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Review Article

CURRY LEAVES AS ALTERNATIVE MEDICINE IN HEAVY METAL INDUCED OCCUPATIONAL HEALTH HAZARDS

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ABSTRACT

Workers in different industries are regularly exposed to heavy metals. Those metals enter their body through several routes (inhalation, food contamination etc.,) and accumulate in the tissues and induce generation of reactive oxygen species (ROS) leading to oxidative damages. Chronic, regular exposures result in health hazards. Certain physiological, biochemical and behavioural dysfunctions cumulate to pathological conditions. Many of the symptoms complained by those industry workers are hardly recognized to be related to occupational exposure to heavy metals, often unidentified as occupational health hazards with a story of metal induced oxidative stress beneath their etiology. Most of the synthetic conventional drugs which are extensively prescribed by clinicians for treatments of these diseases have adverse side effects and potent cytotoxicity. Herbal remedy can be a safe substitute. The heavy metals induce generation of ROS and the phyto-components have the potential to scavenge those and boost the body's endogenous antioxidant system. They have no reported cytotoxic or adverse side effects, if not over consumed. Some specific or a perfect blend of potent phyto-constituent(s) from curry leaves can be suggested for or adapted as alternative medicine or integrative medicine for preventing or treating or curing or protecting against heavy metal-induced occupational health hazards.

Keywords: Heavy metals, Oxidative damages, Phyto-components, Reactive oxygen species

INTRODUCTION

Heavy metals like lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) are alarming environmental toxins present extensively in the environment as pollutant. These metals are widely used in various industries like mining, metallurgy, paint, batteries, cosmetics, electronic, electroplating and metal finishing. These heavy metals are toxic to higher and lower organisms [1].

The industrial effluents contain these heavy metals. People who work in different industries like metallurgy, bullet manufacturing, paint, dye, fashion and glamour (i.e., models etc.) in different parts of the world, are regularly exposed to and get affected by heavy metals like lead, cadmium, mercury, arsenic etc. Metals accumulate in the soft organs like heart, liver, kidney, spleen, brain and induce oxidative stress which brings about tissue damage and dysfunction. Heavy metals like lead causes deteriorative changes to blood cell counts and lipid profile [2]. Metals bind to the blood cells and lead to reduced life span and enhance their fragility [3]. Exposure to heavy metals and their accumulation in body results in generation of ROS and induce oxidative stress which may in turn result in oxidative damages which leads to pathological conditions i.e., neuro-degeneration, anaemia, nephrotoxicity, hepatotoxicity, pulmonary oedema, infertility, immune compromisation etc [3]. Involvment of oxidative stress behind heavy metal toxicity often goes unnoticed or is revealed at late stage. There are reports of significant interactions between Cadmium, Calcium and Magnesium, and thiobarbituric acid reactive substances (TBARS), superoxide dismutase and catalase activity [1].

The conventional treatment for metal toxicity involves use of certain drugs for mobilization of the metals from living system and thus their removal. Chelation therapy is also in use [4]. Certain drugs are used for addressing metal toxicity related pathological conditions [2]. Those conventional medications in practise are reported to possess cytotoxicity and deleterious side effects on prolonged use. In the Indian Subcontinent several hundreds of herbal formulations are in use for treating different pathological situations [5,6]. Leaves, flowers and bark of plants with reported medicinal potentials as observed in folk medicine and traditional uses (i.e., *Murraya koenigii*, *Ocimum sanctum, Terminalia arjuna, Gingko biloba, Hypericum perforatum* etc.) are a better option to treat different pathological conditions resulting from metal induced oxidative stress [5, 6]. These alternative medicines derived from herbal origin are effective and have no or minimum side effects if administered in a definite dose unlike the conventional synthetic drugs [2].

Phyto-composition of curry leaves (*Murraya koenigii)*

Cocktail of various polyphenols, flavonoids, tannins, antioxidant polyphenolic glycosides, antioxidant polyphenolic peptides, alkaloids [table 1],vitamins [table 2], minerals [table 3] and other aromatic phytochemicals in the leaves of *Murraya koenigii* (popularly known as curry leaves) are the prime players for the potent antioxidant and free radical scavenging activity of this medicinal spice herb.

Phyto-chemicals present in the leaves of *Murraya koenigii* can protect against metal-induced oxidative stress, damage and subsequent health hazards. We have confirmed qualitatively and quantitatively the presence of certain potent antioxidant phyto-constituents in curry leaves. Our study revealed the antioxidant and protective activity of certain compounds in the aqueous preparation of the extract which we predict to be strictly polar in nature [2].

