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Article

Chemical Mechanisms and Protective Role of Natural Products Against Heavy Metals-Induced Neurotoxicity in Various Herbs/Plants

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Abstract: Heavy metal pollution of the environment is a persistent concern to both biotic and abiotic elements. Numerous harmful effects, including neurotoxicity and apoptotic cell death, have been connected to heavy metals like mercury, arsenic, cadmium, and lead. Despite the fact that these metals are necessary for regular biological processes, their biomagnification within cells has negative consequences. The generation of free radicals in heavy metal-induced neurotoxicity upsets the equilibrium between the oxidative and antioxidative defense mechanisms, leading to oxidative stress. Necrosis, DNA damage, and neurological diseases are linked to this stress. This brief study summarizes what is now known about the ability of natural compounds derived from various herbs and plants to protect against neurotoxicity caused by heavy metals. Knowing these defense mechanisms helps develop mitigation methods for the harmful impacts of heavy metal exposure.

Keywords: Heavy metals; Neurotoxicity; Free radicals; Reactive nitrogen species

1. Introduction

Inorganic elements with a specific gravity five times that of water are commonly referred to as heavy metals. Heavy metals that are present in the d-orbital elements of the periodic table include arsenic, cadmium, mercury, and lead. These metals' pathophysiological relevance makes them extremely important. They can seriously harm important organs like the neurological system, reproductive systems, gastrointestinal tract, and mucosal tissues when they build up in living systems.The exact mechanism by which these heavy metals can cause disease is still unknown, but reports from various laboratories indicate that their presence or excessive accumulation in bodily tissues can cause free radicals, namely reactive oxygen species (ROS) and reactive nitrogen species (RNS), to be produced. This can ultimately result in the development of oxidative stress [1,2]. Free radicals have been tied to lipid peroxidation, which is linked to the onset of several diseases, oxidation of protein thiol groups, and damage to DNA. Numerous factors can release heavy metals into the environment, such as mining operations, groundwater, commercial products, industrial waste, automobile emissions, paints, fertilisers, lead-acid batteries, treated wood, plastics in the ocean, aging water supply infrastructure, traditional medicines, and tainted foods [2]. Land, water, and agricultural and animal products are all contaminated by heavy metals. The human body can absorb these substances by eating, inhalation, direct contact, and other pathways. Heavy metals accumulate and become poisonous to the body's systems, which has a host of negative consequences. This article seeks to give a general overview of the ways in which phytochemicals might shield animals, including humans, against the neurotoxicity resulting from particular heavy metals.

2. The Impact of Heavy Metals on Cholinergic and Noncholinergic Systems

It has been established that both cholinergic and noncholinergic systems are adversely affected by heavy metals. It is commonly known that there is a link between the onset of Parkinson's and Alzheimer's diseases and the presence of heavy metals. The brain's primary regulator of neurotransmission systems, the cholinergic system regulates a number of physiological and cognitive processes, including learning, memory, neuronal

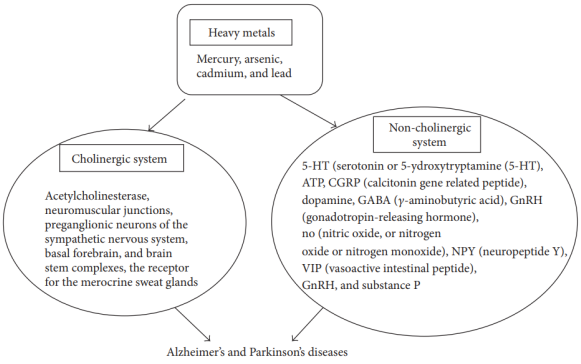

Figure 1. Heavy metals' effects on the cholinergic and noncholinergic systems linked to Parkinson's and Alzheimer's disease

development, and differentiation [4,5]. Cholinergic substances include any chemicals or ligands that can produce, alter, release, or mimic the effects of acetylcholine at a certain type of acetylcholine receptor. Similarly, acetylcholine is a neurotransmitter, and any receptor or synapse that uses it is called cholinergic. Because they depend on acetylcholine to function, the parasympathetic nervous system, the sympathetic nervous system's preganglionic neurons, neuromuscular junctions, the brain stem, the basal forebrain, and the receptor for the merocrine sweat glands are all cholinergic. On the other hand, the autonomic nervous system (ANS) includes the noncholinergic system, which is mediated by the neurotransmitter nonnoradrenergic, noncholinergic (NANC). ATP, Calcitonin gene related peptide (CGRP), Dopamine, γ-aminobutyric acid (GABA), Gonadotropin-releasing hormone (GnRH), nitric oxide or nitrogen oxide or nitrogen monoxide (NO), Neuropeptide Y (NPY), Vasoactive intestinal peptide (VIP), and substance P are some of the substances that are included in this system. The oxygen, nitrogen, or sulfur-containing components of cells can form complexes with the heavy metals 1.

