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Overview on the heavy metal toxicity mechanisms and the role of alimentary factors in detoxification

Abstract. People are continuously subject to various environmental and chemical pollutants originating from industrial and agricultural activities. Heavy metals can be identified as a separate group of xenobiotics that pose a danger to human health. They affect almost all body systems, exerting toxic, allergic, carcinogenic, and gonadotropic effects. The toxicity of heavy metals to the body, their neutralization and elimination from the body depends on several factors, including nutritional status, as there are detoxification mechanisms in the human body, which require the intake of certain nutritional compounds. The quality of nutrition directly affects the state of the body since the essential compounds are mostly obtained from the food. Consumption of nutritional compounds is a significant factor that determines human health, growth, development, physical and mental activities and promotes more effective recovery during illness. The use of knowledge on the intoxication mechanisms and the role of alimentary factors in the body detox contribute to a deeper understanding of the processes in the development of the ways to neutralize the negative effects of various toxic compounds. At the same time, a large number of articles and reviews are devoted to the study and analysis of the manifestation of toxic effects of heavy metal compounds, mechanisms of their transformation in the environment, as well as damaging effects on the body systems; articles devoted to the study of the neutralization of the poisoning effect of various xenobiotics are aimed at investigating the detoxification effect of finished dosage forms. The importance of examining how nutritional factors like proteins, probiotics, vitamins, and dietary fiber contribute to the body detoxification processes is significant. This review analyses literature data of scientists from Kazakhstan, far and near abroad on the mechanisms of toxicity of a wide range of heavy metals, as well as the role of key nutrients in the process of their detoxification.

Key words*:* heavy metals, nutritional status, biotransformation, detoxification, alimentary factors.

Introduction

Nutrition is an individual's most significant physiological need and one of the crucial exposome factors, which directly affects human health, growth, development, physical and mental activities as well as tolerance to injurious factors [1].

Food items consist of intricate, multi-component combinations of chemical compounds, including nutrients such as proteins (valuable facts of which are presented on Figure 1), fats, carbohydrates, vitamins, and dietary fiber, which possess energetical, structural, and regulatory significance, as well as biologically active compounds such as organic acids, saponins, alkaloids, and polyphenols that take part in regulation of metabolic processes [2].

Importantly nutritional status of an individuum is defined as the state of food supply with major macro- and micronutrients, influenced not only by the quantity, but also by the quality of ingested food [4]. Epidemiological studies conducted in the past twenty years indicate a continuous rise in illnesses and disorders related to changes in the structure and quality of nutrients [5].

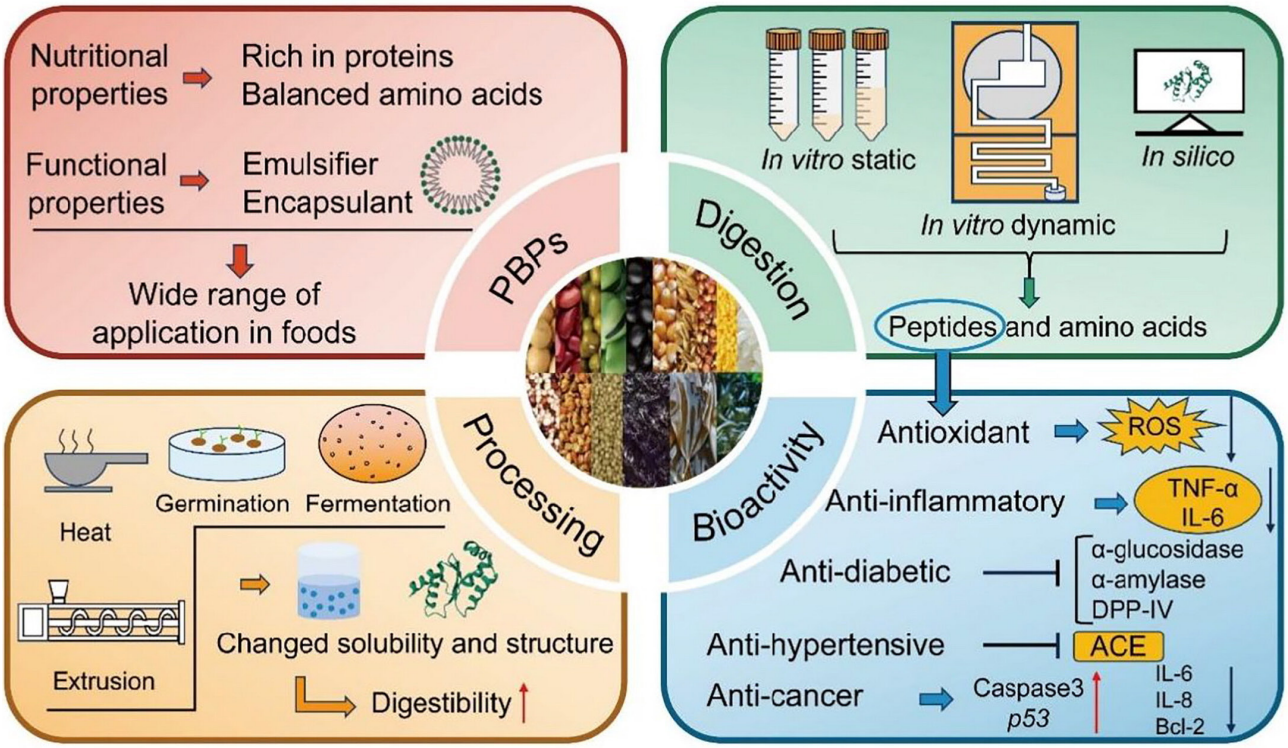

Figure 1 – Plant-based proteins (PBPs): advances in their sources, digestive profiles *in vitro* and potential health benefits [3]

An unbalanced diet can cause disorders of the digestive and respiratory systems, dermatological, musculoskeletal disorders and a number of nervous ailments, poor health and even death [6].

The problem of nutrition shortage, or "hidden hunger," characterized as lacking or deficiency of nutrients associated with food deficiency for vital functions of the body, is an issue in a range of African and Southeast Asian countries [7]. Unbalanced nutrition and consumption of nutrients in quantities exceeding the body's needs is the other side of the coin. Undernutrition and obesity can lead to effects across generations as both maternal undernutrition and obesity are associated with poor health in offspring [8].

Nutrition is an integral component of a person's lifestyle and may contribute to the development of many chronic diseases such as obesity, cardiovascular disease, hypertension, stroke, type 2 diabetes, metabolic syndrome, cancer, and presumably some neurological disorders. In addition, impairment of one of the body functions may entail the development of other pathological conditions. For example, obesity appears as a risk factor for type 2 diabetes, hypertension and metabolic syndrome, among others [9]. Therefore, maintaining good health and preventing diseases heavily relies on proper nutrition and equivalent physical exertion, as the nutritional component is a fundamental aspect of nearly every disease [10].

Additionally, food may contain anti-nutritional elements (e.g. phytic acid, saponins, alkaloids, certain oligosaccharides, protease inhibitors, glucosinolates, tannins, and cyanogenic glycosides) displaying varying biological activities (Figure 2).

However, there exist certain chemical compounds (including non-essential and essential heavy metals) whose metabolic byproducts can directly induce toxicity.

