 expression, which is a tumor suppressor was seen too [131].

Cr (+6) exposure is associated with inflammation occurrence. Studies have shown an increase in enzyme activity of lysosomes after Cr treatment. A rise in the expressional levels of iNOS, p65-NF-κB and TNF-α was documented too upon Cr (+6) treatment [132]. In vivo studies have shown cutaneous inflammation in mice in their ear skin upon Cr (+6) treatment with a rise in the IL-1β levels and TNF-α levels. Cr (+6) treated HaCaT cells also showed the induction of IL-1β and TNF-α via the p38 MAPK/MAPK-MK2 pathway [133]. K2Cr2O7 treated HK-2 cells showed a rise in the caspase-3 and PARP levels, indicating apoptosis induction. Moreover, a surge in BAX and cyt C was observed too. Induction of FasL and caspase-8 (cleaved) involved in extrinsic apoptosis pathway as well as caspase-independent apoptosis pathway (AIF) was seen in recent studies with K2Cr2O7 treatment [134]. K2Cr2O7 treated rat kidneys showed a rise in Bax levels and the levels of caspase-3 (cleaved). A decline occurred in the Bcl-2 levels. p53 was also induced indicative of apoptosis [135]. Cr exposure in *Sousa chinensis* led to depletion in the membrane potential of mitochondria. A decrease in the level of ATP and Cyt C release was seen. Caspase-9 activation and induction of p53 were observed, resulting in apoptosis [136] (represented in Table 1).

3. Bioactive natural products: hesperidin and hesperetin

3.1. Natural sources of hesperidin and hesperetin

The compound Hesperidin (HSD) is a flavonoid subclass called flavanone glycoside, found in citrus-type fruits. Hesperidin (HST) is its aglycone form. Initially isolated from the peel of Citrus, HSD is called a bioflavonoid, owing to its biological activity [137]. Separated initially from orange albedo by Lebreton in 1828, HSD is present in high amounts in Citrus reticulate and Citrus sinensis [138]. HSD presence has been demonstrated to be more in the membranes of citrus species and their albedo and pith compared to its presence in their juice or seeds.

Along with that, HSD has also been present in some species of Betulaceae, Papilionaceae, Fabaceae and Lamiaceae families [139]. Certain species of Zanthoxylum like Z.spruce have also shown HSD presence [140]. Hesperetin (HST) is another bioflavonoid extracted from citrus plants [141].

3.2. Structure and chemistry of hesperidin and hesperetin

HSD has an aglycone called HST (a methyl eriodictyol) bound to rutinose. It has a glycoside moiety made of glucose and rhamnose, a disaccharide. It is said to be present in two isomeric forms, rutinose and neohesperidose, and this neohesperidose is said to be present in citrus plants in the form of 7-O-neohesperidoside [142]. ChemicallyHST is a 3′, 5,7-trihydroxy-4-methoxyflavanone [143]. The molecular formula of HST is C16H14O6. On the other hand, HSD has C28H34O15 as its molecular formula and is a 3′,5,7-trihydroxy-4′-methoxyflavanone-7-rutinoside chemically. It is a β-7-rhamnoglucoside form of HST [144].

3.3. Pharmacological properties of hesperidin and hesperetin

Studies have shown that HSD administration has benefits in treating diabetes, cancer, cardiovascular diseases, Alzheimer's, and cutaneous conditions [145]. Recent studies have also demonstrated HSD has the potential of blocking coronavirus from entering into the cells of a host. Its anti-viral potential and its anti-inflammatory nature have been seen to control cytokine-storm upon COVID-19 occurrence [146]. HSD has shown glucose-lowering and ameliorative effects on dyslipidemia, atherosclerosis models, obesity prevention effects, and antioxidant and antihypertensive effects [147].

Hesperidin via the ERK/Nrf2 pathway causes an increase in the levels of antioxidants, thereby leading to a decrease in oxidative stress and lipid peroxidation resulting in the protection of cellular elements, DNA, proteins, and lipids; it brings down the levels of inflammatory markers which had been elevated due to heavy metal toxicity causing a downregulation in MAPK activation and ERK phosphorylation; the flavonoid showcases pro-apoptotic property by an increase in the activity of caspase-3, p53 and Bax while it exhibits anti-apoptotic property by increasing the levels of caspase-3 and caspase-9 and decreasing the levels of Bcl-2. Further, it had been seen that it protects the cardiacvascular tissue by altering the levels of markers such as MMP-9, MMP-2, PPAR-γ, TGF-β1, and TNF-R1 [41–44,147].

Hesperetin via the ERK/Nrf2 pathway causes an increase in the levels of HO-1, GSH, SOD, CAT, GPx, and downregulation of MDA, causing a reduction in the oxidative stress; it has a protective effect from inflammation by downregulating inflammatory markers such as COX-2, iNOS, CD45, TNF-α which had been elevated due to heavy metal toxicity; Hesperetin shows pro-apoptotic property by the upregulation of Bad and

Bax and downregulation of Bcl-2 and via NF-kβ inhibition leads to apoptosis. On the other hand, it counters the effect of neuronal apoptosis by an increase in Bcl-2, Bax and a decrease in the levels of caspase-3. Hesperetin exhibits protection against inflammation in the cardiac tissue via the inhibition of the NF-kβ pathway [40,41–44].

3.3.1. Antioxidant property

The antioxidant property of HSD has been observed as it counters oxidative stress by facilitating lipid peroxidation in brain cells of rats exposed to acrylonitrile [148]. Studies have shown both HSD and HST counter oxidative stress by enhancing the antioxidant cellular response by involving the ERK/Nrf2 pathway [137]. HSD has been found to play a significant protective role for DNA, proteins and lipids from damage induced by the generation of free radicals. Studies have shown HSD to cause a reduction in oxidative stress-induced hepatotoxicity by causing a decline in the oxidative stress induced by mercuric-chloride. Reduction in oxidative stress induced by LPS (Lipopolysaccharide) by HSD was also observed [149]. HST too counters oxidative stress and has been seen in studies, enhancing the antioxidant response via Nrf-2 and HO-1 (heme oxygenase-1) upregulation. Other studies have also shown HST causing a decline in levels of lipid peroxidation, TBARS (thiobarbituric acid reactive substances) and elevating levels of reduced glutathione (GSH) [150]. A study on rat brains under oxidative stress showed HST enhanced the levels of SOD (superoxide dismutase), CAT (catalase), GPx (glutathione peroxidase) and also caused a decline in MDA levels [151].