2.1. Mercury (Hg)

Any naturally occurring type of mercury, whether chemical or physical, can have harmful effects at high concentrations. Mercury can be found in many different forms, including organic mercuric compounds, elemental mercury vapour (Hg), inorganic mercurous (Hg II), and mercuric (Hg III) [6,7]. These variations negatively impact several organs, including the kidneys, lungs, and brain [8,9]. When the oxidation state of mercury is zero, it exists in its elemental form as a liquid. According to the current periodic table, it is categorized as a transition metal because of its high toxicity and reactivity.undertook a thorough investigation of the chemistry of mercury recently, including its different chemical forms, the metabolic changes they go through in different organs, the range of detrimental effects they have on mammalian systems, and possible response mechanisms. Mercury poisoning results in disruption of cellular function in the brain and other organs because of its interaction with thiol groups of cellular proteins and enzymes. The three forms of this heavy metal—solid, liquid, and gas—that an individual is exposed to are linked to the pathophysiology of mercury toxicity. Mercury can readily cross the blood-brain barrier (BBB) and build up in the dense lysosomal bodies found in neurons, which can lead to neurotoxicity.In both adults and children, mercury toxicity presents as headaches, nausea, dysphagia, depression, hypertension, and neuromuscular symptoms. Mercury toxicity can be treated with a number of drugs, including dimercaprol (BAL), D-penicillamine (DPCN), and 2,3-dimercapto-1-propanesulfonic acid (DMPS). The user also highlights the existence of antioxidants like glutathione and N-acetylcysteine (NAC). The most common treatment for mercury toxicity is long-term chelation therapy. However, several plant-based concepts have shown great promise in protecting against or lessening the negative consequences of mercury toxicity in humans and animals. A separate section has addressed the protective and beneficial properties of several phytochemicals, which are listed in Table 1.

2.2. Cadmium (Cd)

Similar chemical characteristics are shared by cadmium, a prominent element in the last d-orbital group of the current periodic table, and by mercury and zinc. Its low melting point and +2 oxidation state are its main states.

Due to an increase in micronucleated polychromatic erythrocytes (MNPE) and micronucleated normochromatic erythrocytes (MNNE), prolonged exposure to calcium might be harmful to both the mother and the fetus [10,11]. One of the fundamental mechanisms causing cadmium's harmful effects is its known capacity to produce free radicals and cause oxidative stress [12].

It inactivates enzymes linked to antioxidant reactions by reacting with their thiol groups. Cadmium negatively affects linked biological processes because it can replace calcium and magnesium in some biological systems [13]. Cadmium exposure has also been shown to alter DNA repair activity [13]. A cadmium intoxicated person may have problems in the respiratory, circulatory, excretory, and gastrointestinal systems in addition to neurotoxicity. Specific clinical symptoms, such as headaches, sleep disturbances, memory problems, increased salivation, breathing difficulties, and kidney and liver failures, emerge with prolonged exposure to cadmium.Changes in the metabolism of neurotransmitters, particularly serotonin and GABA, are connected to these symptoms. Similar to mercury poisoning, the treatment of cadmium poisoning involves the use of phytochemicals, chelators, and antioxidants [2]; they are covered in more detail in a later section and in Table 1.

2.3. Arsenic (As)

The chemical element arsenic (As) has an atomic number of 33. There are two types of arsenic found in nature: pentavalent arsenate (As V) and trivalent arsenite (As III). Seafood intake, inhalation, and skin absorption all cause arsenic to bioaccumulate in the body. Numerous issues with the respiratory system, blood circulation system, gastrointestinal tract, and neurotransmission result from this buildup. It is known that exposure to arsenic can cause free radicals to develop, which can then cause oxidative stress. It adversely affects the levels and activities of antioxidant components found in human systems, including heme oxygenase-1 (HO-1) and glutathione peroxidase (GPx), as well as nonenzymatic components including peptides and proteins with sulfhydryl groups. The oxidative phosphorylation cycle and the Krebs cycle are negatively impacted by arsenic poisoning, which lowers energy levels and quickly reduces thiol-containing critical peptides and proteins [14,15]. Burning and numbness in the hands and feet, along with abnormalities in the cardiovascular and neurotransmission systems' operation, are characteristics of arsenic poisoning. Arsenic toxicity in particular has been linked to the development of neurological and vascular issues in people with diabetes mellitus [16,17]. While the usual blood level of arsenic is less than 1 mg/dL, the urine result is often less than 50 mg/L [14,15]. The main treatment for arsenic intoxication is chelation therapy, which uses aqueous garlic extract and dimercaprol or succimer (2,3-dimercaptosuccinic acid, DMSA) [18]. But several phytochemicals have also demonstrated to be quite successful in preventing arsenic toxicity, as Table 1 illustrates and is covered in the section that follows.