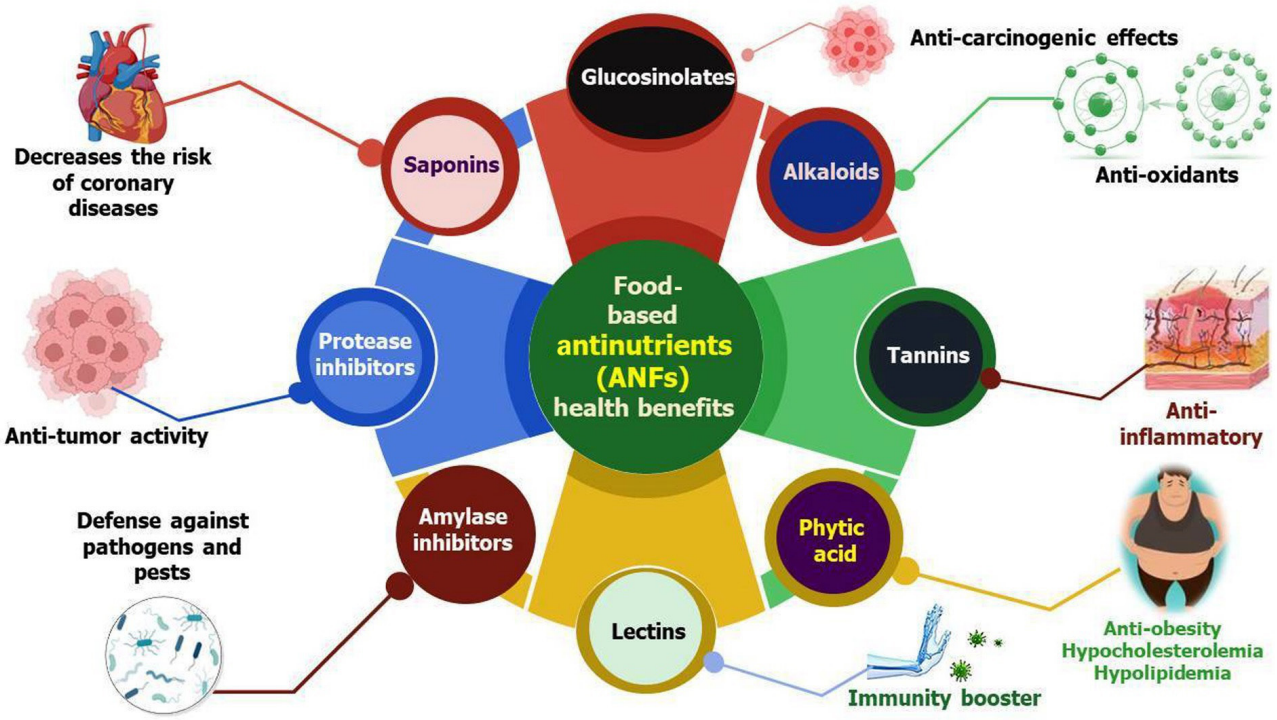

Figure 2 – Schematic representation of ANFs role in human life [11]

Toxic effects of non-essential heavy metals

The current pace of life involves considerable physical and emotional strain, compounded by unfavorable environmental circumstances, the infiltration of toxic compounds into the body, inadequate nutrition, and a decline in the quality of the food we consume. The cumulative effect of all these factors leads to chronic intoxication caused by the buildup of substances with varying degrees of toxicity. According to the World Health Organization (WHO), unsatisfactory environmental circumstances result in the demise of over 13 million individuals annually [12]. Toxic substances can accumulate in the body either by external exposure from the environment (e.g. chemicals at the workplace, Figure 3) or by being synthesized within the body itself. All toxins have the potential to generate free radicals, which can trigger oxidative stress and initiate pathological alterations within the body [13].

Heavy metals (HM) can be identified as a distinct category of xenobiotics that pose a threat to human health. Today, from a biological point of view the term heavy metals refers to metals with a relatively high atomic mass that can have a harmful impact on living organisms [9]. The ingress of HMs, and their salts into the human body occurs with the inhalation of air, the use of water from the water supply system, and some food products.

Forty chemical elements of the Mendeleev periodical system belong to the group of heavy metals. The heavy metals arsenic (As), cadmium (Cd), chromium (Cr) (VI), mercury (Hg), and lead (Pb) can have poisonous effects at extremely low concentrations. These heavy metals are known as the most toxic. Pollution of the environment with these toxins occurs due to the activities of a number of industries and some natural processes. High concentrations of heavy metals are found everywhere, including the atmosphere, hydrosphere, and lithosphere. The resulting heavy metal poisoning of ecosystems has devastating effects on all living organisms [15].

Toxic metal pollution in the environment has a greater impact on children due to the high accumulation of various toxic elements, including in the placenta. This can result in congenital malformations, weakened immunity, and the development of chronic diseases, as well as delays in mental and physical development [16-19].

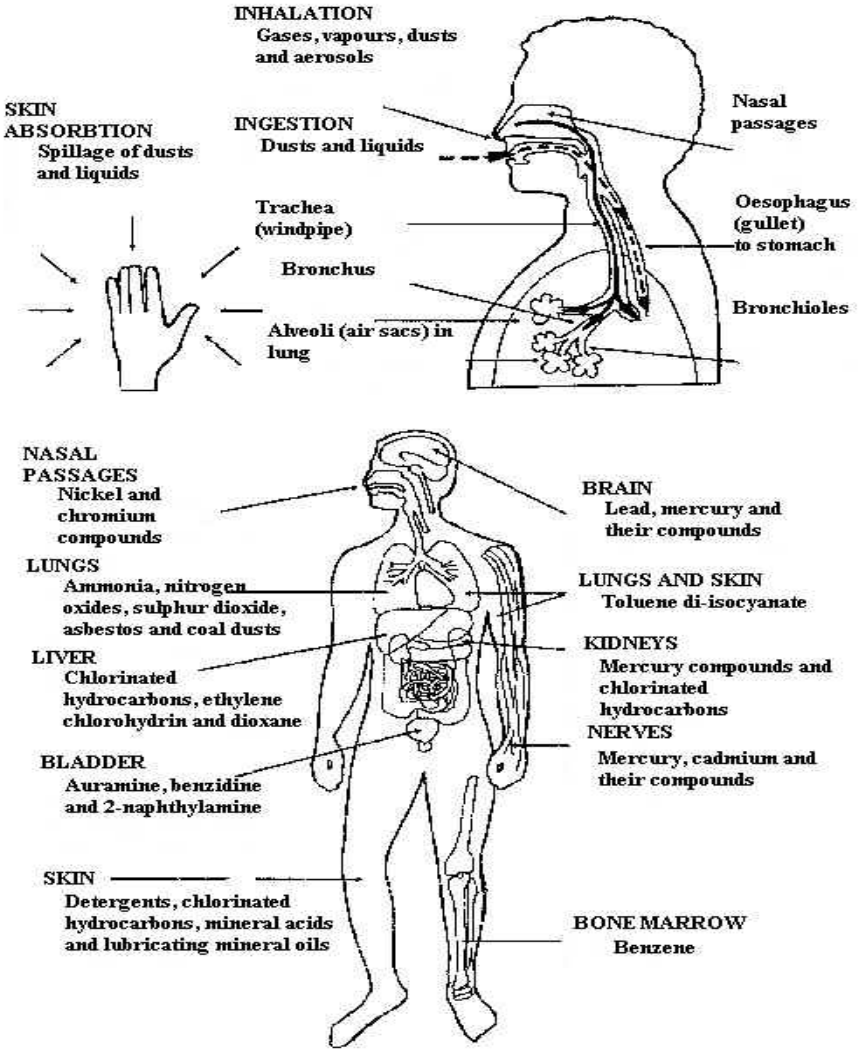

Figure 3 – Different organs and tissues that can be affected by certain toxic industrial chemicals [14]

Lead is a noxious element that has detrimental effects on the human body. Lead is classified as a highly hazardous substance, along with other elements such as arsenic, cadmium, mercury, selenium, zinc, fluorine, and benzo(a)pyrene, based on its adverse effects on living organisms. The danger of lead to humans is determined by its significant toxicity and ability to accumulate in the body. Lead enters the human body from various sources such as food (accounting for 40-70% of intake in different countries and age groups), drinking water, the air we breathe, smoking, and accidental ingestion of lead-containing paint or soil. The main sources of environmental pollution with lead are vehicles using lead-containing gasoline, and stationary sources of non-ferrous metallurgy enterprises [20].