3.3.2. Anti-inflammatory property

The compound, HSD, has the property to cause a reduction in NF-kB, COX-2 and iNOS levels reported by many studies conducted in vivo or in vitro. Further, a reduction in NO and PGE2 (prostaglandin E2) levels upon HSD treatment was observed. Studies on rats have also shown HST metabolites causing a decline in levels of iNOS and COX-2 induced by LPS [151]. Other studies have also demonstrated HSD causing inhibition in the IkB phosphorylation NF-kB activation. Also, COX-2 elevation was seen to be decreased in colorectal tissues in the event of COX-2 upregulation induced DMH [47]. HSD-based study in mice models showed HSD causing a decline in levels of markers of inflammation, namely, TNF-α, IL-6, IL-1b, VCAM-1 expression induced by TNF-a and MCP-1 as well [152]. HSD treatment in HMC-1 cell lines caused inhibition of HIF-1α expression. Inhibition of IL-1b, TNF- α and IL-8 was observed, indicating a reduction in ERK phosphorylation and MAPK activation by HSD [144]. Another study on rat models upon HST induction saw a decline in CD45 and TNF- α and helped prevent colon damage [153].

3.3.3. Antidiabetic property

Reduction in the activity levels of carbonic anhydrase, as well as α-glycosidase in rat models, has been reported after treatment with HSD [154]. Another study on diabetic rat models showed that HSD treatment ameliorates the diminishing serum insulin levels and the impairment in the oral glucose level of tolerance. It also reduced the decreased glycogen content of the liver and the rise in the activities of glycogen phosphorylase and liver glucose-6-phosphatase. Elevated levels of serum ALT (alanine aminotransferase) and AST (aspartate aminotransferase) were ameliorated too by HSD [155]. In vitro study on HSD and HST and their antidiabetic potential inhibited the protein glycation non-enzymatic. The uptake of glucose was enhanced in L6 myotubes. L6 myotubes also showed upregulation of Akt, GLUT4 and IRS and downregulation of PI3K-activity, suggesting overlap with insulin pathway of signaling [156]. HSD has also been seen to alleviate the increase in glucose levels and a decline in serum insulin. A reduction in the levels of PPAR-γ in adipose tissue was also ameliorated by HSD supplementation [157,158]. A study on rats induced by streptozotocin upon HST treatment showed a decline in glucose levels in plasma. An improvement was also seen in insulin levels in plasma and glycogen levels. Restoration in the levels of carbohydrate metabolic enzymes was also seen [159].

3.3.4. Antiobesity property

The flavonoid, HSD, has been shown in studies regulating glucose and lipid metabolism by interacting with PPAR and AMPK signaling pathways. It has also been seen to cause a reduction in hepatic steatosis to inhibit the synthesis of cholesterol and its absorption. An increase in HDL-C (high-density lipoprotein-cholesterol) levels and decline in levels of LDL-C (low-density lipoprotein-cholesterol) in plasma and VLDL-C (very low-density lipoprotein-cholesterol) was observed too with HSD treatment [160]. HSD supplementation has been found in studies to regulate the levels of ALT and AST in serum. Serum levels of triglycerides and cholesterol were also decreased by HSD [161]. HST has also shown inhibitory actions on the accumulation of lipid as well [162].

3.3.5. Antihypertensive property

Supplementation with the flavonoid HSD has shown the property of vascular relaxation in studies rat models [163]. Recent studies have also demonstrated that HSD can reduce systolic blood pressure and pulse pressure in mildly hypertensive [164]. In spontaneously hypertensive rats, HSD caused a decrease in the heart rate. $P22^{phox}$ gene expression and $P47^{phox}$ were decreased, subunits and heterodimer of NADPH oxidase. HST also reduced the activity of NADPH oxidase in vascular endothelial cells. A decrease was also seen in TXA_2S action in the aorta countering hypertension [165]. Studies on rats showed HSD enhanced vasodilation, which is endothelium-dependent. The study also indicated that HSD enhances Kv channels' functions and thereby enhances the endothelium-dependent vasodilation in the event of hypertension [166].

3.3.6. Anticancer/proapoptotic property

HSD upregulates the accumulation of p53. Studies have shown HSD to promote proapoptotic actions through the involvement of pathways dependent and independent of PPARγ in NALM-6 cells [167]. A survey of lung cancer (non-small cell) and HSD showed a rise in the caspase-3 activity levels with HSD treatment [168]. HSD; treated MCF-7 cells have shown downregulation in the levels of Bcl-2 and upregulation in the levels of Bax. Upregulation has also been seen in miR-16 and miR-34a and downregulation in miR-21 levels [169]. Studies on endometrial cancer cells have shown that HSD promotes apoptosis by upregulating the activity of caspase-3 and a loss in mitochondria membrane potential. Also, there was an upregulation in Bax and Bik's expression and a Bcl-2 downregulation. ESRI (estrogen receptor I) was also downregulated by HSD treatment [170]. In colon cancer cells of humans, HSD downregulated Bcl-2 mRNA expression. Bax and caspase-3 levels were found to be upregulated [171]. The flavonoid HST has also been seen to downregulate Bcl-2 expression and upregulate BAD and Bax expression in prostate cancer cells. It has been found to induce apoptosis by NF-kB inhibition [172]. Treatment with HST in esophageal cancer cell lines showed an increase in cytochrome C expression levels in cytoplasm and caspase-3,9, Bax and Apaf-1 and a decrease in Bcl-2 surviving level indicating HST inducing apoptosis by an intrinsic pathway mediated by mitochondria [173].

3.3.7. Anti-apoptotic property

Studies have found that HSD prevents apoptosis by downregulating the caspase-3 and caspase-9 levels and upregulating Bcl-2 levels, thereby protecting human keratinocytes from damage by UVB radiation [174]. Another study on rat pancreas showed HSD upregulating Bcl-2 levels, inhibiting PARP activation and downregulating the Bax and caspase-3 levels, thereby preventing apoptosis [175]. HSD has also demonstrated a protective effect on RCG-5 cells by enhancing the downregulation of caspase-3,− 9. It was also found to restore mitochondria' loss of function and reverse the release of cytochrome c [176]. In HT22 cells, HST was found to decrease levels of caspase-3 as well as PARP-1, thereby conferring protection from apoptosis [177]. In another study, HST has been found to counter neuronal apoptosis by decreasing caspase-3 and Bax levels and p-jnk expression and upregulating Bcl-2 levels [178].

