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REVIEW ARTICLE

Toxicity of Mercury and Its Compounds: Impacts on Human and Animal Health, Ecosystems, Mechanisms, and Bioremediation Strategies – A Systematic Review

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Abstract

Mercury is a pervasive, environmentally toxic global pollutant that significantly impacts ecosystems and human health. Its chemical and toxicological properties contribute to environmental contamination through natural processes like volcanic eruptions and human activities such as industrial emissions and agriculture. Over the past century, mercury levels in the environment have nearly doubled due to rapid industrialization, leading to bioaccumulation and biomagnification in food chains, especially in aquatic ecosystems, which significantly impact human food safety.

This review examines mercury's toxic effects on multiple organ systems through acute and chronic pathways. Mercury induces neurotoxicity, nephrotoxicity, immune dysfunction, cardiovascular damage, and endocrine disruption, including cancer promotion in both humans and animals. Mercury compounds and mercury-containing xenobiotics interfere with cellular and molecular mechanisms, leading to oxidative stress, DNA damage, mitochondrial damage, apoptosis, epigenetic alterations, and impaired signaling pathways.

The review also highlights mercury's environmental persistence, affecting biodiversity by impairing various species' growth, reproduction, and survival, from microorganisms to higher vertebrates and invertebrates. It explores mercury's broader ecological footprint, including its role in disrupting food web dynamics, soil health, and plant productivity, ultimately impacting global biodiversity and ecosystem stability. The potential for mercury-induced bioaccumulation in aquatic life is emphasized, highlighting its cascading effects on human food safety. Addressing these challenges, the review discusses advances in remediation strategies, such as chelation therapy, natural antioxidants of phytochemical origin, and innovative biotechnological interventions. By incorporating documented research findings, this review aims to inspire future research and policymaking to mitigate mercury's adverse health effects and ensure environmental sustainability.

Review Highlights:

· Mercury is a toxic pollutant harming ecosystems and human health globally.

· It bioaccumulates in food chains, impacting food safety and biodiversity.

· Mercury causes neuro, nephro, hepato, cardio, and endocrine toxicity, harming organs.

· It disrupts DNA, mitochondria, and cell signaling, leading to severe toxicity.

· Advances in remediation include chelation, antioxidants, and biotech solutions.
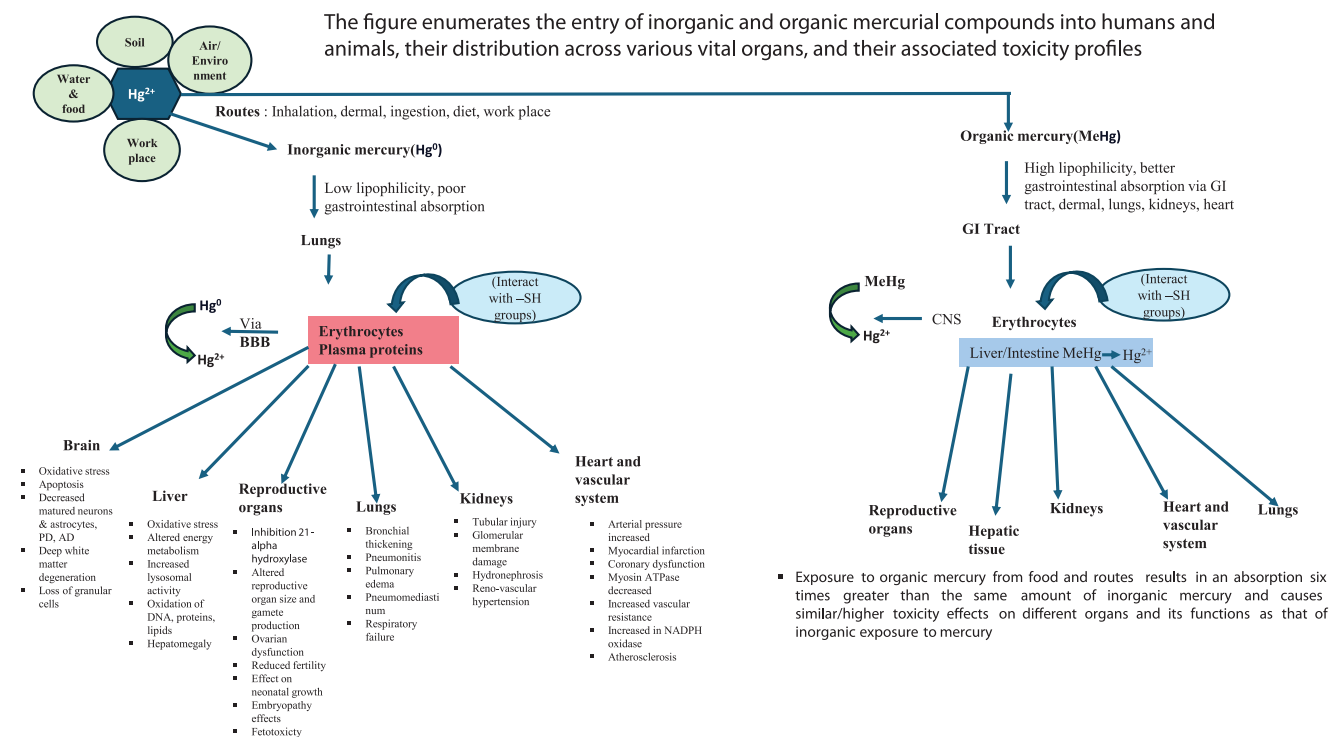
Keywords

- ➤ Mercury toxicity
- ➤ Environmental pollution
- ➤ Bioaccumulation
- ➤ Biomagnification
- ➤ Toxic effects
- ➤ Organ dysfunction
- ➤ Remediation strategies

Scan Me

TOPICS: TOXICOLOGY ● PUBLIC HEALTH ● INTERNAL MEDICINE

The figure enumerates the entry of inorganic and organic mercurial compounds into humans and animals, their distribution across various vital organs, and their associated toxicity profiles

Graphical Abstract

Introduction

Heavy metals (metals and metalloids) are defined as metallic elements of relatively higher density as compared to water and are major pollutants in the environment (also known as xenobiotic metals), metal toxicity is both acute (shorter period) and chronic (long period) exposure (maybe months or years) lead to health disorders like other chemical and gaseous environmental pollutants [1,2]. Among metals, mercury has a unique feature and physical properties that confer its specific toxicological effects via metal accumulation in different tissues and organs known to interact with accumulated mercury [3](Figure 1b).

The possible clinical symptoms of mercury both organic and inorganic compounds poisoning reported are: headache, disequilibrium, incoordination (gait impairment), tremors muscle weakness "pins and needles" feelings usually in hands, feet, and around the mouth, atypical movements, paresthesia in the distal part of extremities, impairment of speech, hearing, walking, hallucination, seizures, disruption of attention, fine motor function and verbal memory and death [4].

Hence, mercury contamination is a serious public health and environmental problem. In the USA, the EPA (Environmental Protection Agency) and the Agency for Toxic Substances and Disease Registry (ATSDR) top 20 hazardous substances in their priority list in 2001. Among these toxic substances are As, Pb, and Hg in the 1st, 2nd, and 3rd positions, respectively, and Cd in the 7th place. Hence, As, Pb, Hg, and Cd metals are considered the most hazardous substances found on the surface of the earth and are toxic to humans, animals, and the environment [5]. During the past 150 years, human activities (increased industrialization) have almost doubled the natural amount of mercury in the environment (soil, water, and air), constituting a grave threat to human health and the ecosystem [6] .Mercury exposure can occur via inhalation of inorganic metallic mercury, ingestion of inorganic complexed mercury compounds, ingestion of organic forms of mercury, or dermal contact [1,7,8]. Further, mercury bioaccumulation occurs especially in aquatic organisms as they take MeHg from water/ingest prey containing MeHg. Such a process leads to higher concentrations of Hg in marine organisms at higher trophic levels due to biomagnification [9].

The major sources of heavy metals, including mercury, in the environment are

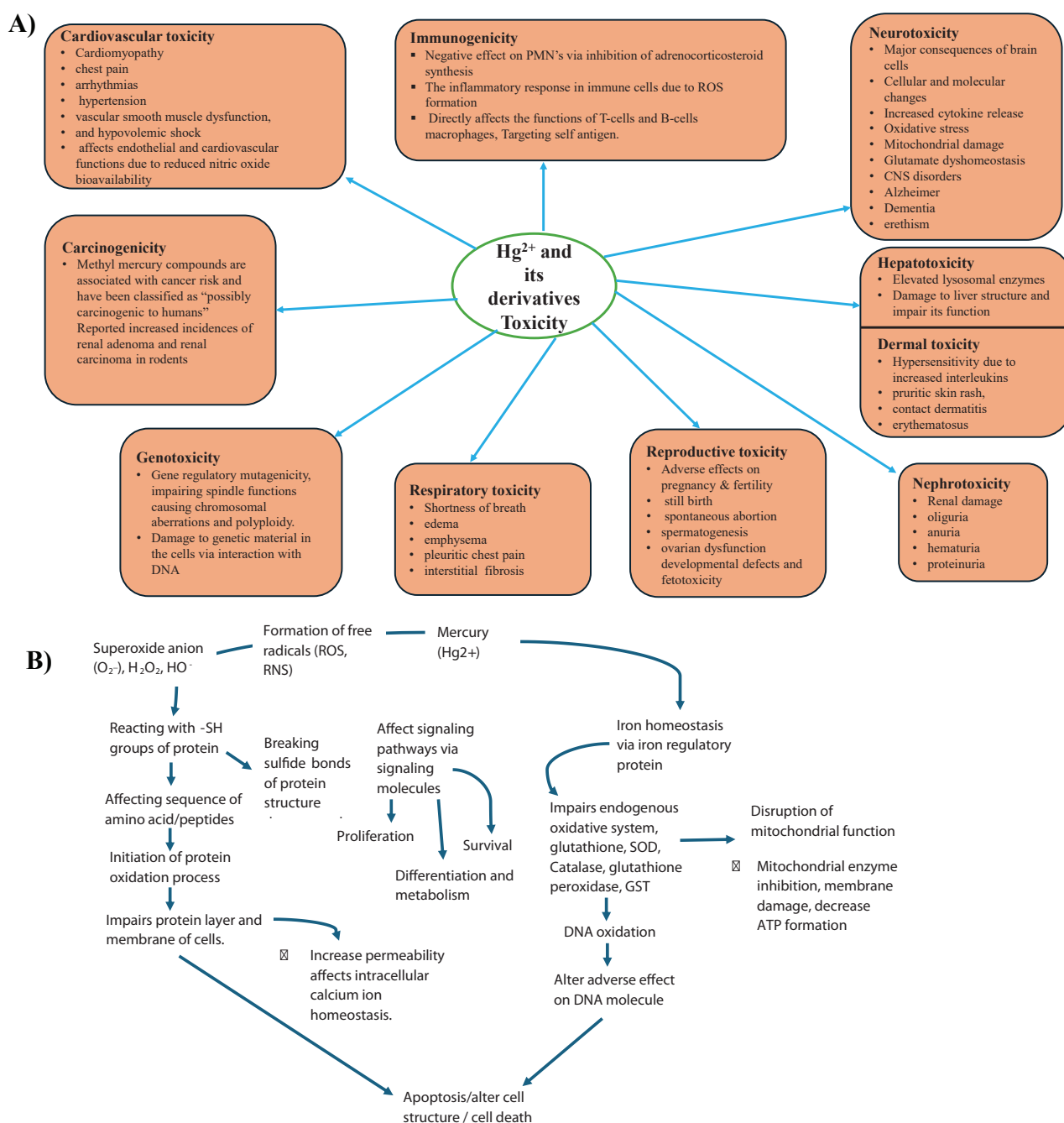a) Natural catastrophic events such as

A)