The first signs of lead's harmful effects typically manifest as central nervous system disorders. Asthenic syndrome tends to occur frequently and can be characterized by symptoms such as headaches, heightened fatigue, memory problems, and signs of autonomic dysfunction, where the parasympathetic tone is dominant. It is crucial, particularly for children, to lower their IQ levels and modify their visual, auditory-motor reaction times, and physical activity. Once lead enters the body, it typically moves into the bloodstream within a matter of minutes and readily attaches to red blood cells. This can lead to disruptions in porphyrin metabolism, heme synthesis, and an increase in anaerobic glycolysis, which may intensify platelet aggregation. Lead can bring about hypochromic anemia by impeding heme

synthesis enzymes. Continued exposure to lead can trigger the production of endogenous oxalic acid, leading to alterations in the renal tubules. Prolonged ingestion of lead can also result in chronic and irreversible nephropathy, ultimately progressing to renal failure. Lead does not have an affinity for the heart muscle. However, prolonged exposure to lead can lead to the development of bradycardia and an increase in blood pressure [21, 22]. Lead compounds affect membrane permeability and lipid peroxidation processes in many organs. Cells of the brain and liver are most sensitive to the influence of solutions of lead salts. Studies have also shown a higher incidence of primary infertility and miscarriage due to lead's ability to easily pass through the placental barrier, accumulate in fetal tissues, and potentially harm both mother and child. Women at risk of giving birth to babies with congenital malformations had a frequency of 4.6 births per 100 newborns. Non-specific gastrointestinal reactions may also be observed [23, 24].

The manifestation of heavy metal toxicity in cells of various organs occurs as a consequence of oxidative stress due to the intense formation of reactive oxygen species (ROS). ROS can cause damage to the liver, kidney, and cardiovascular system and cause diseases associated with inflammation. The damaging effects of ROS are usually neutralized by internal and external antioxidants, which helps to reduce the toxic load; however, in some cases, the toxic effects of heavy metals can damage antioxidant defense mechanisms [25, 26]. Lead's impact on mitochondria may be attributed to its transport into subcellular structures through a calcium transmembrane transport system. Pb has a high affinity for processes involving divalent metals. Thus, the mechanisms of lead toxicity have the property to modulate a number of processes in mitochondria, which leads to disruption of oxidative metabolism. Lead is potentially hazardous for human health, even in small amounts. There are a lot of molecules that could be targeted at Pb poisoning in the body. Disruption of bioenergetic homeostasis in cells exposed to Pb leads to a loss of cell ability to synthesize ATP. In addition, lead disrupts processes of homeostasis maintenance, such as apoptosis, mitophagy, and mitochondrial dynamics [27, 28].

Cadmium is toxic non-essential HM that precipitates adverse health effects in humans and animals. The detrimental effects of this HM are more widely recognized. Cadmium and its compounds are classified as Class I hazards [29]. Cadmium oxide is considered the most hazardous form of cadmium, as inhalation of its vapors can lead to acute poisoning and even death. A significant amount of cadmium enters the human body through smoking. Cadmium can be ingested through food when using ceramic dishes as it is present in the paints and glazes used to coat the surface of ceramics. The initial signs of cadmium poisoning include renal impairment (presence of protein in urine), heart muscle damage, nervous system dysfunction, and dysfunction of the reproductive system and lungs [30]. Later, individuals may experience severe bone pain in their legs and back. Cadmium salts, as well as such of many other HMs, causes peroxidation in membrane lipids [31, 23]. Cadmium induces the formation of free oxygen radical species and the inactivation of the cellular antioxidant system, leading to damage to various biomolecules [32]. Moreover, some studies have shown that cadmium may act as a carcinogen [30]. Oxidative stress is one of the mechanisms of cadmium-induced carcinogenesis [33-36]. The latter can easily occur because cadmium is excreted from the human body very slowly, even after a certain amount has been absorbed. Individuals with diabetes, pregnant and lactating women, children, and smokers are at higher risk of exposure to metals [37-39]. The metabolism of cadmium is strongly interrelated with many microelements, whereby the deficiency of calcium and copper significantly enhances the absorption and accumulation of HM in the human body. Conversely, with the adequate intake of zinc and selenium, the deposition of cadmium by internal organs markedly reduces [40]. Moreover, iron acts as an antagonist to cadmium [41].

Arsenic is considered a potentially vital and immunotoxic element for humans [42]. Acute and chronic poisoning can be caused by a wide range of toxic compounds, including arsenic. Arsenic compounds can enter the human body through various sources such as drinking and mineral water, grape wines and juices, seafood, medicines, pesticides, and herbicides [43].

Continuous intoxication by arsenic salts results in various pathologies like skin damage, neuropathies, and cancer [44, 45]. The gastrointestinal tract absorbs approximately 80% of arsenic, while 10% enters the body through the lungs and about 1% through the skin. Inorganic arsenic compounds, which make up more than 90% of arsenic, are soluble and therefore easily absorbed. Afterwards, inorganic arsenic is transported to the liver, where it undergoes methylation. The accumulation of arsenic occurs in several organs including the lungs, liver, skin, and small in-

testine. Arsenic primarily deposits in the reticuloendothelial system, possibly due to the binding of arsenite with SH-groups of proteins that are abundant in these tissues [46, 47]. Arsenic has a long retention time in the body, and its toxicity targets various organs such as the bone marrow, gastrointestinal tract, skin, lungs, and kidneys. There is abundant evidence supporting the carcinogenic effects of inorganic arsenic compounds [48]. Workers in pesticide production, gold mining, and smelting of arsenic alloys with other metals, as well as non-ferrous metals (particularly copper), have reported high mortality rates from lung cancer. Extended exposure to arsenic-contaminated water or drugs has been linked to the development of poorly differentiated skin cancer, known as Bowen's cancer. Additionally, liver hemangioendothelioma may also be a tumor that is dependent on arsenic exposure [49, 50].

The inhibition of dehydrolipoic acid and coenzyme A by arsenites disrupts the tricarboxylic acid cycle. The inactivation of ketoglutarate dehydrogenase disrupts the synthesis of citric and oxaloacetic acids, while the blockage of DNA polymerase results in the disruption of DNA synthesis and decoupling. The inhibitory effects of arsenic compounds on enzymes such as monoamine oxidase, urease, pyruvate oxidase, alanine aminotransferase, aspartate aminotransferase, and fumarase are also associated with their toxic effects. In the process of oxidative phosphorylation, arsenic comes into contact with phosphates, disrupting the formation of ATP from ADP. This action makes it an uncoupler of phosphorylation and oxidation [51, 26].

Mercury is an exceptional chemical element, as it is the sole metal that exists in a liquid state on Earth. Mercury is highly toxic and ubiquitous in the environment, with a tendency to bioaccumulate and transfer through food webs [52]. Mercury is introduced into the environment through various sources, such as the mining and smelting of mercury-containing ores, non-ferrous metal smelting from sulfide ores, gold extraction from ores, cellulose bleaching, chlorine and caustic production, vinyl chloride and electrical equipment manufacturing, production of measuring and control instruments (e.g. thermometers, pressure gauges), use of mercury-containing medical products and pesticides, cement production, and combustion of coal and fuel oil. Waste incineration is a significant source of mercury release into the environment [53].

Mercury primarily enters the human body through inhalation of air, consumption of food products, and drinking water. From the point of view of human pathology, mercury has a broad spectrum of toxic effects on human health, which vary depending on the form in which it enters the body (metallic mercury vapor, inorganic or organic compounds), the route of exposure, and the dose [23]. Mercury exposure can result in acute poisoning (occurring quickly and abruptly, usually at high doses) or chronic poisoning (resulting from low doses of mercury exposure over a prolonged period of time). Inorganic mercury compounds and fumes can lead to the development of contact dermatitis [54]. Mercury vapor is absorbed upon inhalation and accumulates in the brain and kidneys. Around 80% of mercury vapor that is inhaled is retained by the human body. Methylmercury is absorbed almost entirely in the gastrointestinal tract. It has been reported that various forms of mercury can penetrate the human body through the skin [55]. Additionally, in pregnant women, mercury can cross the placental barrier and affect the developing fetus. Furthermore, methylmercury can be transferred to breast milk, leading to dangerous levels in the bloodstream of nursing infants [51].