2.4. The element lead (Pb)

According to the Centers for Disease Control and Prevention (CDC)-USA, a blood lead level (BLL) of 10 μg/dL or more is deemed concerning [19]. Human peripheral and central nervous systems, blood circulation, cardiovascular system, excretory system, metabolic system, and reproductive system are all affected by lead-induced poisoning in a variety of physiological, biochemical, and behavioral ways [20]. Although it usually causes neurotoxicity, it significantly lowers children's cognitive abilities [21].

Excessive production of free radical species and oxidative stress are associated with mediated neurotoxicity, which may impair regular brain activity [1,22]. Lead is a substance that may easily cross the blood-brain barrier (BBB) and substitute calcium ions, which can interfere with calcium's ability to regulate brain cells and disturb intracellular processes. As a result, the pathological expressions of lead toxicity include peripheral motor neuropathy, anemia, hypertension, and gastrointestinal issues. Chronic lead toxicity in children may cause recurrent periods of unconsciousness, seizures, and mental state changes if lead levels are higher than 70 mg/dL. Chelation therapy, administration of specific herbal remedies, and preventive measures are required to treat lead toxicity effectively (Table 1).

3. Phytochemicals employed for mitigating the neurotoxic effects caused by heavy metals

Because of their antioxidant qualities, phytochemicals like flavonoids and polyphenols may be able to lessen the negative effects of heavy metals on people and other animals. Studies have shown that ingesting Arthrospira maxima (Spirulina) can significantly lessen the deleterious effects of cadmium on genes. The antioxidant characteristics of this specific kind of algae provide some evidence for this conclusion [17,18]. It has recently been discovered that adding soybean supplements to the diet significantly reduces the risk of cadmium-induced arterial and heart damage [23]. It has been shown that Nigella sativa seed oil has strong antioxidant properties that may protect vital organs

from oxidative damage, including the kidneys and brain. It has been proposed that employees at cement firms, where mercury is frequently emitted into the environment, can make use of virgin olive oils and Nigella sativa seed oil. Certain cyanobacterial species, such as Spirulina and Chlorella, include phytochemicals, such as carotenes, phycocyanobilin, vitamin C, and vitamin E. According to research [2,21,22], these phytochemicals have been shown to shield rats exposed to lead and cadmium.

It has been demonstrated that taking vitamin E in addition to cadmium can greatly reduce the build-up of this metal in a number of vital bodily tissues, including the kidney, liver, and blood. Water soluble vitamins (C, B1, and B6), like fat-soluble vitamin E, have been found to protect rat organs from lead and cadmium toxicity [16,20]. When vitamin C and E were given together to rats that had been exposed to cadmium, the amount of oxidative stress was significantly reduced. In the same experiment, vitamin E treatment of erythrocytes treated with Pb led to a significant reduction in lipid oxidation and δ-aminolevulinic dehydratase activity [21,22]. β-Fruits and plants are rich sources of the fat-soluble chemical compound known as beta-carotene. It has been found to function as a precursor to vitamin A (retinol), and it is a reddish-orange color. It is associated with an increased risk of lung cancer among smokers, according research [24,25].

A team of researchers effectively demonstrated a reduction in lead and cadmium-induced mitochondrial damage and programmed cell death in tissue culture models by using garlic extract. In addition, scientists saw damage to the rats' nervous systems, livers, kidneys, and haematic systems (which deal with blood). It has been shown that garlic has a higher antioxidant capacity than onion, which could be because garlic contains allicin [6] showed that lead poisoning in rats can be effectively treated with a mixture of garlic extract and dimercaptosuccinic acid (DMSA). In addition to its many health advantages, garlic contains compounds that slow down aging and strengthen the immune system. Studies have shown that garlic extract may be able to mitigate the harmful effects of sodium arsenite [26,27]. Garlic is thought to have a preventive effect against arsenic toxicity because its extract contains thiosulfur components. When these elements interact with arsenic chemical species, they create stable chemical complexes that counteract the negative effects of arsenic [12]. Based on existing research, it appears that the chelating action of arsenic may include multiple components found in liquid garlic extracts, particularly allicin. Concomitant administration of plant extracts, such as curcumin, Hippophae rhamnoides, Centella asiatica, Aloe vera barbadensis, and Allium sativum, has been shown to reduce arsenic-induced toxicity. Evaluation of the experimental animals' hepatic, renal, and haematological characteristics allowed for this observation. Only a limited number of plants have been investigated for their potential use as medicine in order to counteract the harmful effects of arsenic [10,11,22].