Cardiovascular toxicity
- Cardiomyopathy
- chest pain
- arrhythmias
- hypertension
- vascular smooth muscle dysfunction, and hypovolemic shock
- affects endothelial and cardiovascular functions due to reduced nitric oxide bioavailability

Immunogenicity
- Negative effect on PMN's via inhibition of adrenocorticosteroid synthesis
- The inflammatory response in immune cells due to ROS formation
- Directly affects the functions of T-cells and B-cells macrophages, Targeting self antigen.

Neurotoxicity
- Major consequences of brain cells
- Cellular and molecular changes
- Increased cytokine release
- Oxidative stress
- Mitochondrial damage
- Glutamate dyshomeostasis
- CNS disorders
- Alzheimer
- Dementia
- erethism

Carcinogenicity
- Methyl mercury compounds are associated with cancer risk and have been classified as "possibly carcinogenic to humans"
Reported increased incidences of renal adenoma and renal carcinoma in rodents

Hg²⁺ and its derivatives Toxicity

Hepatotoxicity
- Elevated lysosomal enzymes
- Damage to liver structure and impair its function

Dermal toxicity
- Hypersensitivity due to increased interleukins
- pruritic skin rash,
- contact dermatitis
- erythematosus

Genotoxicity
- Gene regulatory mutagenicity, impairing spindle functions causing chromosomal aberrations and polyploidy.
- Damage to genetic material in the cells via interaction with DNA

Respiratory toxicity
- Shortness of breath
- edema
- emphysema
- pleuritic chest pain
- interstitial fibrosis

Reproductive toxicity
- Adverse effects on pregnancy & fertility
- still birth
- spontaneous abortion
- spermatogenesis
- ovarian dysfunction developmental defects and fetotoxicity

Nephrotoxicity
- Renal damage
- oliguria
- anuria
- hematuria
- proteinuria

B)

Formation of free radicals (ROS, RNS) — Mercury (Hg2+)

Superoxide anion (O_2-), H_2O_2, HO·

Reacting with -SH groups of protein → Affecting sequence of amino acid/peptides → Initiation of protein oxidation process → Impairs protein layer and membrane of cells. → Increase permeability affects intracellular calcium ion homeostasis.

Breaking sulfide bonds of protein structure

Affect signaling pathways via signaling molecules → Proliferation / Survival / Differentiation and metabolism

Iron homeostasis via iron regulatory protein → Impairs endogenous oxidative system, glutathione, SOD, Catalase, glutathione peroxidase, GST → DNA oxidation → Alter adverse effect on DNA molecule

Disruption of mitochondrial function
- Mitochondrial enzyme inhibition, membrane damage, decrease ATP formation

Apoptosis/alter cell structure / cell death

Figure 1 (a) Effects of mercury on different organ systems, cellular and biochemical alterations, and organ dysfunction. (b) Illustrates the toxic effects of mercury and the underlying cellular and molecular mechanisms associated with oxidative stress.

biomagnification, volcanic eruptions, atmospheric depositions, and metal evaporations from water resources to soil and groundwater have also contributed significantly (biogeochemical cycle of mercury movement and transformation via various environmental compartments) [10].

b) Metal processing in refineries, coal burning in power plants, and petroleum combustion led to further complex environmental pollution and also increased massive exposure to humans and animals [1].

c) Industrial (coal combustion and industrial processes) and agricultural activities, drugs, and pharmaceuticals, including radioisotopes and nanoparticles, Indigenous medicines,

magico-ritualistic practices, domestic effluents, and atmospheric sources [11]. EPA rules indicate the maximum allowable level limit of mercury in water is 2 ppm, and the safe dose of mercury in food is 0.1 µg/kg of body weight [12]. A maximum inhalation concentration is 0.3 µg/m3 for atmospheric Hg0 is acceptable [13]. The acceptable level of mercury in the soil is 720 ppm with a safety factor of 10, the limit would be reduced to 72 ppm [14] (Table 1).

Mercury's chemical and physical state determines its pharmacokinetics and biotransformation pattern. Acute and especially chronic toxicological studies of metallic elemental mercury and its compounds, both organic and inorganic, are known to elicit effects on different body organs such as the gastrointestinal tract, renal system, central nervous system, hematopoietic, hepatic, cardiovascular, respiratory, immune, and reproductive systems, including cancer promotion [15-17] (Figure 1a) Toxic mercury especially (methyl mercury) is recorded to be a significant threat to marine wildlife (both inside and outside) of the oceans particularly dolphins, whales, seals, and predatory fish (tuna and swordfish)[18-20]. The reproductive problems in birds suffering from mercury poisoning have also been documented. The isolated adverse effects of mercury in avians and mammals are hepatic, renal damage, and neurobehavioral alterations [21].

The present review deals with the toxic/adverse effects of mercury and its environmental pollutants (both organic and inorganic) on human and animal health and briefly refers to its effects on other ecosystems. It also discusses the manifestation of clinical symptoms and adverse toxic effects on different organ systems, and physiological functions with an underlying profile of mechanisms both at cellular and molecular levels, which are assessed with the help of advanced analytical methods and state-of-the-art techniques. The review also elucidates mercury toxicity to human health in detail, covering neurotoxicity, nephrotoxicity, cardiac toxicity, respiratory disorders, immune toxicity, adverse effects on endocrine organs, pregnancy and reproductive system, ecosystem, and cancer promotion. Furthermore, it includes different remedial approaches to mitigate the adverse effects of mercury strategies to overcome mercury toxicity using the new generation chelating agents, and probable therapeutic interventions from natural product origins based on the toxicity mechanisms of Hg. Finally, to provide future perspectives by updating the compendium of mercury toxicity that may be useful for further research and development, and consultation reference sources from documented studies.

The Effect of Mercurial Compounds and Mercury-Contaminated Xenobiotics on Various Organs and their Functions, along with the Clinical Symptoms and Underlying Mechanisms of Action, has been Explained Under Different Sections Below

Nephrotoxicity

Mercurial compounds are absorbed through inhalation, ingestion, or dermal exposure and transported via the bloodstream to the kidneys. Mercury accumulates in the proximal tubular epithelial cells due to active uptake by Organic Anion Transporters (OATs) and metallothionein [23].

Table 1: Major sources of mercury pollution in the environment.

Natural sources	Industrial activities	Industrial products	Diet/food/medicines
Anthropogenic sources, weathering and volcanic eruption release from oceans, earth crust volcanoes, forest fires, evaporation from natural bodies, atmospheric deposition, principal earth reservoir of mercury comprises of atmosphere, terrestrial ecosystems, and aquatic compartments, sunlight, radiation	Fossil fuels, burning of coal-fired power plants, boilers in industries, petroleum combustion, heavy metal pollution, mining, and precious metal extraction, Chloro-alkali process, industries: steel and cement plants, plastic, paper, and pulp industries, incinerations of medical waste and electronic waste	Fungicides, pesticides, batteries, thermometers and barometers, dental amalgam, disinfectants, paints, fluorescent bulbs, switches, and medical devices.	Rice, seafood, grains, vegetables, vegetable oils, wine, skin creams, herbal medicines, herbal tea, high fructose syrup, vaccines

Accumulated mercurial compounds exert their effects on organelles and cellular components, namely mitochondria, nuclei, lysosomes, cell membranes, enzymes, and other biomolecules such as amino acids, peptides, proteins, and dissolved organic matter [24]. Mercury, like other heavy metals, interacts with the proteins and DNA, thereby inhibiting protein synthesis, disrupting and inhibiting enzymatic activity, and nucleic acid functions, impairing DNA repairs, and altering DNA stability [25]. It also induces Protein Phosphatase 2A (PP2A), which enhances the formation of Reactive Oxygen Species (ROS), leading to oxidative stress and irreversible inhibition of thioredoxin reductase, (a selenoenzyme) which is known to play a role in redox regulation, protein expression, selenium metabolism and restore vitamin C and vitamin E, including the increased membrane permeability [26,27]. In biological pathways, Hg affects both oxidation and reduction processes, eliciting its speciation and affecting its biological uptake. Furthermore, mercury is known to alter cellular homeostasis, Nuclear factor Kappa-light chain enhancer activation (NF-kB) driving inflammatory responses, activation of tumor protein (p53) and c-Jun N-terminal kinases (JNK) pathways (JNK also known as Stress-Activated Protein Kinase (SAPK) (all leading to apoptosis[28]. Mercuric ion Hg^{2+} has the greatest affinity for binding thiol groups that lead to activation of NF-kB, which results in the release of cytokines (e.g. IL-6, TNF-α) and is thus responsible for the manifestation of chronic inflammation, exacerbation of renal damage and fibrosis[28,29]. Furthermore, DNA binding at extremely low concentrations of Hg in renal tissues induces damage to the cytoskeleton structure, and tight junctions compromise epithelial integrity. These effects are mainly observed in proximal tubule cells with segments affecting primarily S2 and S3 [30,31]. In addition, mercury exposure has been shown to alter stress-responsive genes, such as those encoding metallothioneins and heat proteins, which are involved in the regulation of endogenous defense mechanisms [32]. It has also been reported that Hg alters gene expression by modifying DNA methylation and histone acetylation [33].