Mercury is a neurotoxin, and its salts can induce glomerulonephritis, where the formation of autoimmune complexes plays a significant role in its development mechanism [56]. Mercury compounds can decrease the function of T-cells, as well as the T-dependent humoral immune response of macrophages. The toxic mechanisms of mercury are related to the deactivation of enzymes containing thiol groups and the disruption of the transport of sodium and potassium across cell membranes [57]. Mercury compounds of inducing lipid peroxidation processes, altering the properties of cell membranes, disrupting their integrity, and leading to cell death and tissue damage at the organ level. It has been established that when mercury enters the body, the activity of the antioxidant defense system is significantly reduced [58].

Toxic effects of some essential heavy metals

Some metals are elements that are present in the environment and in small amounts in human bodies as essential components. Cobalt, chromium, copper, magnesium, iron, molybdenum, manganese, selenium, nickel and zinc are involved in physiological and biochemical processes, and their deficiency can lead to various disorders, but excessive exposure can also be hazardous to health [59].

Iron toxicity. The liver plays a key role in iron metabolism. Experiments *in vivo* prove that iron exposure leads to the growth of oxidative damage in this organ [36]. The mechanisms underlying iron toxicity are linked to the conversion of ferrous iron in the blood to ferric iron through oxidation. Ions of the latter form complexes with plasma proteins such as transferrin and gamma-globulin [60]. Acute iron poisoning can impair the function of cytotoxic T-lymphocytes, while chronic overdose can disrupt immunoregulation. These effects could be causally relevant to the development of cancer and infections that are linked to excessive iron in the body [61]. Individuals with excessive iron may experience a reduction in the phagocytic activity of macrophages, as well as T-helpers and natural killer cells in some cases. T-lymphocyte response can also be suppressed in mixed cultures, and the number of circulating T-suppressor cells may increase. Excess iron deposition in numerous brain regions has been seen in many neurodegenerative disorders, including Alzheimer's and Parkinson's disease, with possible toxicity. Due to its role as the primary biological catalyst of free radical reactions and the Fenton reaction, iron has been linked to all diseases associated with free radical pathology and tissue damage [41].

Cobalt toxicity is linked to the inhibition of iron absorption, which leads to the blocking of hemoglobin synthesis, impaired tissue respiration, inactivation of various oxidases including α-ketoglutarate dehydrogenase and pyruvate dehydrogenase, and interaction with thiol groups of lipoic acid [62]. In addition, insoluble cobalt compounds can be phagocytosed by macrophages when administered intravenously. Exposure to high doses of cobalt can lead to polycythemia, while a concentration of 35 mm cobalt chloride can inhibit the immune response of human thymocytes. Cobalt salts exhibit strong sensitizing properties and are known contact allergens. Contact with cobalt may even trigger asthma attacks [63, 64].

Magnesium toxicity is usually caused by overuse of magnesium-containing medications or insufficient renal excretion of magnesium [65]. At high doses, magnesium acts as a calcium antagonist and suppresses the activity of the central nervous system and neuromuscular synapses by reducing the release of acetylcholine from the postsynaptic membrane of the nerve fibers that innervate the muscles, as well as in the synapses of the autonomic ganglia [66]. When administered intravenously, it acts as a general anesthetic. Deficiency of magnesium in food can lead to impaired humoral immune response [67].

Manganese toxicity mechanisms are linked to the displacement of calcium and reduced iron absorption and metabolism due to manganese's iron antagonistic nature. These effects can lead to a decline in hemoglobin synthesis. At high doses, manganese affects glucose metabolism by altering the activity of enzymes involved in glycolysis. Low concentrations of manganese activate these enzymes, while high concentrations inhibit them. Manganese has both essential and neurotoxic properties and causes the development of neurotoxic and neurodegenerative diseases in humans [68]. Manganese also inhibits respiratory enzymes found in mitochondria [69].

Copper toxicity is linked to various mechanisms. Excess copper induces not only oxidative stress but also DNA damage and reduced cell proliferation [70]. The interaction of copper with sulfhydryl groups of erythrocytes leads to increase cellular permeability, inhibition of glutathione reductase and a subsequent decrease in reduced glutathione, agglutination of erythrocytes, and excessive stimulation of the hexose monophosphate shunt. In high doses, copper exhibits selenium-antagonistic properties, leading to selenium deficiency. Copper plays a role in maintaining immune homeostasis, but excessive amounts can suppress the T-dependent immune response and reduce the synthesis of IL-1B and IL-2, as well as leukocyte chemotaxis [71].

Nickel toxicity is caused by the variable oxidation state of the element, which inhibits oxidative enzymes [23]. High doses of nickel salts decrease the function of T-cells, natural killers, and T-dependent antibody production. Furthermore, the metal is known to cause allergic reactions such as contact dermatitis and has a carcinogenic effect [72].

Selenium toxicity mechanisms are linked to the induction of oxidative stress and the disruption of sulfur metabolism in the body. The replacement of sulfhydryl groups with selenol groups (SeH) in various enzymes leads to the inhibition of cellular respiration, a reduction in the activity of dehydrogenases, blockage of the tricarboxylic acid cycle, and glutathione metabolism. The functioning of enzymes can be disrupted due to a change in their tertiary structure caused by the formation of

selenium trisulfide complexes. Selenium as well as zinc, iron, copper, and germanium are classified as immunomodulatory elements [73].

Chromium is the second element that induces contact hypersensitivity after nickel [74]. In this case, the mechanisms involved are associated with both the action of chromium itself and its conjugation with proteins. Chromium exhibits significant allergic and autoimmune effects, enhances the functional activity of B-lymphocytes, and decreases the T-dependent humoral immune response. Chromium plays a crucial role in insulin-mediated carbohydrate metabolism [75].

The toxicity of Cr(VI) is strongly linked to the generation of ROS during its reduction process. The latter cause oxidation of cellular macromolecules, such as proteins, lipids, and DNA, thereby altering their functions. A major genotoxic effect of Cr(VI) that contributes to carcinogenesis is the formation of DNA adducts, which can lead to DNA damage [46]. Modulations of cellular signaling pathways, as evidenced by the modulation in p53 signaling pathway, and epigenetics may also contribute to the carcinogenic effects of Cr(VI). Several studies demonstrated that Cr(VI) induces cellular death through apoptosis and autophagy, genotoxicity, functional alteration of mitochondria, endocrine and reproductive impairments [76]. Cr(VI) has a major impact on many aspects of mitochondrial biology, including oxidative phosphorylation, mitophagy, and mitochondrial biogenesis [77]. It was concluded that occupational exposure to Cr(VI) can cause lung cancer, nose and nasal sinus cancer in humans. Cr(VI) is suspected to cause stomach cancer and laryngeal cancer in humans. It is currently insufficiently clear if Cr(VI) can cause cancer of the small intestine, oral cavity, pancreas, prostate or bladder in humans [78, 79].

Mammals, including humans, are exposed to Cr, including Cr (VI), frequently through inhalation, drinking water, and food.

Zinc is an element commonly found in the Earth's crust. It is released to the environment from both natural and anthropogenic sources. The primary anthropogenic sources of zinc in the environment (air, water, soil) are related to mining and metallurgic operations involving zinc and use of commercial products containing zinc. Although zinc has a rather low toxicity, and a severe impact on human health by intoxication with zinc is a relatively rare event people living near smelters or industries using zinc could be exposed to higher levels of zinc by drinking water, breathing air and touching soil that contains the metal [80].

Ingestion of zinc and zinc-containing compounds can result in a variety of chronic effects in the gastrointestinal, hematological and respiratory systems along with alterations in the cardiovascular and neurological systems of humans. Prolonged zinc exposure via these routes has been shown to result in copper deficiency characterized by hypocupremia, anemia, leucopenia and neutropenia; some subjects additionally report headache, abdominal cramps and nausea. The antioxidant enzyme Cu, Zn-superoxide dismutase (SOD) is said to be very sensitive to changes in plasma Zn/Cu ratio and alterations in SOD activity with zinc supplementation may result in excess free radicals that are damaging to the cell membrane. Studies have also noted some competitive interaction between zinc and iron that can result in decreased serum ferritin and hematocrit concentrations especially in women [81, 82].