3.3.8. Cardiovascular disease prevention

The modulatory effect of HSD was observed on several cardiovascular risk points. It has shown atherosclerosis and obesity-preventing impact [47]. Another study on L-NAME rats showed HSD causing a suppression in levels of TGF-β1 and TNF-R1 and MMP-9 and MMP-2 expressions, thereby exhibiting cardioprotective ability [179]. A decrease in systolic and diastolic pressure was seen upon HSD treatment. A significant reduction in glucose levels was observed upon HSD treatment [180]. A rise in PPAR-γ levels was observed upon HSD treatment indicating its cardioprotective potential [181]. The compound HST has also been found to cause a decline in connective tissue GF (growth factor) and collagen I and collagen III expression the cardiac fibrosis markers. It also inhibited NF-kB activation, preventing cardiac inflammation [182] (represented in Figs. 1 and 2).

4. Hesperidin and heavy metal-induced toxicity: molecular mechanisms of mitigation

4.1. Hesperidin and heavy metal-induced neurotoxicity

In a study, it was observed that it led to oxidative stress when Cd was administered. A majority of the cell constituents are made up of lipids and proteins (as biomembranes). Therefore such oxidative stress resulted in the oxidation of these biomacromolecules because of an increase in ROS and free radicals [44]. The amount of oxidation inside the cell can be known by the level of LPO, the lipid forms that have been oxidized, and act as oxidative stress markers. Cd exposure could have been stimulated the superoxide anion production, which caused an elevation in the levels of LPO. Previous studies have indicated the involvement of heavy metals like Cd in the mechanisms leading to lipid peroxidation resulting in toxicity. It was observed that HSD acted against detrimental effects of oxidative stress induced by Cd and caused a reduction in the LPO levels, thereby increasing the activity of antioxidants such as GSH [183]. HSD, being an antioxidant, has been known to mitigate the oxidation effect on proteins induced by Cd. It has been observed that the amount of protein carbonyl level has been decreased in the brain of animals by introducing HSD [44].

The high affinity of Cd towards cellular thiol groups boosts its bonding with proteins such as metallothioneins (MT) and antioxidants such as GSH, with an increased toxic effect. When Cd is externally administered, it binds to GSH and MT in the liver, modifying the amino acid structure leading to alterations in the antioxidant, leaving it inactive, which disrupts the entire antioxidant system. This is because of the formation of a complex – mercapeptide, that is both non-reactive and in a thermodynamic stable state, which forms as a result of the interaction of Cd and the sulfhydryl (SH) groups that are present in the cysteine region of GSH; such groups have been known previously to chelate with metals. Such changes lead to depletion in the number of antioxidants, consequently causing a rise in oxidants such as hydrogen peroxide, superoxides and hydroxyl radicals. In the brain tissue, it has been observed that Cd exposure has disrupted the normal functioning of GSH; also other metabolizing enzymes such as GR and GST [44,184]. This flavonoid - HSD disrupts the mechanism of metal chelation between the sulfhydryl group and GSH, followed by the removal of free radicals and its antioxidant nature [185].

Neurotoxicity has been linked with the levels of a few biomarkers such as MAO, AChE and ATPase [44]. It has been reported in a study that in the brain of rats, due to the Cd toxicity by the generation of free radicals, the enzyme activity of acetylcholinesterase had been inhibited; leading to accumulation of the neurotransmitter acetylcholine, and resulting in convulsions, hyperactivity of choline and status epilepticus; disrupting learning and memory [183,186]. It has been observed that many natural antioxidants have had a protective effect against Cd toxicity. Similar to them, treatment with HSD had been seen to ameliorate the AChE inhibition in Cd neurotoxicity, indicating that HSD could be considered a potential therapeutic agent. Further, the examination of the brain tissue before and after HSD administration showed varied differences. Histopathological view with Cd exposure showed almost complete degeneration of neurons. On the other hand, administration of HSD to pre-treated rats with Cd showed partial degeneration

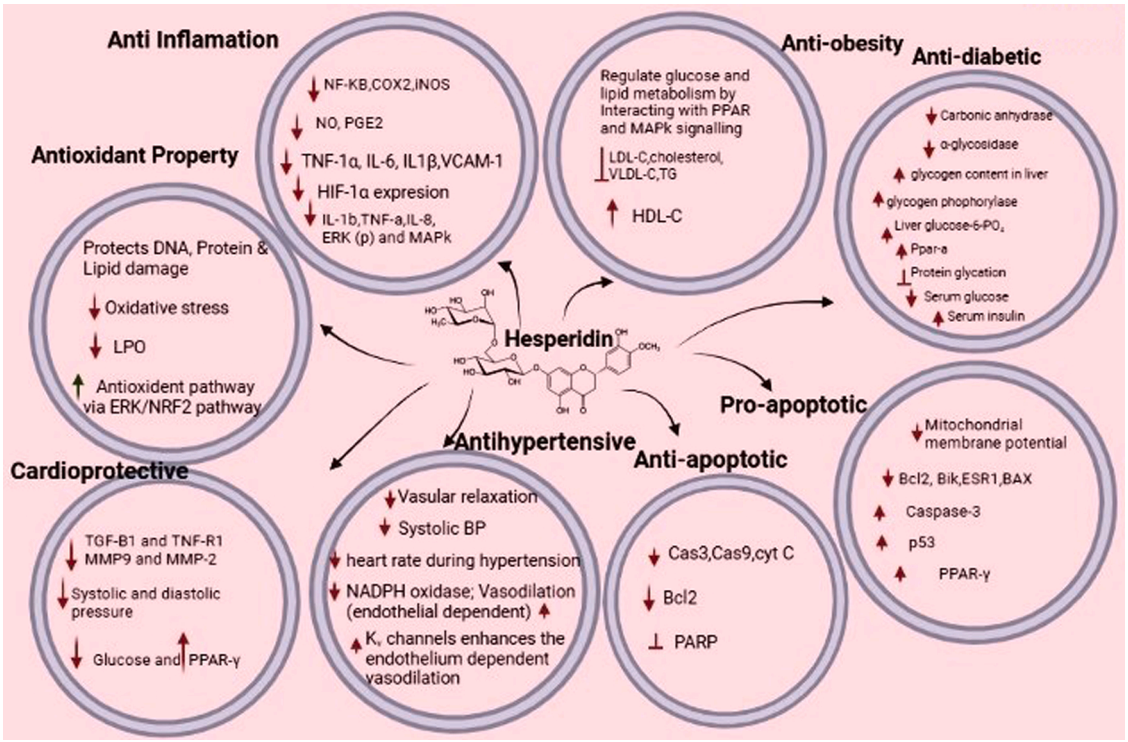

Fig. 1. The above Fig. 1 shows the mitigation effects and various properties of Hesperidin (HSD) including the antioxidant property, anti-inflammatory property, anti-obesity, anti-diabetic property, anti-hypertensive property, pro-apoptotic property, anti-apoptotic property, and cardiovascular protection.