Kidney dysfunction following exposure to mercury inhalation in humans manifests in the form of proteinuria, increased blood urea and plasma creatinine, decreased alkaline and acid phosphatase, glutathione-S-transferase, increased thiobarbituric acid reactive substances thereby clearly indicating increased free radicals formation mainly due to accumulations of high levels of mercury compounds in kidney tissues accompanied by proximal tubular and glomerular changes [31,34]. Clinical studies in humans have reported that plasma mercury is
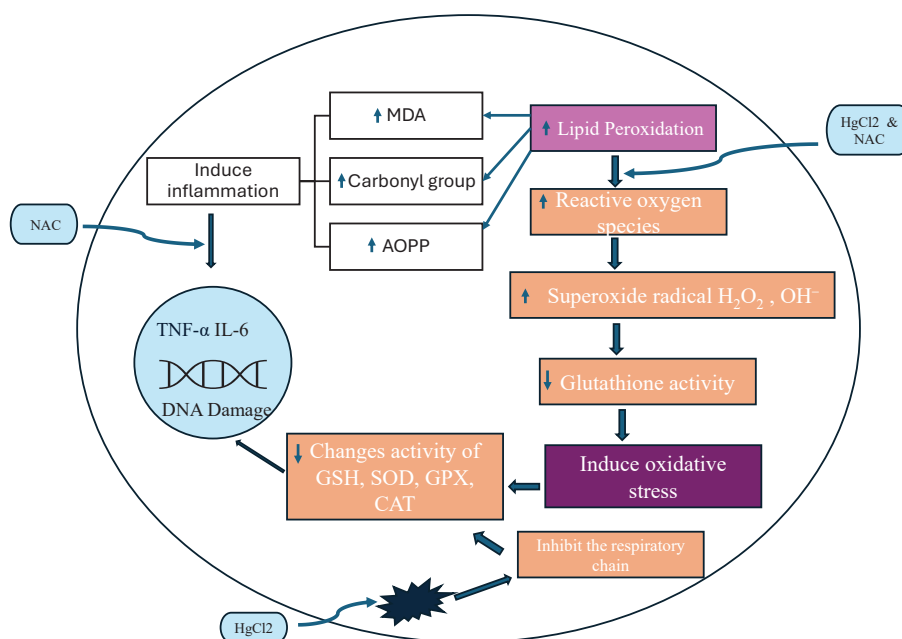

Figure 2 Mercury toxicity leads to a cascade of reactions at the cellular and molecular levels. The various changes are explained and correlated to renal damage and function.

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a reliable biomarker after acute and high-level exposure. In contrast, the urine mercury level is a dependable biomarker in chronic exposure to both elemental and inorganic mercury, and also an indicator of the body's burden of mercury [35]. A person died following acute poisoning of alkyl Hg, revealing necrosis of the tubule epithelium, swollen granular protoplasm, and non-stainable nuclei in the kidneys [36,37]. Glomerular kidney functions are also altered in humans who are exposed to u-Hg or Hg0, and the same has been confirmed by urine levels of creatinine and alpha-1-microglobulin, and Gamma-Glutamyl Transferase (GGT) in the luminal brush border of the proximal tubule [31]. In addition, chronic exposure of persons at occupation is known to cause kidney damage and glomerular proteinuria, assessed by excretion of albumin, IgG, and transferrin in urine [38]. However, recent developments in proteomics profiling have emerged as a major detection tool that has facilitated tracing of the early targets of Hg in kidney structural damage and can be a novel biomarker in nephrotoxicity studies [39].

In mice, orally administered MeHg is excreted in the urine largely as the conjugate of cysteine (Cys-MeHg). Among the most predictive, reliable biomarkers, bismethylmercury sulphide (MeHg-S) and Cys-MeHg are the most critical parameters for detecting impaired kidney functional status before their irreversible damage [40,41]. In addition, determining the urinary enzyme, Gamma-Glutamyl Transferase (GGT) in the luminal brush border of the proximal tubule is also considered an important biomarker in predicting kidney damage [42]. Experimental research studies in animals indicate that nephrotoxicity and cell death progression are the reflection of the release of intracellular enzymes, namely, Lactic Acid Dehydrogenase (LDH), N-acetyl-beta-D-Glucose-amidase (NDG), and are subsequently excreted in the urine [43]. Furthermore, alpha-1, beta-2 microglobulin, and Retinol-Binding Protein (RBP) are also found to be reliable biomarkers of tubular dysfunction [44]. Animal experimental studies also indicated that Kidney Injury Molecule-1 (KIM-1) is closely associated with nephrotoxicity [45]. Studies in rodents showed dose-dependent renal damage, including tubular necrosis, glomerular injury, and interstitial inflammation, which agrees with clinical reports of renal system damage in humans exposed to Hg2+[46].

Mercury chloride (HgCl2), a hazardous, stable industrial toxin enters the body through various routes mentioned earlier and via circulation accumulates in renal and hepatic tissues and is bio-transformed into toxic metabolites and induces biochemical, cellular alterations, and generates oxidative stress that brings out conformational and cytoskeletal structural changes in kidney cells [47]. Also, known to elicit membrane nephropathy, histologically tubular necrosis, interstitial nephritis, vacuolation, onset of nephritic syndrome, secondary focal segmental glomerulosclerosis, syncretistic nephrotic syndrome, and membrane glomerulonephritis [48]. As described earlier, the characteristic property of mercury binding to the sulfhydryl group (mainly GSH) forms a glutathione mercury complex, which leads to oxidative stress. This is evidenced by the depletion of endogenous antioxidants, viz. GGT, GSH-reductases, reduced GSH, Catalase (CAT), Glutathione-S-Transferase (GST), and upregulation of expression of KIM-1 mRNA (by many folds), largely due to mercury accumulation in tubules and glomeruli of kidneys (Table 2). Furthermore, mercury chloride renal damage initiates (ERK ½) extracellular signal transducer, which in turn activates Signal Transducers and Activator of Transcription-3 (STAT-3) (Figure 3). Subsequently, interacts with the (KIM-1) Kidney Injury Molecule-1 promoter and induces the elevation of mRNA and protein levels as demonstrated by the histopathology and immunohistochemistry techniques [49]. HgCl2 treatment is known to produce renal damage through abnormal autophagy pathway: a) promoting apoptosis via excessive degradation of cellular components by worsening tissue injury b) accumulation of damaged organelles and proteins, contributing to fibrosis and inflammation, and correlated to oxidative stresss [50,51], c)HgCl2 activates the mechanistic Target of Rapamycin(mTOR) pathway, which negatively regulate autophagy [52].

Some of the documented studies suggest that exposure to nephron toxicants (mercurial compounds from the environment) to individuals with compromised renal functions (due to aging, disease, or a combination of aging and disorders) are particularly more susceptible and may be detrimental to these elderly and aged individuals [34,54]. Mercury impairs mitochondrial respiration by inhibiting electron transport chain complexes, decreasing ATP production, and causing energy deficits in renal cells. Mitochondrial damage triggers intrinsic apoptosis pathways [55]. It is now established by multiple studies that suggest that exposure of individuals

Table 2: Renal toxicity studies of short-term and long-term mercury compound exposure in Rats and mice [Table content adopted from (Francis Y, et al. [53]]).

| Animal species	Duration of study	NOAEL mg/kg/day	LOAEL mg/kg/day	Physio-pathological and pharmacological effects
Rat	3-12 weeks	None	0.84	Fibrosis, inflammation
	12 weeks	None	0.08	Cytoplasmic masses in proximal tubules
	2 years	0.02	0.01	Increased renal weight, decreased renal enzymes
	0-21 days of age	None	1.0	Altered renal function and renal hypertrophy
	2 years	None	0.4	Nephrosis
Mouse	26 weeks	0.15	0.6	Degeneration of proximal tubules
	-	0.03(Males) 0.13(Females)	0.14(Males) 0.6(Females)	-
	once	8 Males 24 females	16(Males) 32(Females)	Decreased phenolsulfonapthalein excretion Increased serum creatinine, swollen tubular epithelium
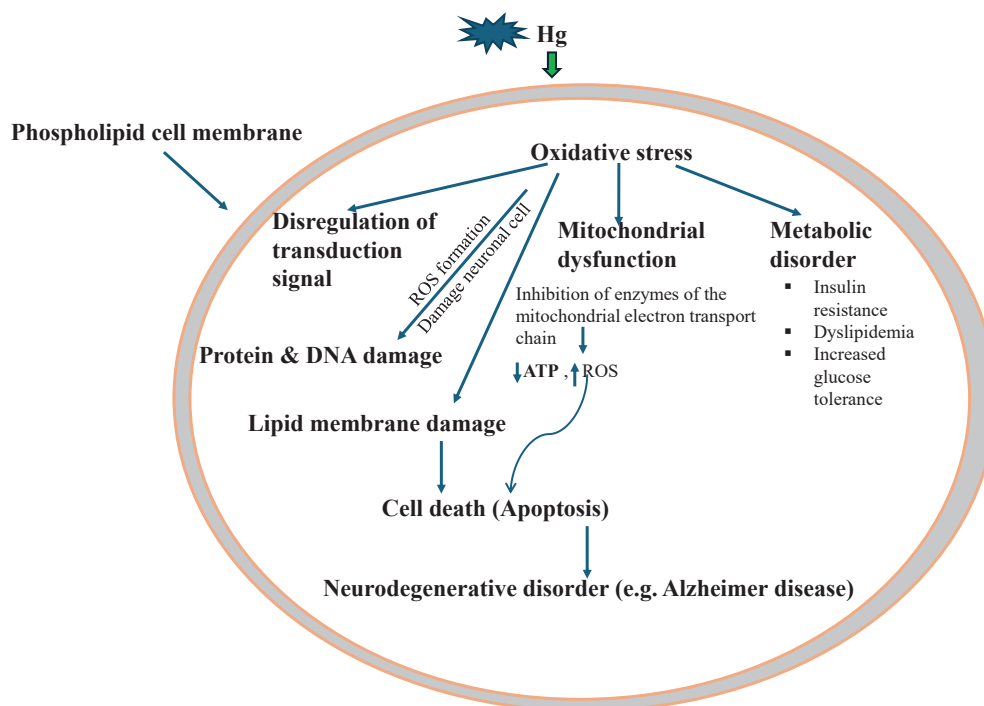
Figure 3 The figure describes chronic mercury exposure that results in a generation of oxidative stress that ultimately leads to numerous cellular and biochemical alterations, leading to neurodegenerative disorders.

with compromised renal function, whether due to aging or disease, or combined effects of both, makes them particularly susceptible to the toxic effects of mercurial xenobiotics. Even animal studies also confirmed that the kidneys of aged rats (characterized by reduced renal mass) are more prone to the adverse impacts of mercury compounds/other mercurial xenobiotics [46,56].