Table 1 – Summary of toxic effects of essential and non-essential heavy metals

Heavy metal	Sources	Effects on human body	Symptoms of poisoning	Chronic exposure risks	References
Lead (Pb)	Lead-based paints, plumbing, contaminated water, soil, industrial processes	Affects nervous system, kidneys, blood, and bones	Fatigue, abdominal pain, headaches, irritability, anemia	Cognitive decline, developmental delays in children, kidney damage, hypertension	[83]
Mercury (Hg)	Fish (especially large fish), industrial emissions, dental fillings (amalgam), thermometers	Affects the nervous system, kidneys, and immune system	Tremors, vision/ hearing problems, memory loss, fatigue	Neurological damage, immune system dysfunction, developmental delays in children	[84]

Continuation of the table

Heavy metal	Sources	Effects on human body	Symptoms of poisoning	Chronic exposure risks	References
Arsenic (As)	Contaminated water, pesticides, industrial emissions, contaminated food (especially rice)	Affects skin, lungs, liver, kidneys, and nervous system	Nausea, vomiting, abdominal pain, skin lesions, diarrhea	Cancer (skin, lung, liver), cardiovascular disease, peripheral neuropathy	[85]
Chromium (Cr)	Industrial processes, contaminated water, air pollution	Affects liver, kidneys, and nervous system	Abdominal pain, nausea, vomiting, skin irritation	Cancer (lung, stomach), kidney damage, respiratory issues	[86]
Nickel (Ni)	Industrial processes, contaminated water, certain alloys, jewelry	Affects lungs, skin, kidneys, and cardiovascular system	Skin rashes, respiratory issues, fatigue, headache	Lung cancer, respiratory diseases, kidney damage	[87]
Cadmium (Cd)	Cigarette smoke, industrial emissions, contaminated food (especially shellfish, rice)	Affects kidneys, lungs, bones, and liver	Shortness of breath, kidney dysfunction, abdominal pain, weakness	Kidney failure, osteoporosis, lung cancer, cardiovascular disease	[88]
Iron (Fe)	Meat, fish, beans, fortified cereals, supplements	Essential for oxygen transport, but excessive iron can damage organs	Nausea, vomiting, abdominal pain, liver damage, fatigue	Organ damage (liver, heart), diabetes, arthritis, neurological damage	[88]
Cobalt (Co)	Seafood, meat, industrial exposure (e.g., batteries, alloys)	Essential in small amounts (vitamin B12), but excessive exposure can damage heart, liver, and kidneys	Vomiting, diarrhea, heart failure, skin rashes	Heart damage, lung disease, neurological issues, cancer	[37]
Magnesium (Mg)	Nuts, seeds, whole grains, leafy greens, supplements	Essential for muscle function, bone health, and metabolism	Diarrhea, nausea, lethargy, difficulty breathing	Hypotension, heart arrhythmias, kidney damage (in excessive amounts)	[89]
Manganese (Mn)	Nuts, seeds, whole grains, industrial exposure (e.g., welding, mining)	Essential in trace amounts for bone health and metabolism	Fatigue, dizziness, tremors, difficulty walking, facial muscle spasms	Manganism (Parkinson-like syndrome), liver damage, reproductive toxicity	[65]
Copper (Cu)	Seafood, meat, nuts, seeds, water (in copper pipes), supplements	Essential for enzymes, but too much can lead to toxicity	Nausea, vomiting, abdominal pain, diarrhea, jaundice	Liver damage, kidney damage, gastrointestinal bleeding, neurological issues	[90]
Selenium (Se)	Brazil nuts, seafood, meat, grains	Essential antioxidant for cellular function, but toxicity can occur	Nausea, vomiting, hair loss, fatigue, garlic-like odor on breath	Liver and kidney damage, brittle nails, hair loss, neurological damage	[91]
Zinc (Zn)	Meat, shellfish, legumes, seeds, dairy products	Essential for immune function, protein synthesis, and wound healing	Nausea, vomiting, loss of appetite, stomach cramps, diarrhea	Immune system suppression, reduced copper absorption, gastrointestinal issues	[82]

General mechanisms of heavy metal toxicity

HMs have an impact on nearly all body systems, causing toxic, allergic, carcinogenic, and gonadotropic effects. Some HMs selectively accumulate in certain organs and tissues, which can lead to structural and functional disruptions [92]. They have been seen to have an embryotoxic effect through the fetoplacental system and a mutagenic effect (Figure 4).

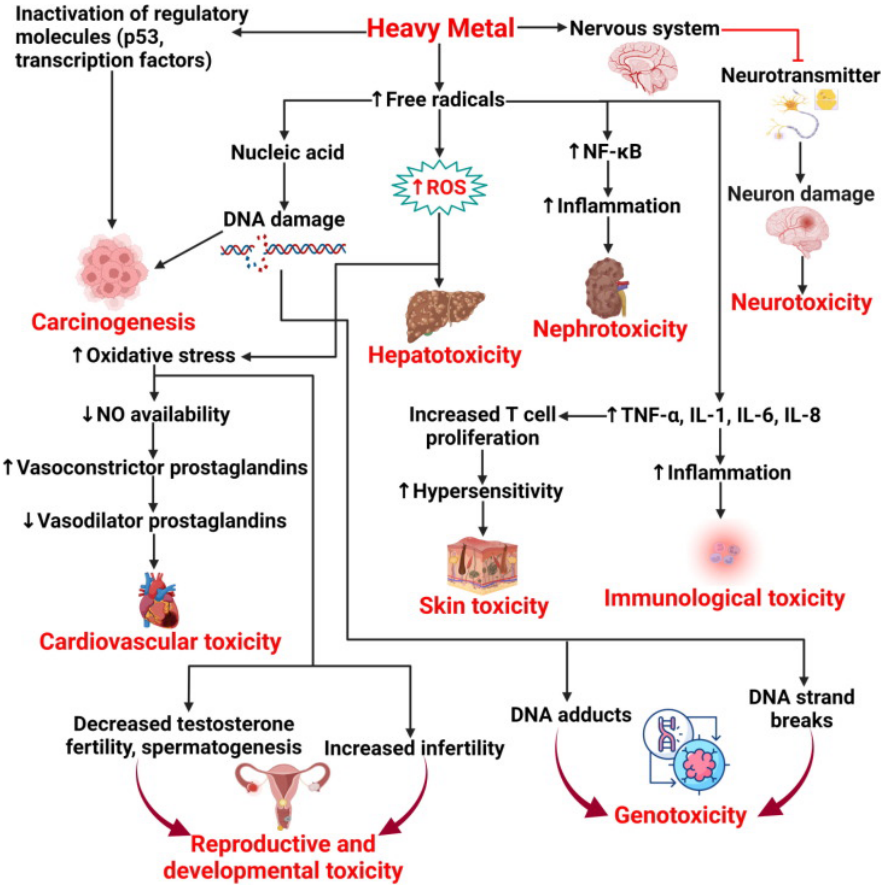

Figure 4 – Various toxicity effects of heavy metal accumulation in human body [93]

HMs toxicity is strongly associated with the extent of protein synthesis inhibition. Metals cause oxidative stress, DNA damage, mitochondrial malfunction, and apoptosis by disrupting molecular processes. HMs effect on specific organs can also depend on the dose and route of their entry into the body [16, 17].

The formation of metalloprotein complexes by HMs is a crucial factor in their distribution throughout the body [94]. This leads to the following model of how HMs behave in the body: binding with organic substances, breakdown of organometallic compounds, and alteration of the metal's oxidation state within the biological system (Figure 5).

The process of biotransformation usually results in detoxification. The amount and duration of metal accumulation are determined by their type and involved organ. Individual metals are distributed in various ways in the body: usually, muscles accumulate nickel, copper, and zinc in the smallest amounts, whereas copper accumulates to a greater extent in the liver and nickel in the kidneys [96].

The metabolism of metals has a considerable influence on their accumulation in the body, their distribution within tissues, and their toxic effects [97].

HMs exert their effects by forming coordinate covalent bonds with various molecules (ligands), which is the underlying mechanism of their action. Metals interact with ligands of biological significance, such as proteins and nucleic acids, which contain electron-donor groups such as oxygen, nitrogen, and sulfur in their molecule [98].