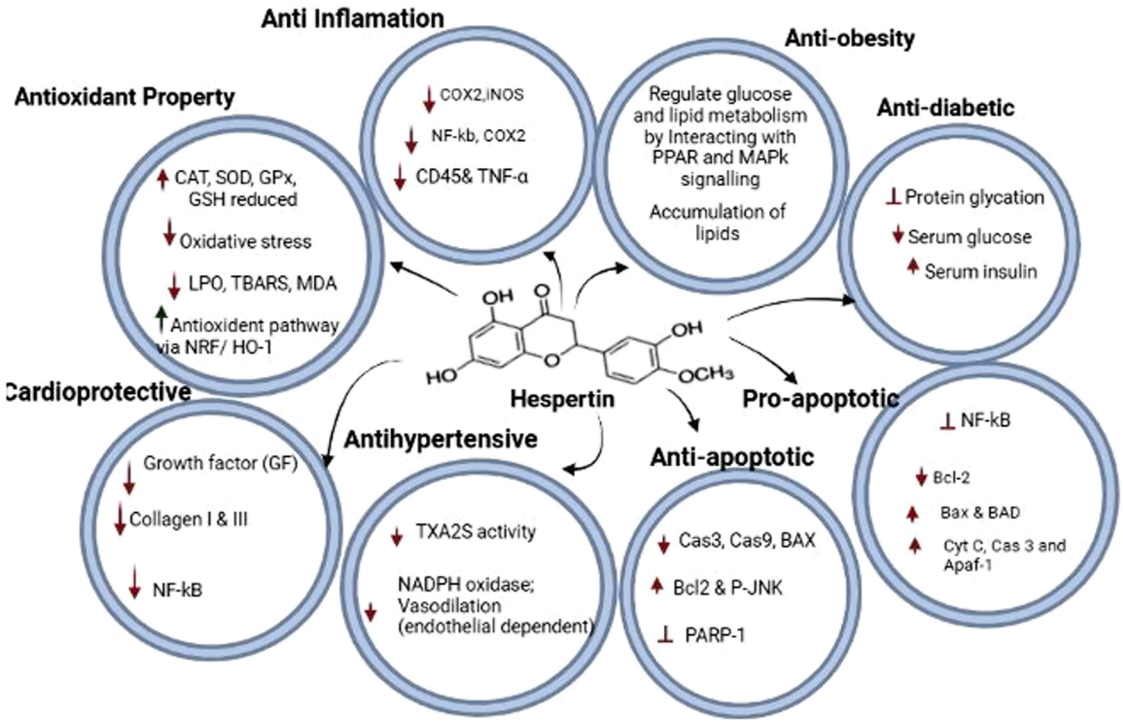

Fig. 2. The above Fig. 2 shows the mitigation effects and various properties of Hesperetin (HST) including the antioxidant property, anti-inflammatory property, anti-obesity, anti-diabetic property, anti-hypertensive property, pro-apoptotic property, anti-apoptotic property, and cardiovascular protection.

of neurons, suggestive of inhibition of neurotoxicity induced by Cd [44].

Cd exposure causes the inhibition of the enzyme ATPase. This enzyme includes a set of other enzymes such as Na+ /K+ - ATPase, which has been known for the production of energy and also for excitation of neurons, as well as Mg2 + ATPase, which has a vital role in the maintenance of Mg^{2+} levels in between the cells in the brain; the functioning of these two enzymes has been seen to be altered by metal toxicity [187]. This has been seen to occur due to the disintegration of membrane molecules and subsequent potential loss in the membrane because of lipid peroxidation; it also could be by the formation of Cd ATPase complexes via SH groups [188,189]. It has been seen that HSD was involved in preventing the Cd ATPase complex formation and possibly seen in the inhibition of lipid peroxidation [44].

The flavonoid HSD has been observed to have the ability to cross the blood-brain barrier, so do heavy metals like Cd, and hence all the damage caused by the metal such as oxidative stress, lipid peroxidation, alteration to the cell membrane integrity and subsequent membrane potential loss, thiol group conjugation – leading to neurotoxicity have been seen to be mitigated by HSD which shows the ability of HSD to serve as a therapeutic agent in Cd toxicity [44]. Another study on rats with the induction of Sodium arsenite and co-treatment with HSD showed similar results – HSD brought back the AChE activity to an average level and displayed a protective effect [190]. Further, an observation on the inflammatory markers – IL-1β, TNF- α, and Nf-κB revealed that the administration of sodium arsenite caused a rise in the markers in the brain tissue, and subsequent treatment with HSD caused the marker levels to reduce. This has been reported by inhibiting phosphorylation mechanisms of p38, ERK, JNK and IκB [144]. It protects from heavy metals-induced neurotoxicity (Fig. 3 and Table 2).

4.2. Hesperidin and heavy metal-induced hepatotoxicity

In a study on rats, sodium arsenite was administered, which showed an increase in the liver marker enzymes – AST and ALT. After histopathological examination, hepatic tissue was observed to have degenerated, followed by necrosis and increased blood in the hepatic vessels. After treating the rats in a dose-dependent manner with HSD, the amount of damage done due to sodium arsenite exposure was seen to be less severe, and the levels of serum enzymes AST and ALT had been brought down comparatively, showing the protective nature of HSD in the liver tissue [46].

Reports have shown that an increase in the level of p53 has been observed with exposure to arsenide by the inability of proteosomes to degrade the p53 protein. As a transcription factor, p53 has been regarded as involved with the enzyme thioredoxin reductase in modulating the DNA-binding activity. This enzyme was seen to be inhibited by arsenite. By the treatment with HSD, the level of p53 was seen to be decreased [46].

It had been reported previously that administration of sodium arsenite caused oxidative stress-induced damage to the DNA by the increase in the 8-OHdG level [191]. It was observed in a study that HSD was seen to have reduced the levels of 8-OHdG in the liver tissue [46] (represented in Fig. 3 and Table 2).