Neurotoxicity

The neurotoxic effects associated with the exposure of mercury vapors, MeHg, EtHg, and mercurial xenobiotics are a well-documented public health concern, affecting both humans and animals [57]. These effects primarily arise from the ability of mercury species to cross the Blood–Brain Barrier

(BBB) and interfere with the central and peripheral nervous system [58]. Inhalation of mercury vapor causes severe neurotoxic effects mainly due to high lipid solubility and penetration into the BBB [59]. Long-term exposure to mercury vapors causes mercurialism, and some of its deposition elicits effects on CNS exhibiting a wide variety of clinical symptoms related to delayed motor skill development and coordination, behavioral disorders such as autism-like symptoms, hyperactivity, anxiety, tremors, irritability, neuromuscular effects, impaired cognitive functions including reduced IQ and learning abilities and many more. These effects are associated with multifactorial biological processes, like oxidative stress, neuroinflammation, and disruption of synaptic and neuronal signaling pathways [60-62]. The most important and critical effect of mercury on the nervous system is interference with the production of energy, which adversely affects the cellular detoxification process, leading to the death of a cell or survival in a state of chronic malnutrition [57]. The mercury compounds are known to interact with the electrophilic and nucleophilic residues of proteins (e.g., Sulfahydryl groups and Selenol), which are critical factors for disruption of redox homeostasis that causes the formation of ROS, leading to lipid peroxidation and neuronal apoptosis [63-65]. Mercury inhibits enzymes in the mitochondrial electron transport chain, decreasing ATP synthesis, increasing ROS levels, impairing calcium homeostasis in neurons, signaling pathways essential for cell survival and synaptic activity [66-68]. Such complex biochemical alterations adversely affect neurotransmitter systems, including glutamate, GABA, dopamine, serotonin, and acetylcholine pathways [69,70]. Astrocytes are the major site for MeHg accumulation and thus, inhibit cystine transport (sulfhydryl-containing amino acid), severely impair the redox status, and lead to depletion of glutathione levels. Such biochemical and cellular alterations inhibit astrocytic glutamate, including aspartate uptake, and enhanced efflux effects, which result in the elevation of glutamate and aspartate levels in extracellular fluid [71]. Accumulated glutamate leads to excitotoxicity, characterized by activation of NMDA and AMPA receptors, increased intracellular calcium, and neuronal damage [71-74]. Reduced GABA levels impair inhibitory neurotransmission, exacerbating excitotoxic damage and contributing to conditions like epilepsy or anxiety disorders [75]. Thus, it appears astrocytic predisposition is also a major factor in MeHg-induced neurological disorders [76].

The available documented toxicity profile points out that methyl mercury exposure to brain cells induces neurotoxicity which is reflected in physiological, cellular, and molecular alterations along with cytokines release, oxidative stress, impaired mitochondrial function, calcium and glutamate dyshomeostasis, and ultimately manifest apoptosis [77,78]. Mercury exposure activates microglia, leading to chronic neuroinflammation, which exacerbates neuronal damage [79]. Some researchers have demonstrated that methyl mercury upregulates both phospholipase-D and phospholipase-A2, which trigger the release of arachidonic acid, which ultimately inhibits glutamate transporter, thereby facilitating an uninterrupted cytotoxic cycle [80-83].

The promotion of oxidative stress, as well as systemic inflammation and potentially influencing brain function in MeHg-induced neurotoxicity, has been confirmed unequivocally both in animal and human research studies with evidence of depletion of the antioxidant defense system and neuroinflammation [84,85]. The disruption of redox due to the formation of Reactive Species (ROS), leading to the inhibition of endogenous antioxidant defence mechanisms, results in cumulative oxidative stress [86]. Endogenous antioxidant molecules such as reduced Glutathione (GSH), Oxidized Glutathione (GSSG), Thioredoxin Reductase (TrxRs), Glutathione Peroxidase (GPx), glutathione reductase (GR), and nuclear factor erythroid 2 related factor (Nrf2) are established major endogenous factors and involved in the maintenance of redox balance in the CNS due to the high energy demand of brain tissues[84,87]. Among these molecules, GSH mainly acts as a ROS scavenger in an endogenous environment, thus minimizing the availability of MeHg for interaction with other biomolecules [88]. Dietary supplements such as selenium, cysteine, special proteins, fibrous foods, antioxidant vitamins, and phytochemicals are also reported to ameliorate oxidative stress and enhance the excretion of mercury in urine[89]. Thus, documented research findings show that co-exposure to antioxidants such as GSH, DHA, and Se is are strong confounder, and their interactions with MeHg may significantly modify cellular oxidative status. Also reported treatment with trolex, a soluble analog of vitamin E, acts as a scavenger of free radicals and chelation of MeHg, thereby significantly elevating antioxidants such as GSH and mitochondrial enzymes [90]. In an experimental rat model, trolex treatment reduced neurobehavioral

deficits, oxidative stress biomarkers, and lipid peroxidation in the brain following chronic MeHg exposure. Human clinical studies reported that trolex co-administration during pregnancy reduced fetal neurotoxicity and oxidative damage caused by maternal MeHg exposure, mainly through diet (fish). Thus, different types of antioxidants can be an effective complementary treatment approach to the existing therapies, particularly in reducing CNS damage and amelioration oxidative stress. A well-designed experimental study in animals, with MeHg treatment, induced the depletion of intracellular antioxidants [91,92] inhibition of antioxidant enzymes[93−95] modulation of activity of transporters, neurotransmitters, and neuro-modulatory receptors' activity[96−98]. In addition, experimental studies in animals also established that low levels of MeHg exposure modify gene expression and induce long-lasting cell cycling signaling (specifically glutamate signaling), which has been explained earlier [99].

The very recent observations suggest that neurotoxicity in the CNS is largely due to increased activity of microglia and astrocytes, leading to chronic inflammation and release of cytokines (e.g., IL-6, TNF-α) that contribute to neuronal injury. With such experimental findings, authors have emphasized the need for extensive research to evaluate low levels of MeHg exposure on the activation of immune cells in CNS and neuronal differentiation, and their effects on the toxicity of neurodevelopmental aspects such as autism and others [99-101]. A glaringly reported clinical case suggests that chronically exposed workers showed mutational changes in the TBK-1 gene linked to ALS, providing (indicating a possible link between mercury exposure and neurodegenerative diseases [102]. Using animal models, authors provided preliminary information on the potential effects of early-developmental exposure to MeHg on the functional status by conducting exploratory activity and swimming ability at one month of age and immune effects after one year of age. Findings suggest delayed neurotoxicity may be due to increased functional impairment with aging, thus, the health-related risks associated with early MeHg exposure could last a lifetime [103,104]. Thus, mercury and mercury containing xenobiotics as critical neurotoxic agents with wide-reaching impacts on human and animal health.

Cardiovascular toxicity

Mercurial compounds, including Methyl mercury (MeHg) and inorganic mercury (Hg2+), can induce cardiovascular toxicity through several mechanisms. Accumulation of MeHg, Hg2+ in cardiac tissue, and very high mercury levels lead to death due to idiopathic dilation of cardiomyopathy [105]. The symptoms of cardiovascular toxicity of mercury poisoning reported are hypertension, chest pain, angina, arrhythmia, myocardial infarction, and atherosclerosis. Such clinical symptoms are directly correlated to mercury concentrations in blood and hair [106,107].

Acute inorganic mercury exposure in vivo promotes a decrease in myocardial force development and depletion of ATPase activity, increased vascular resistance, and hypertension, leading to coronary heart diseases and myocardial infarction [108]. Mercury oxidizes Low-Density Lipoprotein (LDL), and LDL particles are closely related to the genesis of atherosclerosis, thereby increasing the risk of stroke, acute coronary insufficiency, and myocardial infarction [109]. The underlying mechanism(s) of cardiotoxicity of mercury are attributed to the inhibition or inactivation of the enzyme, paraoxonase, which acts endogenously as a controller or reducer of the LDL oxidation process and is known as an endogenous anti-atherosclerotic biomolecule [110]. Chronic mercury exposure enhances ROS production (free radicals) due to the Fenton reaction, leading to lipid peroxidation and inhibition of endogenous antioxidants (glutathione peroxidase, selenol) [36]. Glutathione peroxidase is a selenium-dependent enzyme, and mercury adversely affects selenium levels. The principal antioxidant enzymes, catalase and superoxide dismutase, are also reduced due to increased ROS formation by mercury intoxication. Such physiological changes increase the risk of developing hypertension, coronary heart disease, myocardial infarction, and cardiac arrhythmia, promoting a decrease in myocardial force development, carotid intima-media thickness, and carotid artery obstruction [111].

Exposure to low concentrations of mercury shown to induce dysfunction of endothelial function and conductance of vessels by impairing nitric oxide (NO) bioavailability which enhances the formation of scavengers like superoxide anion production from NADPH oxidase, which is involved in the expression of SOD-2, NOX-1, and NOX-4 (two major isoforms of NADPH oxidase), results in vasoconstriction,

increased vascular resistance and hypertension [112,113]. Chronic exposure to mercurial compounds enhances free radical formation, leading to lipid peroxidation, DNA damage, and endothelial dysfunction (described earlier). The impact of such vascular oxidative stress damages vascular smooth muscle cells and compromises vascular integrity [114,115].

Mercury interacts with mitochondrial enzymes, leading to ROS overproduction, creating a vicious cycle of oxidative stress and facilitating MAPK-mediated cellular damage. Inhibition of antioxidant enzymes increases reliance on MAPK pathways to manage stress, which becomes detrimental when overactivated[88]. Mercury disrupts intracellular calcium signaling, which is tightly connected to MAPK activation, exacerbating cardiomyocyte dysfunction and arrhythmias [116-118].

Furthermore, mercury exposure can activate phospholipase-D through phospholipase-A2 and lipid oxygenase via oxidative stress and alterations in thiol redox induce COX formation and LOX-derived eicosanoids disrupt endothelial homeostasis [119,120]. Mercury also alters the functions of the renin-angiotensin system via the activation of Angiotensin-Converting Enzyme (ACE), leading to renal hypertension [121].