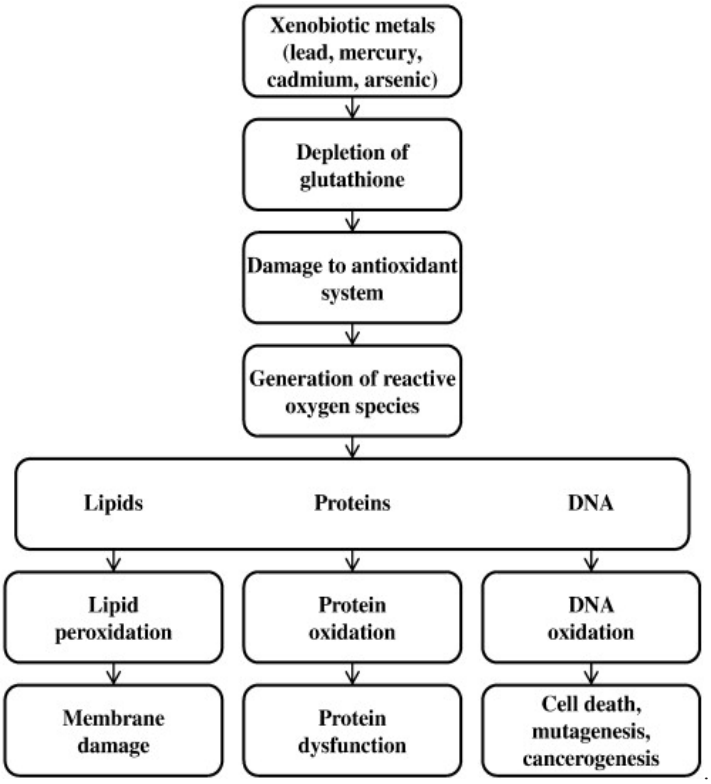

Figure 5 – Hypothetical mechanisms of metal toxicity [95]

There are various outcomes of the interaction between metals and ligands. The primary effects of this interaction include the disruption of hydrogen bonds within the macromolecule, the displacement of other metals bound to the ligands, and consequently, alterations in the tertiary structure of the complex. This leads to changes in their biological properties such as enzyme activity inhibition, alteration of transport properties, and others. The binding of metals to membrane structure ligands primarily results in the disruption of active or passive transmembrane transport processes. The inhibition of enzymes that participate in the DNA repair process may also have a role in the onset of mutagenesis and carcinogenesis [99].

Each metal exhibits a distinct pattern of affinity constants for different ligands across various tissues. Metals with an increased affinity for SH- groups are among the so-called thiol poisons (mercury, arsenic, etc.). The non-competitive inhibition of enzymes happens when metals interact with the structural components of the enzyme molecule and alter its conformation, even if the active center remains intact. Interacting with nucleic acids, metal cations can disrupt hydrogen bonds and create coordination-covalent bonds with phosphate groups and nitrogen atoms of nitrogen bases, they may destabilize DNA structure, what results in the disturbance of both transcription and translation processes [100].

At times, metals can serve as enzyme activators and participate in nucleic acid synthesis and repair. For instance, thymidine kinase activity requires zinc. However, when other metals, such as cadmium, replace zinc during intoxication, the enzyme activity is disrupted, and DNA synthesis is impeded. The inhibition of DNA repair enzymes is partly linked to the mutagenic activity of arsenic compounds. In this regard, investigation of how toxicants interact with ligands that are bound to membranes is crucial. The ability of metals to interact precisely with these structures is determined not only by their specific properties but also by their position [101].

Metals primarily interact with the outer surface of the cell membrane. Slowly penetrating substances can bind strongly to ligands and consequently alter the properties of the membrane. For instance, the organomercury compound chlormerodrin inhibits the transport of sugars through the membrane by interacting with the -SH groups of erythrocytes. Thereby metals can interact with any organelles that are enclosed by a membrane, including mitochondria, endoplasmic reticulum, and lysosomes. However, the

substances that can easily cross the membrane, such as methylmercury, are unlikely to have a significant effect on its properties [102, 103].

Certain metals may have a harmful impact because they compete with crucial elements necessary for proper functioning. Thus, tungsten acts as a competitor to molybdenum and inhibits xanthine oxidase, while lead hinders the utilization of iron in heme synthesis and therefore inhibits ferrochelatase activity. There is evidence that cadmium inhibits the transfer of zinc from the mother to the fetus through the placenta, leading to teratogenic effects [104].

Body detoxification mechanisms

Under normal circumstances, a healthy organism is a comprehensive and integrated system, capable of eliminating various toxins by converting them into water-soluble molecules. Detoxification is a metabolic process aimed at inactivating and removing toxic substances from the body. The process of metabolic detoxification includes a series of enzymatic reactions that neutralize and dissolve toxins, eventually transporting them to secretory organs (such as the liver and kidneys) for complete elimination from the body, what enables the converted toxins to be excreted directly through the renal tubules or gallbladder [105].

The enzymatic system that transforms xenobiotics is a mechanism that helps the body adapt to the impact of both exogenous and endogenous toxins Metabolic detoxification reactions are crucial not only for shielding the body from unfavorable environmental conditions, but also for sustaining homeostatic equilibrium within the body [106].

The detoxification or biotransformation system includes 3 steps: bioactivation, conjugation and evacuation (Figure 6).

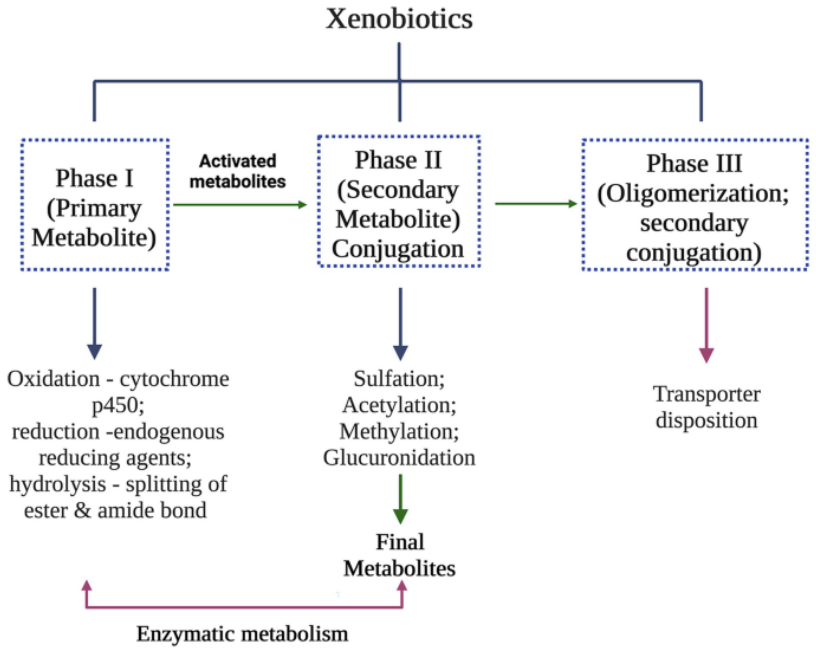

Figure 6 – Simple scheme of xenobiotics detoxification [107]

During the initial stage of metabolism, biotransformation reactions take place to convert fat-soluble toxins into water-soluble molecules prior to their entry into the circulation system. In some cases, toxins can even be detoxified before reaching the liver through the same biotransformation reactions that occur in the intestinal tract [108, 109]. A number of chemicals, such as 3-MC, benzpyrene, and DDT, once in the body, spread through the lymph stream to cells and tissues of various systems and organs, bypassing the inactivation process in the liver. which exacerbate their toxicity. The enzymes that metabolize xenobiotics, located in the endoplasmic reticulum of the intestine, have biochemical characteristics similar to those of the liver. In general, the rate of xenobiotic metabolism

by the intestinal enzymes is lower than that of similar hepatic enzymes. [110].