4.3. Hesperidin and heavy metal-induced nephrotoxicity

Researchers identified in a study on Sprague Dawley rats that on the administration of sodium arsenite, there was a rise in the marker levels – creatinine and urea, that serve as an indicator to know the extent of kidney damage. These findings were similar to those reports, which included administration of mercury chloride – elevation in the serum levels of the renal markers [192]. When this tissue was carefully examined, there was necrosis degeneration, and the tubules' epithelium was under hyperemia. Treatment with HSD mitigated the effect and lowered the damage caused due to sodium arsenite in the kidney [46].

Exposure to As_2O_3 disrupts the normal functioning of the mitochondria. It has been seen to cause the permeability transition pores to open, causing a shift in the potential maintained across the mitochondrial membrane and resulting in the release of cytochrome c release. The release of this cytochrome c causes the activation of caspase-3, which

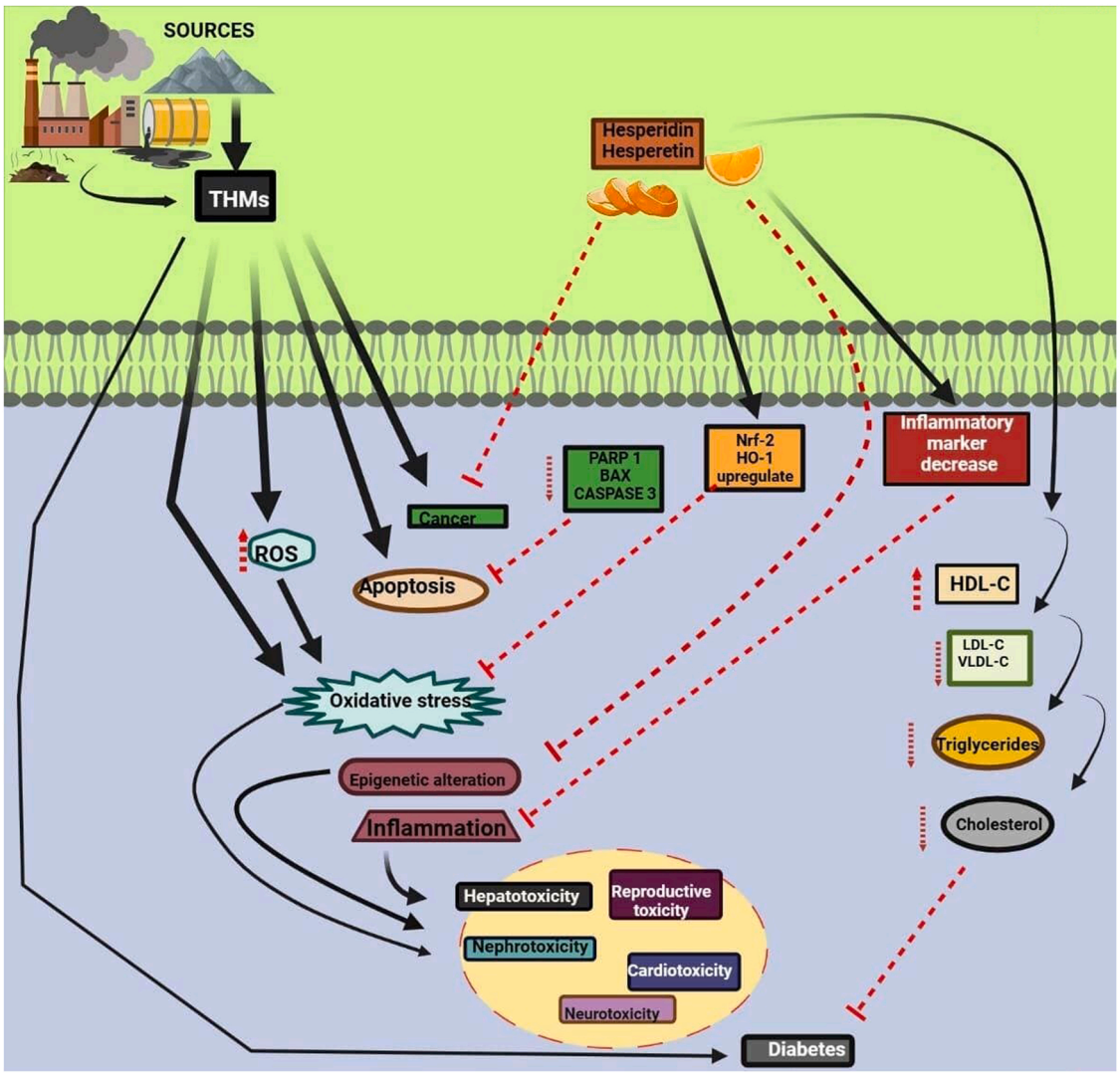

Fig. 3. Therapeutic effects of HSD and HST. Both Hesperidin and Hesperetin downregulate the mechanisms of apoptosis, oxidative stress, epigenetic alterations and inflammation. It protects from hepatotoxicity, reproductive toxicity, cardiotoxicity, nephrotoxicity, and neurotoxicity.

has been previously defined as one of the primary apoptosis markers, which activates the other caspases [193]. The activation of the caspase-3 enzyme causes condensation of chromatin in the nucleus, breakage of DNA and finally leading to cell apoptosis [194,195]. The expression of interleukin-6 was elevated due to the over-activity of caspase – 3 in the glomerulus region after As administration; on treatment with As+ HSD, mild expression was observed.

Further, HSD was seen to have decreased the activity of caspase-3 oxidized by ROS, which results in modifications to the nitrogenous base and breakage in DNA [196]. 8-OHdG has been oxidized by ROS, which alters the nitrogenous bases and breakage in DNA [197]. According to a report published previously, when sodium arsenite was administered to rats, the level of 8-OHdG was seen to be elevated and causing DNA damage in the kidney [191]. Dose-dependent treatment with HSD caused a reduction in the level of 8-OHdG. The same effect was observed in the case of diabetic nephropathy rats when HSD was introduced for treatment; 8-OHdG levels were reduced, and so was DNA oxidative damage [196,198]. It protects from heavy metals-induced nephrotoxicity (Fig. 3 and Table 2).