However, research indicates that Annona muricata leaf extracts can effectively reduce the detrimental effects of arsenic on the nervous system. When compared to the aqueous extract, the methanolic extract of A. muricata leaves demonstrated higher activity. Depending on the dose, a decrease in arsenic toxicity was found. Additionally, these authors have demonstrated the potential usefulness of tea extract in reducing the toxicity linked to arsenic poisoning. Hippophae rhamnoides is a rich source of organic acids, carotenoids, and vitamins A, C, and E. These compounds' strong antioxidant content has been associated with their protective properties against arsenic-induced toxicity [23,25]. It has been observed that the existence of this material has the capacity to mitigate the deleterious impacts of free radicals, which arise from exposure to arsenic. Whether the drug is administered alone or in combination with a thiol chelator, the same effect is observed. Research has indicated that the use of a nanocapsulated drug delivery technology for quercetin is superior than bigger doses of the herb in terms of avoiding harm caused by arsenic [18,19].Traditional medicinal herbs including Moringa oleifera, A. barbadensis, and C. asiatica have been shown to have advantageous effects on safeguarding the body's important organs. These outcomes are probably attained by lowering tissue arsenic content, oxidative stress reduction, and phytochemical interactions with cysteine and methionine rich proteins [12,13,19].

Research has indicated that tomato extract possesses strong antioxidant qualities and can reduce the build-up of heavy metals. Additionally, it shields rats against the harmful effects of lead and cadmium. This tomato trait may be related to the presence of specific metal chelating proteins and phytochelatins. It has been shown that phenolic acid molecules such as caffeic acid, chlorogenic acid, vanillic acid, p-coumaric acid, and ferulic acid (in both cis and trans forms) are present in some Indian spices, such as coriander [24,25]. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), a diferuloyl methane molecule, is present in turmeric, on the other hand. It has been demonstrated that curcumin contains antioxidant and anti-inflammatory qualities. Furthermore, it has been noted that curcumin can shield rats from nephrotoxicity when they are exposed to cadmium. During a field investigation carried out in West Bengal, curcumin was isolated from turmeric [12,13].

Research has demonstrated that the catechins green tea, along with the flavonoids and phenols in grapes and curry leaves, offer similar protective advantages against lead and cadmium toxicity. (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), (-)-epicatechin (EC),

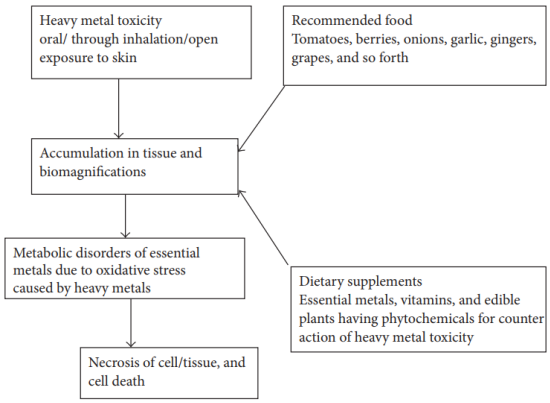

Figure 2. Impact of heavy metals on human system

(+)-gallocatechin (GC), and (+)-catechin are the main green tea polyphenols that are renowned for their antioxidant properties [4,9,15].

Authors in [28] discovered that giving oral S. nigrum and S. trilobatum leaf extract to albino mice for 30 days was an effective way to reduce the neurotoxic effects of lead. They observed that lipid peroxidation had decreased and that antioxidant enzyme levels, such as those of SOD, CAT, and GPx, had significantly increased. S. nigrum is a weed that can be hazardous to humans and animals. Some variants of the plant are dangerous. This herb is frequently used in traditional medicine.