Enzymes such cytochromes P450, dihydropyrimidine dehydrogenase, butyrylcholinesterase, paraxonase, alcohol hydrogenase, aldehyde dehydrogenase, etc., offer the first stage of the biotransformation process. Microsomal oxidation is caused by the cytochrome P-450 superfamily (CYP-450), a collection of enzymes with over 1000 different isoforms that not only metabolize medicines but also take part in the creation of cholesterol, steroid hormones, and other chemicals. Hepatocytes, as well as organs like the intestines, kidneys, lungs, brain, and heart, contain the greatest number of cytochromes [111].

The intestinal mucosa is responsible for approximately 25% of biotransformation processes in the body, making it the second most actively involved tissue in the detoxification process. All cells in the intestinal lining possess the ability to detoxify [112, 113]. Numerous transferases involved in the metabolism of bilirubin, other hormones (thyroxine, triiodothyronine), morphine, chloramphenicol, paracetamol, and other substances cause further alterations to toxic chemicals created during biotransformation [108].

Currently, the third phase of biotransformation is distinguished: the so-called evacuation phase, in which the main role is assigned to specific transport systems – proteins (P-glycoproteins – P-gp), involved in the regulation of absorption, distribution, and excretion of xenobiotics (into bile, blood). P-gps remove xenobiotics from cell membrane and cytoplasm, preventing the absorption of xenobiotics in the intestine. The activation of transporters may result in diverse alterations (primarily an elevation) in the levels of a substance in the bloodstream, based on the role of that particular transporter. Transporters that carry organic anions and cations are responsible for excreting hydrophilic xenobiotics and their metabolites into bile by the liver and urine by the kidneys [114, 115].

Role of nutrients in detoxification processes

The process of detoxification can be significantly influenced by normal digestion. The ingestion of food is recognized to influence the absorption of chemicals by affecting gastric emptying, intestinal transit, pH, and bile production. Metabolites of toxins and drugs that undergo conjugation in the intestinal tract are primarily excreted through bile and eventually eliminated in feces [116].

Nutrients play a crucial role in supporting biotransformation, beyond just aiding in excretion. An adequate supply of nutrients is essential not only for energy production but also for the formation of new enzymes and protein synthesis, which are critical for the detoxification process. Hence, it is necessary to have sufficient intake of carbohydrates, energy-supporting fats, and high-quality proteins to maintain the body's defense mechanisms against toxic damage [117].

The mechanisms of detoxification related to metal ions are not well understood at present. HMs can be harmful as they are not efficiently eliminated from the body. However, some of the metals can be transformed into less hazardous forms through several ways, including the formation of insoluble complexes in the intestinal tract, transportation of metal via the blood to other tissues where it can be immobilized (such as Pb^{2+} in bones), and conversion into less toxic forms by the liver and kidneys [81, 113].

Detoxification can be facilitated by the binding of toxins to protein molecules. The breakdown of poisons or conversion into a soluble form by liver enzymes is especially crucial for detoxification in humans, as it leads to their quick elimination [108].

Maintaining a balanced, normal, and complete detox requires the preservation of numerous conjugation processes. The conjugation pathway with glutathione has received more research attention compared to other pathways. Glutathione, a tripeptide composed of glutamic acid, cysteine, and glycine, participates in the conjugation reaction of over 40 various compounds of both exogenous and endogenous origin. The conjugation reaction involving glutathione proceeds through three or four stages, with the resulting conjugates being successively cleaved of glutamic acid and glycine. The remaining complex containing xenobiotics and cysteine can be excreted from the body in this form. However, the fourth stage is more commonly observed where the amino group of cysteine is acetylated, resulting in the formation of mercapturic acid, which is then excreted through the bile [118].

Another significant role of glutathione is in neutralizing endogenously formed peroxides that can cause toxicity. Amino acid conjugation in humans usually involves glycine, glutamine, and taurine, although other amino acids can also be utilized. The last two types of conjugation reactions involve the transfer of either a methyl or acetyl radical to the xenobiotic compound. These reactions are catalyzed by methyl or acetyltransferases found in various organs such as the liver, lungs, spleen, and adrenal glands [119].

Proteins involved in the ABC transporter superfamily are among the many transport proteins that can participate in safeguarding cells against harmful substances. These proteins, present in all living organisms, transport various substances (lipids, many xenobiotics, etc.) through the cell membrane. The functioning of P-glycoprotein (a transport ATPase) is a crucial mechanism for removing hydrophobic xenobiotics from cells. Present in the plasma membrane of various tissues, particularly the kidneys and intestines, P-glycoprotein is a phosphoglycoprotein with a molecular weight of 170 kDa. Its primary role is to remove chloride ions and hydrophobic toxic compounds from cells. Have been shown that utilization of biogen amins like serotonin and hydroxitripthophane provides defense of the body from damaging effect of non-symmetrical dimethylhydrozine and cadmium salts. Results of experiments allow us to predict their correcting action on the cell membrane state and reducing the organism's inner medium's hazards from chemical agents [120].

Metallothioneins play a crucial role in binding HMs, forming mercaptides that can bind up to seven HM ions per molecule. They are also capable of replacing glutathione in the glutathione peroxidase system [121]. As these molecules contain up to 30% cysteine, it is important to consume dietary proteins that are balanced in their amino acid composition. Therefore, a balanced diet is essential for neutralizing any chemical compounds [122].

Various reactions in the body, including detoxification processes, require many vitamins and minerals as essential components for the production of enzymes. Vitamins are involved in various mechanisms in the metabolism of foreign chemicals and drugs [123].

Xenobiotics undergo various changes during their metabolism, including the formation of new functional groups in functionalization reactions. These reactions take place in the liver's endoplasmic reticulum, with the cytochrome P450 system, which is part of the NADPH-dependent monooxygenase system, being the most important enzyme involved. Conjugation reactions, the formation of paired compounds with glutathione, sulfuric, and glucuronic acids, represent the second crucial step in the transformation of foreign substances [106]. Vitamins play a direct role in these processes, acting as coenzymes in detoxification reactions, as well as an indirect role through the synthesis of components of the microsomal oxidation chain and other detoxification reactions. Fat-soluble vitamins also play a critical role in the biotransformation of xenobiotics by regulating the structural integrity of membranes, including microsomes, to ensure their normal functioning [124].

Among the vitamins associated with the metabolism of foreign substances, the most important can be considered ascorbic acid, vitamins PP, A, E, B12, folic acid, and other coenzymatic B vitamins. Studies have shown that the presence of foreign compounds in the body can lead to a decrease in the levels of ascorbic acid, which is stored in the liver and adrenal glands. Additionally, there is a direct correlation between the concentration of ascorbic acid and the levels of cytochrome P450, a crucial component in the system responsible for transforming foreign substances [117].

The role of vitamin A in the biotransformation of xenobiotics has been under study in recent years due to interesting reports on the anticarcinogenic properties of retinol and carotenes, specifically their effect on chemically induced tumors. It has been found that there is a strong correlation between the concentration of vitamin A and cytochrome P450 levels in the liver of rats fed with varying levels of vitamin A [125, 126].

Similar results were observed for vitamins B12 and B6 when their effect on the microsomal oxidation system was studied. These vitamins act as transmethylation coenzymes along with folic acid and methionine, which donate methyl groups, and affect the metabolism of xenobiotics. The deficiency of these three nutrients in the diet resulted in a significant reduction in cytochrome P450 concentration in the liver microsomes of experimental animals [117].

Tocopherol is undoubtedly also involved in the detoxification of foreign substances. During the biotransformation of drugs, toxic free-radical compounds can be formed, which require antioxidants, in particular vitamin E, to "extinguish" them. Studies have demonstrated the function of vitamin E in mitigating the harmful impact of the foreign toxic substance heptachlor on liver microsomes. It has been established that the metabolization of this poison in liver microsomes is accompanied by the active formation of free radical products, which are the main cell-damaging factor. At the same time, the leading role in the activation of LPO is played by microsomal enzymes – cytochromes P450 and P448. Vitamin E has been found to have a significant positive effect by reducing the intensity of lipid peroxidation and activating antioxidant defense mechanisms in cases of liver damage caused by chemical agents. This leads to the preservation of cell membrane structure and function [127].