4.4. Hesperidin and heavy metal-induced cardiotoxicity

It has been observed that HSD increases the level of GSH and brings down the levels of MDA and 8-OHdG in case of co-treatment with sodium arsenite; it also elevates the levels of other antioxidants such as CAT, SOD and GPx and thus helps in the antioxidant defense mechanism and consequently the removal of As from the body. It has also been reported that HSD causes an elevated expression of Nrf2 and simultaneous degradation of Keap1 protein, which is also helpful in antioxidant production [145,190].

The extent of cardiac damage could be known by a change in the CK-MB, cTn-I and LDH marker levels which are considered as most reliable in assessing the amount of cardiotoxicity [199]. It was observed that in rat cardiac tissue, the level of these markers was increased after exposure to sodium arsenite. Histopathological findings were supportive of the same. It had been further supported with two previously reported results that sodium arsenite causes an increase in these cardiac markers [200–202]. The observed changes were interstitial & perivascular fibrosis, fibrosis of the muscle fiber and degeneration of the rat cardiac tissue [203].

Due to sodium arsenite exposure, oxidative stress has been induced in cardiomyocytes, and their membrane integrity was disrupted, leading to an increase in biomarker levels [204]. It was observed that HSD co-treatment showed to have a preventative damage effect in rats' heart tissue. The antioxidant property of HSD concerning the heart has already been established in previous studies [199].

Table 2
Mitigation effects of Hesperidin.

Organ	Animal	Metal	Effect on organ	Flavonoid co-treatment	Amelioration effect of flavonoid	Reference
Brain	Wistar rats	Cd	Oxidative stress,Increase in H_2O_2, LPO, lipid peroxidation, generation of free radicals, Inhibition of acetylcholinesterase	Hesperidin	Increase in the activity of GSHReduction in the level of protein carbonylDisruption in metal chelation mechanism,Prevention of formation of Cd-ATPase complex	[41]
	Sprague-Dawley male rats	Sodium arsenite	decrease in the activity of the antioxidant enzymes, Inhibition of AChE activity, the impaired learning function	Hesperidin	AChE activity to regular level,Curative effect on the cholinergic system	[193]
	Wistar rats	Sodium arsenite	A rise in inflammatory markers - IL1 β, TNF- α, and Nf-κB	Hesperidin	Decrease in the marker levels,inhibition of phosphorylation mechanisms of p38, ERK, JNK and IκB	[141]
Liver	Male Sprague Dawley rats	Sodium arsenite	Increase in AST, ALT, Degeneration of hepatic tissue, necrosisIncrease in 8-OHdG leading to oxidation	Hesperidin	AST & ALT levels are comparatively low, Damage less severe,Decrease in 8-OHdG level	[43]
Kidney	Sprague Dawley rats	Sodium arsenite	Rise in creatinine and urea, Necrosis, hyperemia and degeneration, Overexpression of Caspase-3, DNA damage due to rise in 8-OHdG levels	Hesperidin	Decrease in levels of creatinine and urea,Lowered the damage caused by sodium arsenite,Mild expression of caspase-3,Reduction in levels of 8-OHdG and oxidative damage to DNA	[43,196]
Heart	Sprague-Dawley male rats	Sodium arsenite	Disruption in the levels of the antioxidant system, Increase in the CK-MB, cTn-I and LDH cardiac marker levels,Disrupted membrane integrity, degeneration of cardiac tissue, increase in the levels of inflammatory markers	Hesperidin	Increases CAT, SOD, GPx& GSH, brings down MDA and 8-OHdG, the elevation of Nrf2, Prevents oxidative damage and cardiovascular problems and prevents inflammatory damage by decreasing the levels of TNF- α, Nf-κB& IL-1β.	[141,193, 203]
	Sprague-Dawley male rats	Sodium arsenite	Increase in caspase-3 levels & overexpression of Bax	Hesperidin	Caspase-3 and Bax levels reduced, regulation of apoptosis	[193]

For oxidative damage induced by As, HSD could be considered a potential therapeutic agent for protecting cardiac tissue and further for cardiovascular-related issues [200,205]. The other property of HSD, the anti-inflammatory property, has been reported wherein the levels of inflammatory markers – TNF- α, Nf-κB & IL-1β were regulated back to normal levels from an increased level [144].

Another study showed that due to As exposure in rats, caspase-3 levels were increased, due to which there was an overexpression of Bax in the heart tissue. And with the co-treatment of HSD, both the levels of Bax and caspase-3 were observed to be reduced compared to only the sodium arsenite-treated group. Therefore, HSD has a regulatory effect on cell apoptosis by altering the expression of caspase-3 and Bax [190]. It protects from heavy metals-induced cardiotoxicity (Fig. 3 and Table 2).

4.5. Hesperidin and heavy metal-induced reproductive toxicity

The ameliorative role of HSD was observed in the event of toxicity in the male reproductive system of rats. Due to heavy metal toxicity, the oxidant-antioxidant system is altered – an increase in the levels of frees radicals & testicular MDA levels and a decrease in the CAT and SOD levels. Moreover, serum testosterone, sperm motility, and the count were reduced. At the same time, there was a rise in the level of abnormal morphology of sperm, histopathological alterations were observed in the testis and DNA fragmentation in the sperm nucleus. After the administration of G-HSD, the levels of the antioxidant system reverted to standard conditions by the exhibition of anti-oxidative property, thereby protecting the testis [206] (represented in Fig. 3) (represented in Table 2).

5. Hesperetin and heavy metal-induced toxicity: molecular mechanisms of mitigation

5.1. Hesperetin and heavy metal-induced neurotoxicity

The compound HST has been shown to alleviate the defense mechanism of an antioxidant system that had been disrupted due to Cd toxicity. It was observed in a study that this flavonoid increased the inhibition process of the ATP enzymes and others such as AChE, thereby reducing the neurotoxic effects of Cd in the brain of Wistar rats. [44, 207] Similar observations were noted when Pb treated rats were administered with hesperetin – the betterment of the antioxidant system, the first line of defense (increase in the levels of SOD, CAT and GPx) [208–210]. It protects from heavy metals-induced neurotoxicity (represented in Table 3).

5.2. Hesperetin and heavy metal-induced hepatotoxicity

Due to heavy metal toxicity, the disturbances that occur to the redox mechanisms cause oxidation by ROS generation. The liver is mostly the primary organ affected, resulting in various modifications happening at the cellular and molecular level [10]. It has been reported previously that the liver counteracts Pb toxicity by causing an increase in transaminase activity [211]. Many scientists working on Pb hepatotoxicity have mentioned the elevated levels of AST and ALT. By treating rat models using Hesperetin, it came to be known that it offered protection against Pb poisoning after observing that AST and ALT levels were reduced [10].