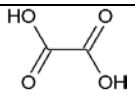
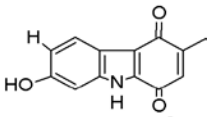
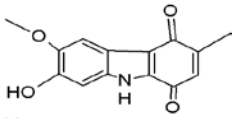
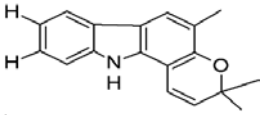
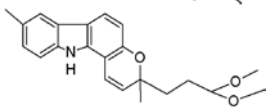
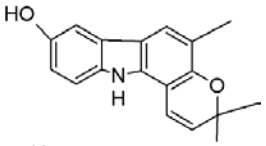
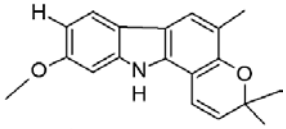
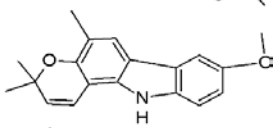
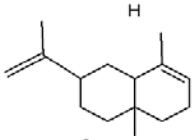
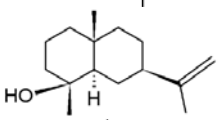
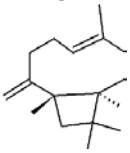
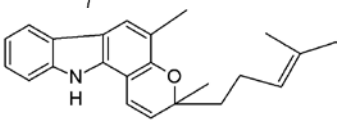
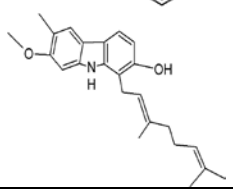
Heavy metals: the toxicants

"Heavy metals" are natural components of the Earth's crust. They can neither be degraded nor destroyed. Often they enter our bodies via food, drinking water and air. The term 'heavy metal' has the framed definition as 'any metallic chemical element that has a relatively high density and is toxic or poisonous at low concentrations'.

Examples of heavy metals include mercury (Hg), cadmium (Cd), arsenic (As), chromium (Cr), thallium (Tl), and lead (Pb). Some heavy metals (e. g. copper, selenium, zinc) are essential for the processes involved in metabolism in the human body. But they can lead to poisoning at higher concentrations. Heavy metal poisoning could result, for instance, from drinking-water contamination (e. g. lead pipes), high ambient air concentrations near emission sources,

or intake via the food chain. Heavy metals like lead, cadmium, mercury, arsenic are not present in living system and are non-essential for the process of life. If they enter in living system, they accumulate and interfere in the normal processes of the cells, organs and organ systems.

Table 1: Some bioactive phyto-chemicals of curry leaves

Name of the compound	Structure	Nature	Formula weight	Medicinal use
Oxalic Acid (Ethanedioic Acid)		$H_2C_2O_4$ Dicarboxylic Acid	FW: 90.035	Its conjugate base, known as oxalate ($C_2O_4^{2-}$), is a chelating agent for metal cations.
Koenigine Quinone A (7-methoxy-3-methylcarbazole-1,4-quinone)		$C_{13}H_9NO_3$ Carbazole alkaloid	FW: 227.215	Scavenges free radicals.
Koenigine Quinone B (6,7-dimethoxy-3-methylcarbazole-1,4-quinone)		$C_{14}H_{11}NO_4$ Carbazole alkaloid	FW: 257.251	Scavenges free radicals.
Girinimbin (Girinimbine(7CI); 3,11-Dihydro-3,3,5-trimethylpyrano[3,2-a]carbazole)		$C_{18}H_{17}NO$ Carbazole alkaloid	FW: 263.334	Scavenges free radicals.
Iso-mahanimbin (Pyrano[3,2-a]carbazole,3,11-dihydro-3,8-dimethyl-3-(4-methyl-3-penten-1-yl)-, (-)-)		$C_{22}H_{25}NO_3$ Carbazole alkaloid	FW: 351.439	Scavenges free radicals.
Koenine (Kenine; 3,11-Dihydro-3,3,5trimethylpyrano[3,2-a]carbazol-8-ol, 9CI)		$C_{18}H_{17}NO_2$ Carbazole alkaloid	FW: 279.333	Scavenges free radicals.
Kenidine (Kenigicine; Kenimbidine; Koenidine; Koenigicine; Koenimbidine; NSC 127151; 3,11-Dihydro-8,9-dimethoxy-3,3,5-trimethylpyrano[3,2-a]carbazole)		$C_{19}H_{19}NO_2$ Carbazole alkaloid	FW: 293.396	Scavenges free radicals.
Koenimbine (Koenimbin; Koenimbine; NSC 127152; 3,11-Dihydro-8-methoxy-3,3,5-trimethylpyrano[3,2-a]carbazole)		$C_{19}H_{19}NO_2$ Carbazole alkaloid	FW: 293.359	Scavenges free radicals.
α-selinene (Eudesma-3,11-diene; 2-Isopropenyl-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene)		$C_{15}H_{24}$ essential oils	FW: 205.351	
selin-11-en-4-*α*-ol (kongol; selin-11-en-4-alpha-ol; 2,3,4,5,6,7,8,8a-octahydronaphthalen-1-ol)		$C_{15}H_{26}O$ essential oils	FW: 222.366	
Caryophyllene ((−)-*trans*-Caryophyllene; *trans*-(1*R*,9*S*)-8-Methylene-4,11,11-trimethylbicyclo[7.2.0]undec-4-ene)		$C_{17}H_{28}$ natural bicyclic sesquiterpene that is a constituent of many essential oils	FW: 232.404	
Mahanimbine (3,5-dimethyl-3-(4-methylpent-3-en-1-yl)-3,11-dihydropyrano[3,2-a]carbazole)		$C_{23}H_{25}NO$ Carbazole alkaloid	FW: 331.450	Scavenges free radicals.
Murrayanol (5-hydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-3,6, 7-trimethoxychromen-4-one)		$C_{24}H_{29}NO_2$ Carbazole alkaloid	FW: 363.492	Scavenges free radicals.