In animal experiments, parental administration of HgCl2 elicits cardiac diastolic failure and pulmonary hypertension. Experimental findings demonstrated that low doses of mercury chloride exposure to rats produced increased heart rate, blood pressure, and vascular reactivity to catechol amines, and these effects have been correlated with the increased formation of free radicals [122]. Long-time exposure produces structural changes in the arterial walls and myocardial fibrosis in rodents [123,124]. Chronic exposure for 30 days at low concentration of mercury in animals induces a negative inotropic effect which is explained based on atherosclerosis and calcium handling mechanisms, associated with protein expressions of Sarcoendoplasmic Reticulum Calcium ATPase (SERCA), sodium- potassium ATPase (NKA) and sodium-calcium ion (NCX) channel disruption and reduction in beta-adrenergic stimulation [125]. Mercurial compounds exposure to rodents induces hyperhidrosis, tachycardia, and ptyalism (hypersalivation), and such adverse effects have been attributed to the inhibition of catecholamine metabolism due to the reduction of S-adenosyl methionine levels, leading to the accumulation of epinephrine [126].

Prenatal exposure to mercury leads to developmental cardiovascular defects in offspring and highlights teratogenic risks [127]. Mercury disrupts mitochondrial respiration by binding to thiol groups in mitochondrial proteins, impairing ATP production and exacerbating energy deficits in cardiac tissues [128]. Thus, mechanistic insight from both human and animal studies suggests that chronic exposure to low doses of mercury produces toxic effects on the cardiovascular system and heart tissues through multiple mechanisms [16]. The other effects on the inflammatory pathways of mercury are the activation of inflammatory cytokines (IL-6, TNF-α) and CRP that can promote atherosclerosis, thrombosis, and myocardial injury. Thus, it has been established beyond doubt in both human and animal studies that mercury exposure is a major risk factor for developing hypertension, myocardial infarction, coronary dysfunction, and atherosclerosis [126] (Figure 4).

Effect on the reproductive and endocrine system of mercury and mercurial salts

The endocrine system is one of three major integrating and regulating systems in the human body. The important endocrine glands are the hypothalamus, pituitary, thyroid, adrenal gland, pancreas, and gonads (ovary and testis) [129]. In Laboratory animal studies, however, mercury was found to elicit a series of impairments of all endocrine glands in a variety of animal models [130]. The endocrine-disrupting effects of mercury have recently become increasingly important public problems.

Mercury exposure (acute, subacute, or chronic) induced pathophysiological alterations by disrupting the hypothalamic-pituitary-adrenal and hypothalamic-gonadal axis, which in turn adversely impacts reproductive functions. These disruptions interfere mainly with circulating hormones, such as FSH and LH, further impacting steroids (estrogens and progesterone androgens). Mercury primarily affects adrenal function and hormone production by inhibiting 21-alpha hydroxylase and also impacts reproductive organs, including gonad size, and gamete production [131,132]. Mercury exposure negatively impacts quality, including alterations in sperm parameters such as sperm DNA and abnormal sperm morphology. Suppression of testosterone
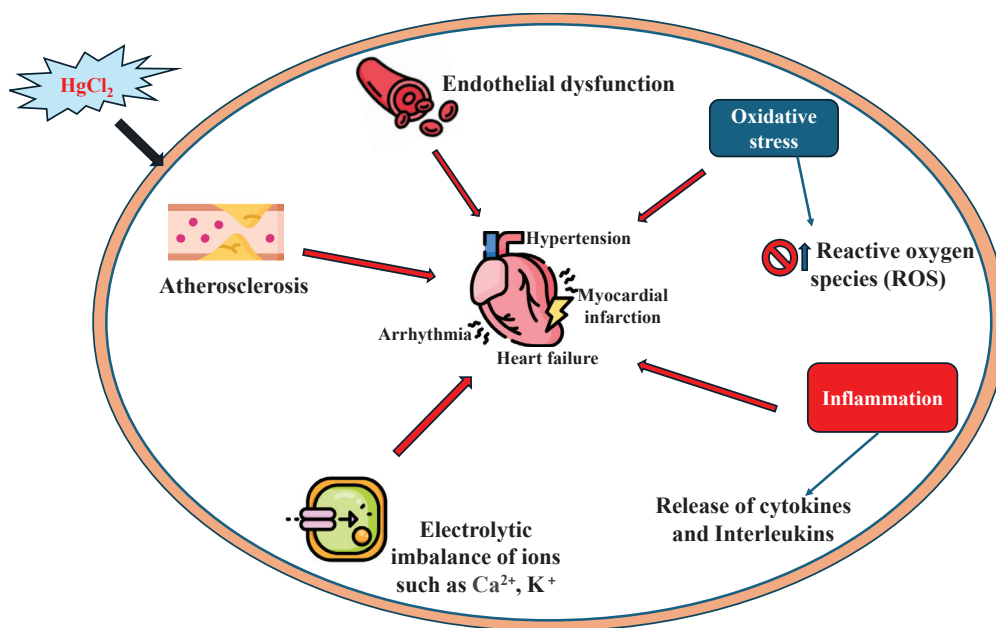
Figure 4 The figure depicts cardiovascular dynamics, biochemical alterations, and oxidative stress in response to Hgcl2 exposure.

levels is due to mercury's inhibitory effects on Leydig cells (closely associated with the process of spermatogenesis) and LH signaling. Oxidative stress induced by mercury on reproductive tissues can lead to disruption of mitochondrial functions (in mitochondria, steroidogenesis occurs due to a) impairment of cholesterol conversion to pregnenolone by the enzyme, cholesterol side-chain cleavage enzyme impaired; b) affect ATP production, and c) disrupting the import and processing of cholesterol into mitochondria by targeting steroidogenic Acute Regulatory Protein, a key regulator of steroid biosynthesis, and cellular apoptosis.) Hair mercury levels have been linked to lower sperm concentration, reduced counts, and decreased progressive mortality. The other reproductive effects associated with mercury exposure are the effects on neonatal growth, altered hormonal levels, placental weight, and gestation period, particularly in women with high seafood consumption [133-135]. Mercury exposure can reduce fertility among dental assistants due to occupational mercury exposure. In men, exposure to mercury-contaminated xenobiotics induces spermatogenesis, epididymal sperm counts, testicular weight, and, in some individuals, erectile dysfunction. In women, mercury inhibits Follicle Stimulating Hormone (FSH) release from the anterior pituitary, disrupting estrogen and progesterone levels which can lead to ovarian dysfunction, painful or irregular menstruation, premature menopause, and retroverted uterus [26,132,136,137]. The

influence of mercury on the binding of hormones by their receptors is also a participating factor in the initiation of mercury endocrine toxicity. HgCl2 was shown to inhibit estradiol binding to rat uterine nuclear receptors, and the presence of divalent ions enhanced the binding [138]. Mercury exposure in pregnant women induces adverse effects on reproductive organs and can lead to miscarriage, spontaneous abortions, stillbirth, and low birth weight. Mercury's oxidative stress in ovarian follicles causes apoptosis and diminished ovarian reserve. In pregnant women exposed to MeHg mainly via diet and or inhalation of environmental pollution, the absorbed MeHg crosses the placenta and accumulates in fetal tissues, which can cause neural tube defects, craniofacial malformations, and delayed fetal growth [139]. Furthermore, MeHg induces embryopathic effects that include cerebellar hyperplasia, decreased nerve cell population in the cerebral cortex, reduction in total brain weight, abnormal neural migration, and disorganized brain layer structure [140,141]. Epigenetic alterations are induced by MeHg such as DNA methylation, and histone modifications in steroidogenic tissues causing the suppression of critical genes like (CYP1A19) aromatase and results in the disruption of conversion of androgens into estrogens that contribute to hormonal imbalance which a profound effect on long-term reproductive dysfunction [142,143]. Thus, these multifaceted mechanisms create a cascade of disruptions in steroid metabolism, leading to hormonal imbalances,

reproductive dysfunction, and broader endocrine pathologies [144].

Mercury binds to sulfur sites of insulin, impairing its normal biological functions and affecting blood glucose levels [145]. It disrupts the endocrine system in humans by impacting the pituitary, thyroid, adrenal glands, and pancreas, possibly through binding to or inhibiting key enzymes and critical steps in adrenal steroid biosynthesis (e.g, inhibition of 21-alpha-hydroxylase) [146]. It has been observed in humans that mercury largely accumulates in the thyroid and pituitary glands due to its high affinity following chronic exposure in working workplace. Accumulated mercury blocks thyroid hormones by occupying iodine binding sites, which can cause damage to the thyroid and alter thyroid hormone action, leading to impairment of body temperature regulation, hypothyroidism, thyroid inflammation, and mental depression [147,148].

In animal experiments, mercury chloride (20mg/kg) administered intramuscularly to rats elicits a marked increase in the thyroid peroxidase activity, with increased T3 levels and decreased T4 levels resulting high T3/T4 ratio, which leads to the onset of acute hyperthyroidism. Also, demonstrated that a small dose of mercury chloride (0.26mg/kg) administered orally daily for 6 weeks to rodents produces thyroid hypertrophy and decreased iodine uptake, elevated protein-bound iodine. All these events in the thyroid gland led to coupling defects in the synthesis of T3 but not T4 [149,150]. Such an effect on T3 synthesis has been correlated to mercury's effect on 5-deiodinase. However, the authors suggested that it may be necessary to investigate the effect of mercury on serum thyroxine levels to understand the exact underlying mechanism of action of mercury chloride on the thyroid gland [151].

Chronic exposure to catfish with methyl mercuric chloride for 180 days or emisan6 resulted in hyperplasia, lymphocyte infiltration, fibrosis even necrosis in the area of the adrenal gland, accompanied by a reduction in plasma cortisol levels. Also, pituitary cells are hypertrophied and degranulated, indicating hypersecretion of ACTH. Further, chronic methyl mercury exposure affects the sensitivity of the adrenal cortex to stress stimulation of ACTH and impairs adrenal steroid production and metabolism (*in vivo*). Mercury's toxic effects on bioplasm (cellular protoplasm) and its broad-spectrum enzyme inhibition can be attributed to mercury's high affinity for thiol group enzymes and proteins. Similar findings are also reported in adrenal and gonadal glands in the experimental seal model [152,153]. The testicular toxicities and steroidogenesis have also been observed in different laboratory animal species (e.g., fish, fowls, rodents, and primates) [154,155]. The effects of mercury on female gonad function were also reported in fish, mice, and hamsters. Fish exposed to mercury-polluted water had decreased gonadal steroidogenesis and pituitary gonadotropin-releasing, inhibited ovarian maturation, decreased ovarian weight, and decreased the number and diameter of oocytes. The meiosis of ova was affected by mercury in mice and hamsters [130,156-158].