Apart from this, the anti-lipoperoxidation property in hesperetin has also been reported wherein it lowered the levels of hepatic marker enzymes (AST, ALT, ALP, LDH, GGT and bilirubin), reduces the levels of antioxidants (SOD, CAT, GSH, GPx, GST, GR, G6PD) [212]. At the same time, other heavy metals, such as Cd, were utilized to induce hepatotoxicity [213]. These results indicate that hesperetin may be considered successful in managing the damage caused due to metals such as Pb& Cd by the process of cell membrane stabilization [10].

It has been previously reported that the increased levels of Lipoprotein cause damage to the liver by oxidation [214]. A rise in the level of MDA and depletion in the level of GSH has been reported in a study where Pb was induced to rat liver to cause toxicity; explained as a result of oxidative stress as a result of high-affinity binding of Pb to metal cofactors or SH groups present in enzymes of antioxidants. When treated with hesperetin, the levels of both the markers were reversed – MDA level decreased, and GSH level increased, owing to that it might lessen oxidative stress and might lead to a rise in the level of antioxidants (GPx, CAT and SOD) which act as the major defense system against oxidation. According to the results published in this particular study, hesperetin treatment has been quite effective in facilitating the antioxidant system's enzymatic actions and the removal of free radicals [10]. It protects

Table 3
Mitigation effects of Hesperetin.

Organ	Animal	Metal	Effect on organ	Flavonoid co-treatment	Amelioration effect of flavonoid	Reference
Brain	Wistar rats	Cd	Inhibition of AChE and ATP enzymes	Hesperetin	Inhibition of AChE with Cd, reduction of neurotoxicity	[135]
	female Wistar albino rats	Pb	Disruption to the antioxidant system	Hesperetin	Increase in the levels of antioxidants SOD, CAT, GPx	[190]
Liver	male Sprague-Dawley rats	Lead acetate	Oxidation by a generation of ROS, Elevated level of AST and ALT, Rise in MDA and depletion in GSH.	Hesperetin	Reduction in levels of AST & ALT, MDA decreased & GSH increased along with an increase in CAT, SOD and GPx.	[215]
	Wistar rats	Cd	Increase in the levels of hepatic marker enzymes - AST, ALT, ALP, LDH, GGT and bilirubin Lower the levels of SOD, CAT, GSH, GPx, GST, GR, G6PD	Hesperetin	Antilipoperoxidative and Protective effect by bringing back the levels of marker enzymes and antioxidants to normal levels	[218]
Kidney	Male albino Wistar rats	Cd	Decreased renal markers, antioxidants and LPO	Hesperetin	Normal regulation of serum and urine urea, uric acid, creatinine levels,Increase in activity of antioxidant enzymes	[221]

from heavy metals-induced hepatotoxicity (represented in Table 3).

5.3. Hesperetin and heavy metal-induced nephrotoxicity

It had been previously reported that urea and creatinine levels were utilized as markers of the normal functioning of the renal organ. Induction of renal toxicity by Pb in rats showed an alteration of uric acid, creatinine and urea. Elevation in these markers directly affects the high production of the oxygen species by the body. Another study indicated a link between the failure of the renal organ and an increase in the serum creatinine level. Treatment with HST has been seen to put back the serum levels of the renal markers, protecting the kidney from further damage [10].

Oxidative stress-induced by Pb alters the levels of antioxidant markers in the kidney, especially SOD, GSH, MDA, CAT and GPx – affinity towards cysteine present in SH groups. Administration of HST increased the levels of SOD, CAT, GSH & GPx while, on the other hand, causing a decrease in the levels of MDA. Thus, a reduction in oxidative stress in the nephritic cells has been observed protecting against ROS [10]. In another study, it was observed that hesperetin displayed protective mechanisms against nephrotoxicity by Cd in rats. It was seen that the depleted urine & renal markers (urine, urea and uric acid levels), antioxidant levels and LPO marker levels were elevated and brought back to nearly normal levels when the flavonoid was administered in various doses [207,215] (represented in Table 3).

5.4. Hesperetin and heavy metal-induced cardiotoxicity

In cardiomyocytes, HST has been reported to show anti-oxidative properties by elevating the levels of SOD, GSH and CAT and diminishing MDA levels in cardiomyocytes. In the case of pro-inflammation, HST caused a reduction in the levels of IL-6 and TNF-α upon treatment. Further, HST mediated the depletion of apoptosis by the upregulation of Caspase-3 and Bax while, on the other hand causing Bcl-2 down-regulation [216].

5.5. Hesperetin and heavy metal-induced reproductive toxicity

The toxic effect of Cd have been associated with the induction of oxidative stress in the testis of rats – reduction in the activities of GSH, GR, G6PD and an increase in the free radicals; occurs due to the chelating metal property of Cd and its binding to sulfhydryl groups causing damage to macromolecules such as DNA, proteins and other vital enzymes by the generation of ROS. This histopathological alteration leads to testicular steroidogenic disorders and reduction in mechanisms leading to spermatogenesis. Depletion in GSH levels leads to reduced motility in sperms due to mid-piece instability of the sperms. Further, it causes a reduction in the activity of ATPases. Cd toxicity, therefore, may lead to male infertility. The administration of HST caused an increase in the levels of the antioxidants, thereby causing a reduction in oxidative stress. The activity of ATPases was seen to be restored after treatment with HST. Besides exhibiting antioxidant and metal-chelating properties, HST has been observed to have anti-lipoperoxidation properties, owing to the restoration of membrane-bound ATPases in the rat testis [189]. In a study, HST has been reported to have restored the motility of sperms [217].

6. Hesperidin and hesperetin protects heavy metals induced oxidative stress and inflammation

A study conducted on heavy metals toxicity in rats found that TNF-α, NF-κB, and iNOS increased. It also altered the insulin, SOD, GPx, GSH and CAT levels – reducing them, while an increase in the levels of MDA was observed along with a rise in the activities of amylase and serum lipase. After treatment with HSD, the amylase and lipase activities markedly decreased, and there was an increase in the antioxidants and insulin. The pro-inflammatory marker levels were also seen to be reduced. Therefore, HSD plays a crucial part in protecting the pancreas because of its pro-inflammatory response and anti-oxidative property [41]. Dyslipidemia mitigation by HSD was reported in cd exposed rats. It decreases cholesterol LDL and increases the level of HDL and triglyceride [218]. It was observed that the HST has protective effects against other toxicities such as inflammation. Hesperidin can attenuate nitric oxide, inducible nitric oxide production, cyclooxygenase-2, prostaglandin E2 in the LPS mediated macrophages (RAW 264.7) or cells of smooth muscle (A7r5). Along with that, it decreases the inflammatory pathways activities such as NF-κB, κB inhibitor (I-κB), p38 MAPKs and c-Jun N-terminal kinase1/2 (JNK1/2) [219]. HSD and HST are highly involved in protecting against heavy metals-induced toxicity (represented in Fig. 4).