Table 1. Phytochemicals as antidotes to heavy metals induced toxicity

Phytochemicals	Sources	Protective functions	References
Allicin	Garlic	Reduces arsenic induced oxidative and arsenic toxicity by complex formation	
Anthocyanin/flavonoids	Cherry, grapes, and berries	Anthocyanin protects against Cd-induced oxidative stress. Anthocyanin appears to effectively diminish Pb induced oxidative stress.	[8,9]
Catechins	Tea, cocoa, peach, and berries	Catechin inhibits Cd absorption and normalises bone metabolic disorders through the bone mineral density, bone mineral content, and bone calcium content. Catechin protects hepatic cell membrane fluidity, increases cell viability, and modulates oxidative stress.	[10,11]
Curcumin	Turmeric	Curcumin protects against Cd-induced lipid peroxidation. Curcumin binds Pb to form an excretable complex, reducing neurotoxicity and nephrotoxicity	[12,13]
Naringenin	Orange and grapefruit	Naringenin quenches free radicals, recovers antioxidant enzyme activity, and chelates Cd.	[14,15]
γ-Oryzanol	Rice	γ-Oryzanol reduces the testicular Cd concentration, improves δ-aminolevulinic acid dehydratase (ALAD) activity, and prevents lipid peroxidation.	[16,17]
Quercetin	Onion, tomato and radish olive oil, red wine, tea, and so forth	nduces the expression of endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). Quercetin modulates the mitogen-activated protein kinases (MAPKs) and nuclear factor kappa B (NF-κB) signalling pathway and forms excretable complex with Pb hydroxyl and superoxide groups scavenge radicals, whereas the phenolic groups act as possible chelating sites.	[18–20]
Phenolics	Coriander, fruits, vegetables, and tea	Act as antioxidants.	[21,22]
Phycocyanobilin	Cyanobacteria (Spirulina and Chlorella)	Probably acting as antioxidants.	[23,24]
Puerarin	Pueraria mirifica plant	Puerarin modulates the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt)/endothelial nitric oxide synthase (eNOS) pathway, reduces reactive oxygen species, and protects against DNA damage and apoptosis.	[25,26]
Vitamins A (β-carotenes), B1, B6, C, and E	Nigella sativa	Act as antioxidants.	[27,28]

A summary of the primary phytochemicals that have been found and investigated for their potential to guard against heavy metal-induced neurotoxicity is provided in Table 1. These phytochemicals were isolated from a variety of plant

sources. The protective effects of dietary supplements against the alterations in biochemical and physiological activity brought on by heavy metals are shown in Figure 2.

4. Conclusion

Heavy metals can create reactive oxygen species (ROS), which can lead to oxidative damage. When there is an imbalance between the production of reactive oxygen species (ROS) and the capacity of biological systems to efficiently counteract or repair the damage caused by ROS, heavy metal-induced oxidative stress results. The capacity of heavy metals to bind directly to thiol groups in proteins and enzymes causes structural changes in three dimensions, which is the source of their toxicity. As an alternative, heavy metals can take the place of divalent metal ions, which are necessary cofactors for proteins and enzymes to function at their best, in the catalytic pocket of these molecules. In each of these cases, the unfolding or denaturation of these biomolecules tends to cause them to lose their intrinsic properties, severely impairing their functions. In the end, this negatively affects their biological activity and, as a result, the health of their cells. Within their cells, all living things maintain a reducing environment. By continuously giving metabolic energy to maintain its lowered condition, enzymes maintain this lowered environment. The regular redox state can be upset by heavy metals, which produces free radicals and peroxides. These dangerous chemicals cause oxidative stress, which harms vital cellular constituents like DNA, lipids, and proteins. Because of their low cost, strong action, and lack of side effects, herbal compounds have the potential to significantly reduce the neurotoxicity produced by some heavy metals. Moreover, trials are being conducted on the use of particular vitamins and different chelating chemical compounds with the aim of forming coordinated complexes with these heavy metals, which would facilitate their removal and lessen the toxicity and burden of these metals on the impacted organs or tissues. Even though the use of antioxidants—natural, herbal, or synthetic—in conjunction with other chelating agents has improved clinical outcomes and enhanced the removal of toxic metals in animal models, more thorough clinical research using both established and newly developed chelating agents is required to achieve meaningful benefits with the least amount of side effects. To define the optimal therapeutic index for the administration of drugs, either singly or in combination, it is important to ascertain the proper dosage and duration of treatment for humans. In the end, what is known about how heavy metals affect biological systems ultimately points to their encouraging the generation of reactive oxygen or nitrogen species and free radicals, which can result in neurotoxicity and other health problems. However, these problems can be effectively addressed by utilising various preparations derived from a variety of traditional medicinal plants.

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