The key mechanisms of mercury toxicity can be attributed to its interference with the intracellular calcium mechanisms in the endocrine system, as well as in the organ functional systems. Mercuric chloride is likely to inhibit the release of vasopressin via disruption of the calcium pumping mechanism in the neurohypophysis. Endocrine gland damage also occurs due to oxidative stress (lipid peroxidation, increased ROS formation, and redox-sensitive signaling pathways that regulate the expression of steroidogenic genes) [159].

The toxicological impact of mercurial compounds and mercurial xenobiotics on the endocrine and reproductive system underscores the need for preventive measures, stricter enforcement of regulatory controls, and in-depth research to understand and unfold mechanisms of toxicity to mitigate health risks [11].

Effects of Mercurial compounds and mercurial xenobiotics exposure on the immune system

Documented findings indicate that elemental mercury and its organic or inorganic salts (known immune toxicants), including those derived from environmental exposure, exert significant and multifaceted effects on both the innate and adaptive arms of the immune system, leading to immunosuppression, autoimmunity, and inflammation [160-162]. These effects stem from mercury's ability to interact with immune cells (macrophages, dendritic cells, T cells, and B cells) and modulate immune signaling pathways, often leading to the deregulation of both innate and adaptive immunity [163-166]. Experimentally, it has been shown that mercurial compounds impair the immune system and its functions, mainly through negative

effects on polymorphonuclear cells (PMNs) due to the suppression of adrenocortical steroid synthesis, which prevents the normal stimulation of PMN function and inhibits their ability to destroy foreign substances [167,168]. Both short and long-term exposure to mercury in the workplace environment or seafood consumption, and usage of skin-lightening creams containing mercury can interact with immune cells leading to stimulation of macrophages (the release of excessive ROS and pro-inflammatory mediators such as cytokines(TNF-α, IL-6 and IL-1β via activation of Toll-like receptors 4, nuclear factor kappa B signaling pathways) causing tissue damage; inhibits the function dendritic cells and major histocompatibility molecules results in a reduction in the efficiency of antigen presentation)[161].

The ability of metal ions to stimulate inflammatory reactions in the absence of a mitogen is well documented. The main cellular mechanism of inflammation is due to stimulation of the innate immune system, due to a) cell death, b) participation of pattern recognition receptors, ability to present antigens to secondary lymphoid organs, leading to activation of the adaptive immune system (associated with TNF-α producing Th1 CD4+ T cells). Mercurial-containing xenobiotics exposure triggers T-helper cell polarization, specifically Th2 and Th17 subsets, promoting autoantibody production and inflammatory responses [169,170]. Thus, adaptive immunity associated with mercury toxicity also acts as a complimentary to the innate immune system. This is supported by the fact that the adaptive immune cells, particularly activated T cells, produce cytokines like IFN-γ, which enhance innate immune responses. All these cellular events in metal-induced immune cell activation are likely to play a significant role in the initiation of inflammation and lead to subsequent immunopathology [171]. Dendritic cells or other antigen-presenting cells exposed to mercury or mercury salts enhance the maturation of dendritic cells, up-regulation of co-stimulatory molecules (CD80, CD86), and present major mercury-modified peptides (histocompatibility complex) to T cells [172]. Thus, activation of various cells such as T cells and B cells, macrophages, increased cytokine production, impaired phagocytosis, and suppression of lymphocyte proliferation depend on the chemical form, dose, exposure duration, and individual genetic predisposition [173] (Figure 5).

Overactive dendritic cells can skew T-cell differentiation toward auto-reactive phenotypes.

Decreased cytotoxicity of NK cells occurs due to adverse effects on calcium signalling and immunity. [174-176]. Mercury exposure can induce DNA Methylation, histone modification, and microRNA dysregulation in immune cells, altering gene expression related to immune responses. Such epigenetic modifications subsequently influence long-term immune dysfunction. From the documented data, it appears that inorganic mercury exposure affects the likely myeloid and lymphoid linkage formation and has a greater impact on inflammatory and immune responses [99,143,177]. In animal experiments (mice, rats), administration of mercury chloride salts was shown to induce chromosomal aberrations in peripheral lymphocytes and bone marrow cells, as well as micronucleus formation in reticulocytes[178-180].

Mercury chloride in vitro induces lymphoproliferative activity in guinea pigs, rats, rabbits, and mice [181]. The micromolar concentration of mercury chloride negatively affects neutrophil functional activities but increases chemical luminescence, H_2O_2 formation, and enhanced release of lysosomal enzymes within the shortest period [168,182].

Mercury exposure alters immune responses and potentially targets self-antigens in a manner akin to autoimmune reactions and molecular mimicry, most probably due to bio similarities within mercury-containing structures leading to autoimmune diseases such as eczema, Amyotrophic Lateral Sclerosis (ALS), autoimmune thyroiditis, etc[11,183-185]. Experimental findings in mercury-induced autoimmunity mouse model throw more insights into the initial modification of antigen fibrillarin by mercury and then followed by a Th2 dominant responses such as increased production of IL-4, IL-5, and IL-13, which may cause allergic and autoimmune responses mainly driven by the modified fibrillarin [185-188]. Mercury-induced cell death results in proteolytic cleavage of fibrillarin to a 19-kDa fragment. As a result of the proteolysis of fibrillarin, the leakage of cysteine occurs, hence unable to bind to mercury and induces fragmentation, which is capable of producing fibrillarin autoantibodies. Such molecular interactions suggest that cell death is likely to generate new types of regimens as a source of antigenic determinants for self-reactive T-lymphocytes. In addition, mercury is shown to alter immunological signaling pathways, such as nitrogen-activated protein kinase and nuclear factor kappa B (NF-kB) [161]. Dysregulation of

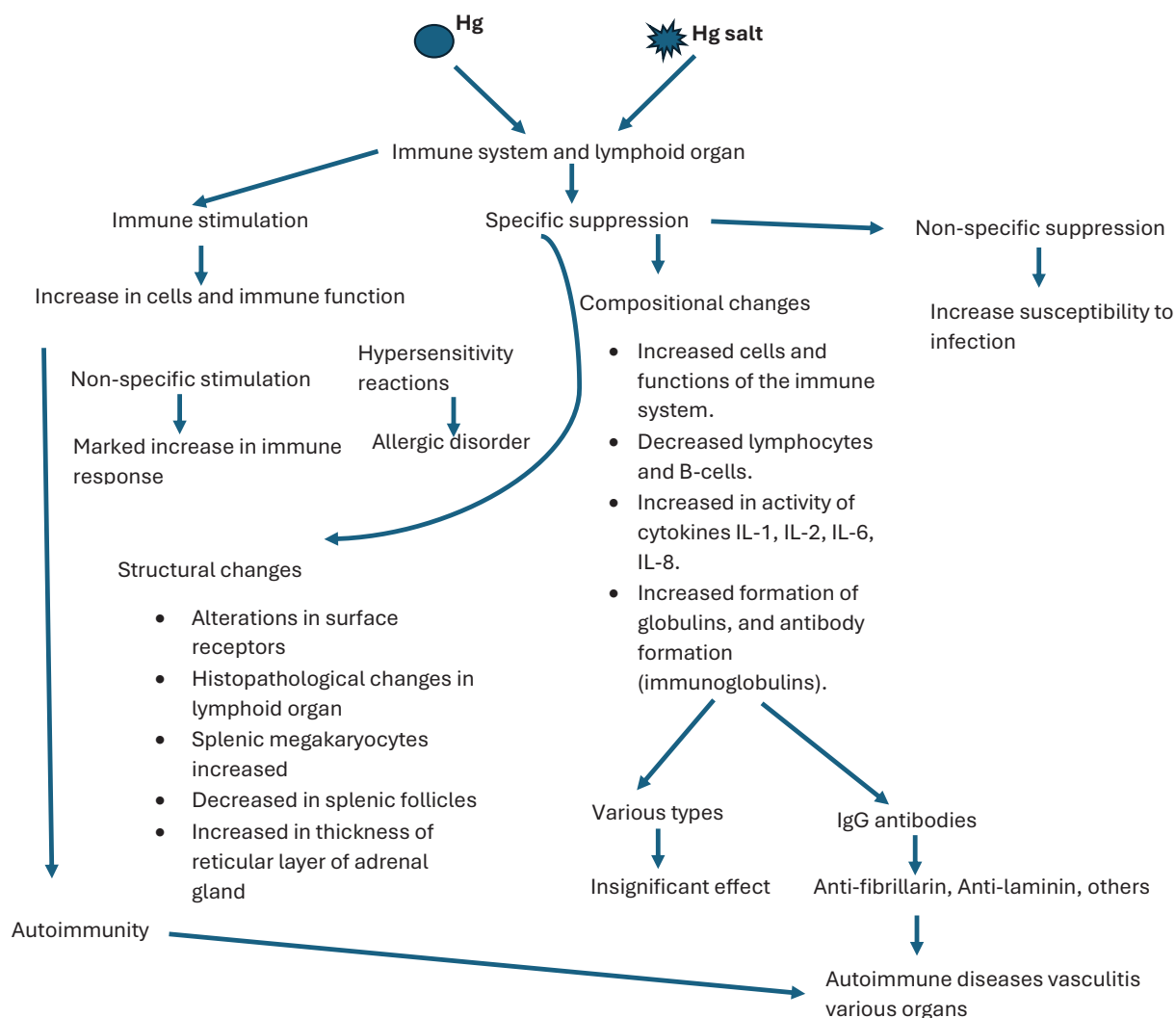TOPICS: TOXICOLOGY ● PUBLIC HEALTH ● INTERNAL MEDICINE

Figure 5 Toxic effects of mercury and its salts on the immune system. (Figure depicts the mercury and its salts on various cellular, biological molecular effects. The above-described effects are produced and manifested under appropriate conditions. There is much overlap between simulation separation, hypersensitivity reaction, and autoimmunity.)

these molecular signaling pathways points out the possibility of the involvement of specific genes in deriving such immunological responses [189]. In an experimental study in mice, mercury chloride (5 mg/kg) treatment intraperitoneally induced spleen damage within 24 hrs [190]. Splenic transcription analysis demonstrated that 3334 genes (2134 upregulated and 1200 downregulated) are expressed differently in mercury chloride-induced spleen damage in mice models. Notably, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment indicated phosphatidylinositol 3 kinase (PI3K) AKT might be a key signaling pathway in mercury-induced spleen damage. In an animal experimental study, mercury chloride-induced autophagic cell death has been explained based on increased protein expression of PI3K, AKT, LC3-II, and p62, and the number of apoptotic cells [191].