7. Conclusion

This work presents a review on the mechanistic role of HSD and HST in modulating toxicity mechanisms of the most dangerous heavy metals, Pb, Cd, Hg, As, Ni and Cr. Exposure to these THMs occurs through various unavoidable means and materials, including foods and drinking water. The metals accumulate in tissues and penetrate cells to incite ROS generation. The toxicity mechanisms of THMs are chiefly oxidative stress, pro-inflammation and apoptosis, which provoke DNA damage, ER stress, dysregulation of signaling proteins and pathogenesis of diseases. It is noteworthy that findings from interesting studies over decades show that HSD and HST could exert preventive effects and therapeutic strategies against toxic and pathological injuries of THMs. However, further research is required to critically evaluate and understand the exact mechanistic actions involved in the therapeutic efficacy of the same

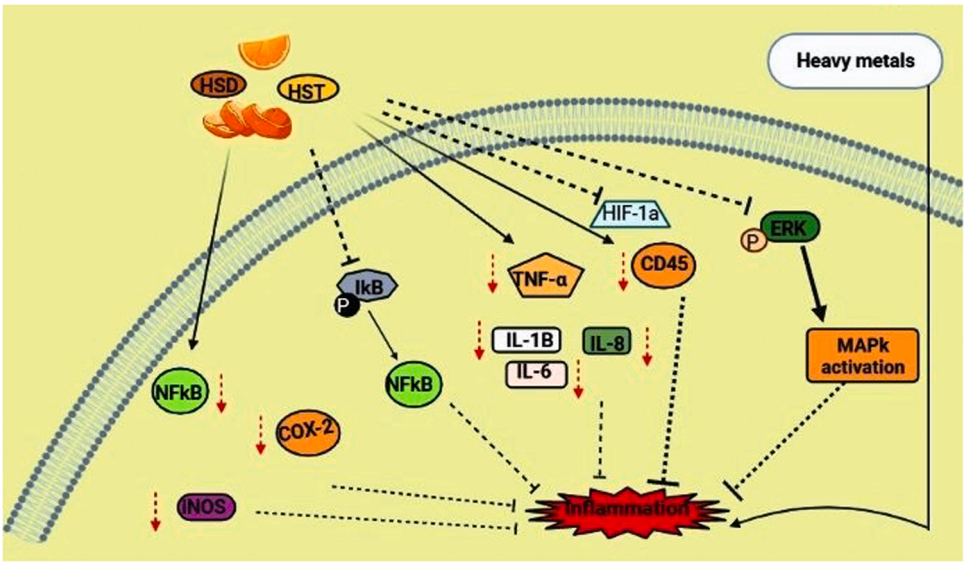

Fig. 4. Hesperidin and Hesperetin curb inflammation by the downregulation of NF-kB, COX-2, iNOS, CD-45 markers and interleukins. Further, also downregulates the MAPK pathway by inhibiting the activation of ERK.

which would help the scientific community design novel treatment strategies to tackle heavy metal toxicity.

Knowledge gap

The knowledge gap we identified when we were writing this article. Some of them are.

1. The HSD and HST protect from heavy metals toxicity via activating different antioxidant systems. Some of the molecular mechanistic pathways behind it are determined, such as the Nrf2 pathway. But need to establish more pathways related to the redox mechanism.
2. In the case of hepatotoxicity and nephrotoxicity, only the biomarkers such as ALT, AST, creatinine have been determined, but its mechanism needs to be checked thoroughly.
3. In the case of cardiotoxicity, there are pathways involved in inflammation apoptosis; a redox mechanism has been established. There are many pathways related to adrenergic signaling, and metabolism needs to be determined in the future.
4. In the case of reproductive toxicity, only sperm DNA damage and toxicity protection have been determined. We need to establish a complete mechanism behind it in the future.
5. In the case of neurotoxicity, some pathways are established like JNK, but there are so many mechanisms behind neuro diseases. This would give an excellent way for the readers to work in the future with HSD and HSP.

Future perspectives

HSD and HST act as a future expectation of medicine for many diseases. HSD and HST have equal prominence with the other flavonoids used for therapeutic activities. It is fascinating that various flavonoids act against different toxicity induced by heavy metals. In our review, we have given the role of HSD and HST working against other toxicity caused by the heavy metals. Robust experimental evidence uncovers that HSD and HST originating from citrus fruits depend on suppressing ROS formation and its detoxification and deactivation of transcription factors NF-κB to downregulate oxidative stress and pro-inflammation. The suppression of inflammatory NF-κB/MAPK pathway and activation of antioxidant Nrf2/HO-1 by HSD and HST consequently inhibits mitochondrial-dependent apoptosis and expression of ER stress modulators in toxicity of THMs. Therefore, the antioxidant anti-inflammatory and anti-apoptotic mechanisms of HSD and HST will be able to provoke clinical trials for possible mitigation of toxicity of heavy metals and poisoning. The main point of this work is to develop the drug.

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CRediT authorship contribution statement

Ademola C. Famurewa: Writing – original draft preparation, Conceptualization, Writing – review & editing. **Kaviyarasi Renu**: Writing – original draft preparation, Writing – review & editing. **Mohamed Ahmed Eladl**: Writing – original draft preparation and reviewing. **Rituraj Chakraborty**: Writing – original draft preparation, **Haritha Myakala**: – Writing – original draft preparation; **Dalia Mahmoud Abdelmonem Elsherbini**: Writing – original draft preparation and reviewing, **Mohamed El-Sherbiny**: Writing – original draft preparation and reviewing, **Balachandar Vellingiri**: Writing – review & editing, **Harishkumar Madhyastha**: Writing – review & editing, **Uddesh Ramesh Wanjari**: Writing – original draft preparation, **Anirban Goutam Mukherjee**: Writing – original draft preparation,**Valsala Gopalakrishnan Abilash**: Conceptualization, Supervision, Reviewing and Editing.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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