Thereby vitamins and minerals needed to support detoxification processes include vitamins A, B2, B3, B5, B6, folic acid (B9), B12, C, and E, iron, calcium, copper, zinc, magnesium, and selenium. It was established that vitamins C and E, sodium selenite protect erythrocytes from disruption by action of 1,1-dimetylhydrazine *in vitro* and *in vivo*. The protective effect of these biologically active compounds is more pronounced when combined [128, 129].

It is known that a small number of ions of such metals as cobalt, lead, cadmium, copper, has a catalytic effect on the oxidative destruction of many vitamins. Metals can affect the activity of retinol, riboflavin, pantothenic acid, ascorbic acid, cholecalciferol, and ergocalciferol. It has been established that during the absorption process in the intestine, many mineral substances compete with each other, such as calcium with iron, copper, magnesium, and lead; copper with zinc, calcium, and magnesium; and iron with calcium, lead, cadmium, and zinc. Cadmium acts as an antagonist to almost all macro- and microelements. Zinc, copper, selenium, and calcium can prevent the absorption of cadmium [130].

Regular bowel movements are essential for their complete removal. Consuming an adequate amount of dietary fiber is crucial for regular bowel movements and the removal of biologically transformed toxins from the body. It helps by binding certain toxins, providing an excretory route. Plant foods are the main source of dietary fiber and various vitamins in the human body. Unlike other nutrients, dietary fiber is not a source of energy. Once consumed, they undergo partial breakdown by microorganisms in the large intestine. The breakdown of cellulose is around 30-40%, while hemicellulose and pectin substances break down by 60-84% and 35%, respectively. The energy released during this process is mostly utilized by intestinal bacteria for their own metabolic processes. The majority of monosaccharides that result from the breakdown of dietary fiber are transformed into volatile fatty acids such as acetic, propionic, and butyric acid, as well as gases such as methane and hydrogen that are essential for regulating the functioning of the large intestine. These substances can be partially absorbed through the intestinal walls, but only about 1% of the nutrients formed during the breakdown of dietary fiber enter the human body [131].

The presence of insoluble dietary fiber in food products can speed up the elimination of different foreign substances from the body. These substances may include carcinogens, endotoxins, exotoxins, and incompletely digested nutrient products. Ballast substances possess a fibrous-capillary structure that makes them effective natural enterosorbents. This structure enables dietary fibers to absorb or dissolve toxins, which decreases the likelihood of toxins coming into contact with the intestinal mucosa. As a result, there is a reduction in the severity of the intoxication syndrome and inflammatory-dystrophic changes in the mucous membrane [132].

The presence of dietary fiber in food products can lower the levels of free ammonia and other carcinogens that are generated during putrefaction, fermentation, or are present in the food. As plant fibers are not absorbed in the intestines, they are promptly eliminated from the body through feces, along with the compounds they have absorbed. Moreover, dietary fibers possess ion-exchange properties that allow them to eliminate HM ions like lead and strontium from the body. In addition, dietary fibers impact the electrolyte metabolism in the body and the electrolyte composition of feces. As a natural product, dietary fibers demonstrate anti-inflammatory activity [133].

Dietary fiber is the substrate on which bacteria of the intestinal microflora develop, and pectins are also nutrients for these bacteria. The regular microbial population in the intestines comprises numerous bacterial species, amounting to several hundred. Beneficial intestinal bacteria rely on dietary fiber to carry out their essential functions. Consequently, the number of bacteria required by the body increases, which has a positive effect on the formation of fecal matter. Additionally, these beneficial bacteria generate substances that are necessary for the human body, such as vitamins, amino acids, and specific fatty acids that are utilized by intestinal cells. Moreover, dietary fiber enhances the production of vitamins B1, B2, B6, PP, and folic acid by the intestinal bacteria [134]. Studies of the intensity level of lipid peroxidation processes in the cells of vital organs during intoxication with lead compounds have shown that the use of dietary fiber from rice husks can reduce the number of peroxide radicals, which is explained by the process of ion absorption [135]. The regular microbial population in the intestines acts as a metabolic organ that participates in the metabolism of both endogenous and exogenous compounds. This structure serves as the primary site for absorption and is responsible for the translocation of all agents. The fact of existence of a biofilm lining the mucous membranes and including numerous microcolonies of various bacteria is not denied [136, 137].

Soluble fibers have been found to be more effective in removing HMs, toxic substances, radioisotopes, and cholesterol from the body. Soluble dietary fibers, such as pectins, gums, alginates, etc., are often utilized in the food industry as processing aids to enhance the structure, taste, texture, and other characteristics of the final product. These fibers are also beneficial for therapeutic and preventive nutrition, as they satisfy two important principles: slowing down the absorption of harmful substances from the gastrointestinal tract and accelerating their removal from the body [138].

Carrageenans are sulfated polysaccharides from red seaweeds. Medical and biological tests have demonstrated that carrageenans aid in the removal of HMs, radioactive isotopes, and excess cholesterol from the body. They cannot be broken down by human gastrointestinal enzymes. Moreover, carrageenans, which are present in food products, play significant physiological roles as dietary fiber: they regulate the function of the gastrointestinal tract and have a beneficial impact on the intestinal bacterial habitat [139].

Clinical and biological tests have shown that alginates have the ability to absorb HMs and their radioisotopes without affecting calcium metabolism in the human body. Food products containing alginates exhibit similar characteristics. Alginates obtained through chemical hydrolysis with low and medium molecular weights have the ability to strongly and effectively bind lead and cadmium ions. The binding efficiency of alginates is dependent on their molecular weight, with low molecular weight calcium alginate exhibiting higher sorption capacity than high and medium molecular weight samples [140].

A significant amount of information has been gathered, suggesting that the gastrointestinal tract's microflora plays a crucial role in the detoxification of specific endogenous and exogenous substances [141]. It also regulates the absorption and excretion of elements such as Na, K, Ca, Mg, Zn, Fe, Cu, Mn, Mo, among others. The study of microorganisms present in probiotic formulations and their ability to absorb HM ions is an area of significant interest. Moreover, research conducted on livestock has demonstrated that the use of probiotic preparations resulted in a substantial reduction in the accumulation of toxic metals [142].

There is evidence that different strains of lactobacilli, propionic acid bacteria, and bifidobacteria can effectively absorb cadmium and lead ions on their surface. Lactobacillus plantarum culture, for instance, was demonstrated to dramatically lower the hazardous burden of cadmium in fish trials by lowering the degree of bioaccumulation, reestablishing intestinal microbiota, and boosting the body's antioxidant reserve. Similarly, studies on mice have demonstrated that the BT36 strain of *Pediococcus acidilactici* efficiently lowers oxidative stress and chromium compound buildup, minimizing liver tissue damage [143, 144]. Thus, the presence of probiotics and alimentary fibers in diet has a beneficial effect on the detoxification of harmful agents in the body.

Conclusion

Despite the extensive research conducted on HMs intoxication over the past few decades, several aspects still require the attention of researchers. One such area is the detoxification of HMs in the body and minimization of the consequences of acute or chronic poisoning. HMs have diverse mechanisms of toxicity, depending on their chemical properties and their affinity for components in the living cells. Some metals are essential for the normal functioning of cells in moderate amounts, but excess amounts can have a damaging effect. Most HMs tend to accumulate in the body tissues. In natural conditions, excess toxins are neutralized through various detoxification mechanisms, including binding, biotransformation, and excretion. These mechanisms involve the participation of different proteins, vitamins, vitamin-like substances, and sorption-active compounds that are present in food products. Despite the numerous studies that have evaluated the detoxification properties of individual components in food raw materials, these investigations remain relevant. The identification of the mechanisms by which dietary factors interact with toxic compounds can facilitate the creation of functional food products with enhanced detoxification capabilities. This review allows us to systematize some scattered data on the data on detoxifying characteristics of various food components and to define a field for future scientific research on the interaction of nutritional factors and xenobiotics, HMs in particular, in the body.

Conflict of interest

All authors are aware of the article's content and declare no conflict of interest.

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