Mercury pollutants of environmental origin interact with the various components of the immune system and significantly alter/modify immune responses [192]. Furthermore, mercury is known to trigger immunological responses in the CNS, modify the formation and function of immune cells, and modulate IFN-γ levels [193,194]. These events consequently escalate the production of anti-nuclear antibodies while diminishing anti-inflammatory cytokines. Thus, there seems to exist a complex bidirectional relationship between the CNS and

immune system via receptors for neuropeptides, neurotransmitters, and hormones in the lymphoid organs, which may be involved in modulating immune functions [195].

Other experimental observations with the animal study demonstrated that mercury chloride treatment in ASW mice elicited an increase in serum IgE and IgG levels, whereas C57BI/6 mice treated with mercuric chloride exhibited an increase only in serum IgE with no change in IgG levels[196]The lack of response in the DBA/2 is due to the absence of inflammation at the site of exposure, coincident with reduced proinflammatory cytokines(IL-1β, TNF-alpha, and IFN-γ) levels, which impair the recruitment and activation of immune cells, thereby dampening the immune response. Reduced activity of cathepsin B likely hinders antigen presentation and reduces the activation of the inflammasome complex, further suppressing inflammation [197].

However, mercury-induced murine autoimmunity (mHgIA) studies with different approaches demonstrated that it increases the gene expression of CD40 ligand (CD40L) on T cells and may be deregulated, intensifying the immune response and contributing to autoimmune phenomena via increased cytokine production [198,199]. Mercury's effect on CD-28 signaling can also lead to abnormal T-cell activation [200,201]. Alternatively, anergic states undermine immune tolerance and are likely to promote the autoimmunity process. This creates a vicious cycle of autoantibody production and immune complex deposition, contributing to tissue damage and autoimmune pathology [201,202].

Such chronic effects of mercury on immune function may lead to vulnerability to infections, prolonged inflammatory responses, and altered vaccine responses. Further, the modifications to self-antigen immune complexes may lead to the immune system misidentifying normal tissue as foreign, thus triggering an autoimmune reaction. Hence, further research is needed to fully understand the exact mechanism by which mercury impacts immune function and also to establish a clear cause-and-effect relationship [164].

Effects of mercury on Gastrointestinal (GI) and Haematological systems

Most human exposures generally occur due to contaminated seafood, outgassing from dental amalgam, or occupational exposure. Mercury exposure

can be absorbed and methylated/demethylated, and HgCl2 in the gut. The impacts of Hg have multiple detrimental effects on the GI system involving a range of mechanisms impacting its structure, function, and gut microbiota. Trillions of microbes inhabit animals and humans and are known to play as the biological barrier in the gut [203]. Both Hg and MeHg were found to cause intestinal microbial disorders, abnormal metabolite production, tight junction damage, and immune responses in the gut. Mercury absorbed via epithelial cells when ingested causes irritation, inflammation in neurons of the enteric nervous system ulceration, which can be manifested as symptoms like abdominal pain, nausea, vomiting, and diarrhoea (due to mercury accumulation in neurons of the enteric nervous system) [203-205].

Mercury interacts with (−SH) groups in proteins, and digestive enzymes leading to loss of catalytic activity of enzymes and rendering them non-functional thereby affecting carbohydrate and fat digestion and protein breakdown; and structural damage in the mucosal epithelial lining contributes to inflammation and promotes pathogenic bacteria[206-209]. Chronic exposure is associated with atrophy and degeneration of intestinal villi and impaired nutrient absorption [210]. Oxidative stress and lipid peroxidation lead to impairment of the GI tract antioxidant defense system and compromise the integrity of cellular membranes, causing cell death, and increasing intestinal permeability (leaky gut), allowing toxins and allergens to enter the bloodstream [211]. Chronic mercury exposure activates immune cells in gut-associated lymphoid tissue, resulting in inappropriate inflammation (e.g., colitis, mimicking autoimmune-like syndrome) [212]. Furthermore, mercurial compounds are also known to interfere through direct interaction with their active sites, alteration of redox homeostasis, and structural modification of the function of xanthine oxidase and dipeptidyl peptidase-4 [7,213,214].

Mercury disrupts the balance of gut microbiota (dysbiosis), causing an increase in undigested food products in the bloodstream that can lead to immune-mediated reactions and resistance to pathogenesis (pathogenic infections), and also impair blood glucose concentration by binding to the sulfur sites of insulin [137,204,215-217].

Mercurial compounds (both organic and inorganic) affect significantly the hematologic or blood system due to oxidative stress formation of free radicals,

(ROS, RNS, FR) leading to various toxic effects: a) particularly in organic forms, can induce hemolysis largely due to the affinity for sulfide groups in red blood cells disrupting cell membrane integrity and causing cell lysis resulting in anaemia (haemolytic anaemia and aplastic anaemia)[218,219]. In addition, mercury can impair erythropoiesis in the bone marrow and oxidize haemoglobin (Methyl mercury haemoglobin), thereby impairing oxygen-carrying capacity. b) Mercury exposure affects lymphocytes, neutrophils, and monocytes. (Figure 6) Experimental studies have demonstrated that mercury compounds can reduce lymphocytes and impair immune responses, making the body vulnerable to infection. Oxidative stress of mercury can alter leukocyte function and adversely affect normal surveillance and inflammatory responses. Enzymes required for platelet adhesion and aggregation are inhibited, leading to the prolongation of bleeding time and the wound healing process [220−223].

Carcinogenic promoting effect of mercurial compounds

It has been documented that worker at occupational exposure chloralkali workers, dentist and dental nurses, nuclear weapons workers, gold mining workers, and other industries and people eating kinds of fish and shellfish, too mercurial compounds especially methyl mercury and inorganic compounds (as determined by their mercury levels in toenail, hair, and plasma/serum) shown to be at risk of cancer and mortality [224]. The toxic manifestations of mercury vary depending on its speciation of bioaccessibility, bioavailability, and kinetic pattern. Some of the case reports revealed that farmers using mercury-based fungicides and seed dressings develop risk factors for lymphocytic leukemia, and people show higher mercury levels in blood, 3.67 µg/L, likely to promote renal cancer [11]. However, low dose of mercury exposure induces proliferative responses both in normal and cancerous cells, accompanied by cytotoxicity. The carcinogenic effects of mercury have been linked to its potential to disrupt cellular homeostasis, induce genetic and epigenetic alterations, and promote chronic inflammation. In experimental animal models, a high dose of mercury exposure has been linked to interference with estrogen receptors, ERK-1/2, JNK, NADPH-oxidase, and potentially Nrf2 signaling. Mercury can mimic or antagonize hormonal activity, such as estrogen receptors. Such endocrine disruptors
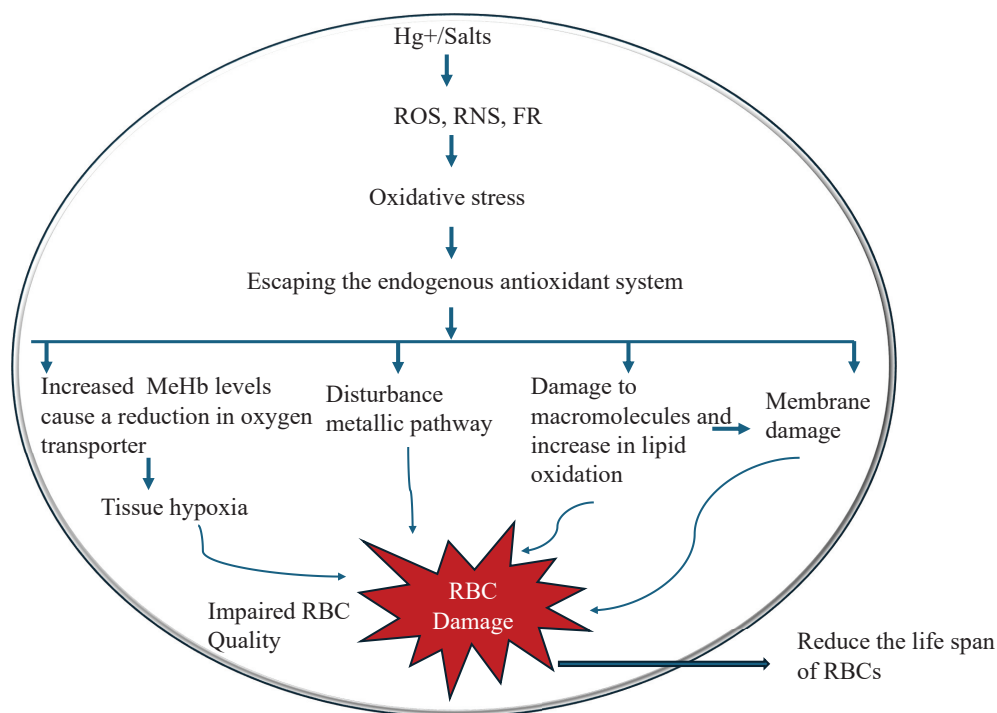

Figure 6 Effect of mercury exposure on the Haematological system in humans.
(The figure illustrates the effect of inorganic mercury salts on haematology, indicating the involvement of oxidative stress (increased ROS and peroxidation process), alterations in haemoglobin and its function, and impaired metabolic pathways, including changes in blood cells like leucocytes and lymphocytes.)

can promote hormone-sensitive cancers like breast and prostate) [225]. Hormonal imbalance likely creates situations favorable for carcinogenesis, such as an increased rate of proliferation of hormone-dependent tissues or organs [226]. Genetic damage and mutagenesis, such as oxidative DNA damage (8-oxo-dG and chromosomal aberration), genotoxicity, and epigenetic effects of Hg, may be collectively involved in cancer promotion [227].

Further, combined with decreased apoptosis and pro-survival signaling upon low-dose mercury exposure, accumulation of DNA lesions in cells may predispose to the risk of malignant transformation [11]. The interference of epigenetics (via gene modification by various molecular processes such as DNA methylation (both hyper and hypo patterns and histone modifications have been documented) is likely to cause abnormal gene expression, and that may be a major driving factor or hallmark of molecular interaction of mercury for carcinogenic effects. Hence, it has been proposed that mercury may be a potential epigenetic metal. All these above-described epigenetic changes modify gene expression without altering DNA sequences, facilitating abnormal cell proliferation, immune evasion, and angiogenesis in the tumor microenvironment (sustained inflammatory signaling creates a microenvironment conducive to tumor initiation). In animal experiments, at very high doses, some mercurial compounds are reported to produce several types of tumors in rats and mice and are considered highly carcinogenic [6]. Although mercury exposure is associated with cancer risk, many available data are contradictory, hence, mercury may be a promoter of carcinogenic risk through modulation of cell proliferation. In a broader sense, mercury might be an example of an epidemic tumor promoter, a mutagenic effector associated with multifaceted complex mechanisms with probable carcinogenic actions of mercurial compounds [228,229].

Ecotoxicity

Mercurial compounds and mercurial xenobiotics can persist in natural environments and accumulate through the food chain, causing toxicity in organisms, disrupting ecological balance, and impacting biodiversity [9]. In plants, low concentrations of mercury improved germination rate, root length, early blooming, plant height, pollen viability, and chlorophyll content. On the contrary, at higher concentrations, mercury slows down and restrains the plant, including the yield of biomass production, impaired photosynthesis, nutritional deficiency, and growth [230]. This impacts the entire food chain. This has been attributed to soil microorganisms, largely influencing the bioavailability of nutrients required for plant growth. Microorganisms are susceptible to heavy metal stress [231].

Mercury's impact on aquatic life, especially in fish, affects development, reproduction, and behavior, reducing populations and disturbing ecosystem dynamics [9,232]. Also influences growth, production, and enzymatic processes in organisms like molluscs and crustaceans, which are key to food webs. Thus, mercury disrupts food web dynamics by altering predator-prey relationships and reducing species diversity. Such events can lead to cascading effects throughout the ecosystem, disturbing ecological balance.

Exposure of invertebrates, arthropods, worms, and Drosophila to mercury/mercury xenobiotics produces deleterious and severe impacts such as locomotion, growth, eating behaviour, poor prey acquisition, and promotion of developmental defects in embryos. The effect of exposure to methyl mercury also developed slowly and was exhibited with patterning, positioning, and maturation of neurons and glia. Thus, it appears from the documented research findings that invertebrates are more vulnerable to mercury exposure in their early life stages, such as eggs, embryos, and Larvae. The adverse effects reported among vertebrate species (amphibians, birds, fishes, reptiles, and mammals with the mercurial compounds, methyl mercury, include endocrine-disrupting activity and impairment of functions of vital organs such as the liver, kidney, CNS, embryos, and changes in the reproductive habits. Mercury is reported to interfere with the reproductive success of birds by causing eggshell thinning, decreasing hatchability, by altering hormone levels. Birds exposed to high mercury levels result in reduced fertility and developmental abnormalities in embryos. Further, birds show weakened immune responses, making them more susceptible to infections and diseases. Cardiotoxicity (such as abnormal heart rhythms, compromised heart structure, and decreased capability to oxygenate tissues), particularly in migratory birds, has been reported. Such adverse toxic effects hinder their survival rates and impact population dynamics. Thus, mercurial xenobiotics pose a threat to biodiversity, as they reduce the productive success and survival rates of sensitive species [9,232-239].

Available Avenues for Mitigating Mercury Toxicity in Humans

As described earlier, mercury is a pervasive environmental toxin with significant health implications, affecting almost all vital organs. Advancements in mitigating human mercury toxicity have concentrated on enhancing chelation therapies. Chelators normally bind to mercury ions, facilitating their excretion from the body. The chelators used are: Dimercaptosuccinic acid (DMSA), 2,3-Dimercapto-1-Propanesulfonic acid (DMPS), dimercaprol (BAL), and NBMI [N, N′-bis(2-mercaptoethyl)isophthalamide][25,240-243]. Their efficacy and safety profiles of these chelators by making esters (e.g., mono isoamyl ester) increased their bioavailability and mercury binding capability compared to the parent molecules. Furthermore, chelators are combined with antioxidants like alpha-lipoic acid. This combination approach helps to mitigate oxidative stress associated with mercury toxicity and is used in conventional and alternative medicine [244]. The German environmental agency (Umweltbundesamt) listed DMSA and DMPS as the two most useful tools and reasonably safe chelating agents. These agents, during the chelating process, also remove vitamin C&E, hence these need to be supplemented [240,244-246]. The side effects of chelation therapy include dehydration, low blood calcium, harm to kidneys, and liver enzymes are elevated, and allergic reactions [247]. The protective effects of Indigenous plants (phytochemicals) and recognizing traditional medicinal system (Ayurveda) significantly elevated mercury-induced toxicity in animal models and in-vitro experimental effects are largely attributed to their antioxidant properties (alleviating oxidative stress induced by mercury), which enhances endogenous antioxidant defenses, reduce cellular damage and some of them may chelate mercury ions, facilitating their excretion from the body [248]. These phytochemicals, along with beta-carotene and alpha-tocopherol tocopherol showed a more prominent ameliorating effect, probably by recuperating oxidative stress, indicating its usefulness in clinical regimens. Thus, these phytochemicals of natural product origin, preclinical mercury toxicity alleviative effects, reveal innate antioxidant properties by repression of mercury-induced oxidative stress by multimodal elevation of endogenous enzymatic and non-enzymatic fortification systems, leading to mitigation of mercury-induced toxicity in experimental animals.

These preclinical studies could serve as a pivot for further discovery of potential agents that may be useful in the clinical management of mercury toxicity. Bio-medicinal plants, Carica papaya leaves (ethanolic extract), Adansonia polygamus, Curcuma longa, flax seeds, Rheum turkestanicum, and Tribulus terrestris alleviate inorganic mercury-induced kidney damage evaluated by biochemical and molecular alterations [49].

The selenium treatment/supplementation in diet supplement has been used because selenium interacts with mercury and forms biological inert complexes (mercury selenide) thereby reducing mercury's affinity for thiol groups in proteins and mitigating its toxic effects (e.g. the mechanism associated in selenium protection is due to amelioration/reduction mitochondrial injury and DNA damage, cellular calcium dyshomeostasis, pro-demethylation of methyl mercury, sequestering of mercury via mercury selenium complexes, and redistribution of mercury inside organisms) via inhibitory effects of selenium on the action of mercury. Selenium and acetylcysteine administration together for 4 days reduced kidney and liver mercury concentration by 70% and 80%, respectively, and restored histopathological architecture in mercury chloride, methyl mercury, and dimethyl mercury-treated rats [249].

Remediation approaches for environmental mercury pollution

The different traditional biological methods employed to remediate mercury with bacteria. Some of them have been mentioned briefly below:

The utilization of mercury-resistant bacteria, such as Pseudomonas, Bacillus, and Enterobacter, possesses a mercury reductase enzyme that converts toxic methyl mercury to less toxic Hg0 through enzymatic reduction [250]. This may lower the burden of mercury exposure through food chains, especially fish containing methylmercury. Bioabsorption is the ability of microorganisms to capture mercury by increasing their biomass. In this process, the mercury capture is retained largely in the bacterial cell wall without the need for intracellular bioaccumulation [251-253]. The application of yeast cells and whole-cell biosensors has also been adapted as a bioremediation technique for mercury contamination in the atmosphere (soil and water). Mercury-volatilizing bacteria inherit the Mer operon, which enables the reduction of Hg^{2+} to volatile Hg^0.

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The Mer operon encodes several proteins: a mercury reductase (MerA), an organomercurial lyase (MerB), a periplasmic mercury-binding protein (MerP), inner membrane proteins involved in Hg^{2+} transport (MerT, MerC, MerE, MerF, and MerG), and regulatory proteins that control operon expression (MerR and MerD) [254].

The phytoextraction process removes heavy metals, including mercury, through plants. Environmental pollutants, such as mercury, induce oxidative stress in plants, leading to the overproduction of Reactive Oxygen Species (ROS) [255]. These ROS include Hydrogen peroxide (H_2O_2), Hydroxyl radicals (HO·), molecular oxygen (O_2), and superoxide anions (O_2^-) [86]. To counteract oxidative damage, plants produce various antioxidant enzymes, such as Superoxide Dismutase (SOD), Glutathione Reductase (GR), catalase, and Ascorbate Peroxidase (APx), which catalyze and degrade ROS into less harmful molecules [256]. Mercury exposure has been observed to enhance the cellular production of APx and other enzymes in certain plant species. This surge in enzyme activity is interpreted as a protective or defensive response to ROS, triggered by the intracellular presence of mercury [257].

Traditional remediation techniques, such as soil excavation, removal, and containment or capping of contaminated sites, are often disruptive and costly. Recent research has explored innovative materials, including synthetic corals made from aluminum oxide nanoparticles that effectively absorb heavy metals like mercury from water sources. Similarly, modern nano-biotechnological techniques (affordable and cost-effective) such as gold-decorated titanium dioxide nanotubes have demonstrated excellent mercury ion removal capabilities through a photocatalytic process, making them efficient for cleaning contaminated water bodies and transposon-mediated in-vitro molecular breeding (ISMoB) (process associated horizontal gene transfer which involves basic mechanisms like transformation, transduction and conjugation process) for effective removal of mercury pollution. The above mentioned techniques seem to be more efficient in the removal of mercury [253,258]. To advance mercury remediation efforts, it is imperative to develop new technologies that leverage microbial species in bioremediation. This requires a deeper understanding of the mechanisms that enhance microbial activity and pollutant metabolism under various ecological conditions.

Conclusion

Mercury and its compounds' toxicity remains a global concern, impacting human and animal health, ecosystems, and biogeochemical cycles. Its multifaceted effects disrupt multiple organ systems, including cardiovascular, renal, endocrine, and immune, and have profound effects on fertility and reproductive processes. Its molecular mechanisms involve oxidative stress, genetic disruptions, hormonal dysregulation, and immune dysregulation. An urgent need for interdisciplinary approaches to develop innovative mitigation strategies coupled with a forward-looking policy vision to curb mercury exposure and safeguard biodiversity, public health, and future reproductive potential. This may ensure safer, sustainable coexistence with our environment.

CRediT Authorship Contribution Statement

Suresh Naik: Supervision, Conceptualization, Formal analysis, Visualization, original draft, review, editing. Dipesh Gamare: Writing – original draft, review, editing, & Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Data Availability

The authors do not have permission to share data.

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