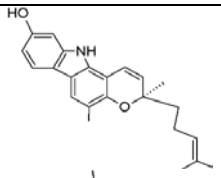
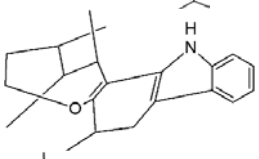
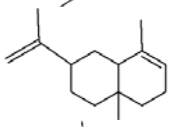
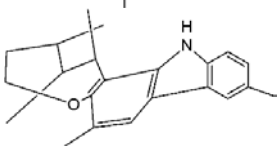
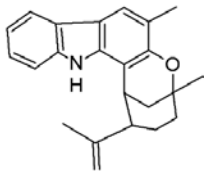
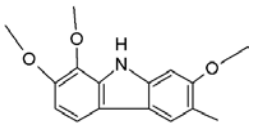
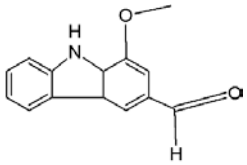
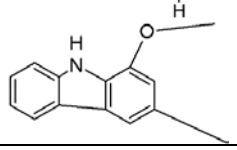
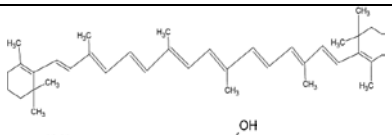
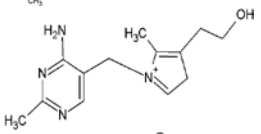
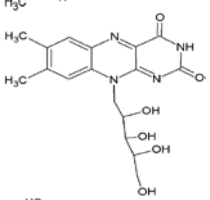
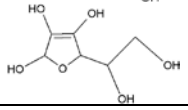
Mahanine (5-methyl-3-(4-methylpent-3-enyl)-3,11-dihydropyrano[3,2-a]carbazol-9-ol)		$C_{23}H_{25}NO_2$ Carbazole alkaloid	FW: 347.450	Scavenges free radicals.
Bicyclomahanimbine		$C_{21}H_{27}NO$ Carbazole alkaloid	FW: 309.445	Scavenges free radicals.
Phebalosin (7-methoxy-8-[(2r,3r)-3-(prop-1-en-2-yl)oxiran-2-yl]-2h-chromen-2-one 6545-99-9)		$C_{15}H_{24}$	FW: 204.351	Scavenges free radicals.
Bicyclomahanimbicine		$C_{22}H_{27}NO$ Carbazole alkaloid	FW: 321.455	Scavenges free radicals.
Cyclomahanimbine (5,7-dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole)		$C_{23}H_{25}NO$ Triterpenoid alkaloids	FW: 331.450	Scavenges free radicals.
Murrayastine, ([3-hydroxy-1-(7-methoxy-2-oxochromen-8-yl)-3-methylbutan-2-yl] 3-methylbutanoate)		$C_{16}H_{17}NO_3$ Alkaloids	FW: 271.311	Scavenges free radicals.
Murrayanine (1-Methoxy-9H-carbazole-3-carbaldehyde)		$C_{14}H_{13}NO2$ Alkaloids	FW: 227.258	Scavenges free radicals.
Murrayafoline (1-Methoxy-3-methyl-9H-carbazole)		$C_{38}H_{38}N_2O_6$ Alkaloids	FW: 211.259	Scavenges free radicals.

Table 2: Vitamins in curry leaves

Name of the compound	Structure	Nature	Formula weight	Medicinal use
Vitamin A (Carotene)		$C_{38}H_{54}$ Vitamin	FW: 510.835	Skin and hair tonic, to cure immunodefficiency
Vitamin B 1 (Thiamine)		$C_{13}H_{19}N_4O$ Vitamin	FW: 247.315	Maintains integrity of epithelial cells, cures eczema, allergic skin rash, burning sensation and dry, dull skin.
Vitamin B 2 (Riboflavin)		$C_{17}H_{20}N_4O_6$ Vitamin	FW: 376.363	Prevents infection
Vitamin C (Ascorbic acid)		$C_6H_{10}O_6$ Vitamin	FW: 178.14	Antioxidant

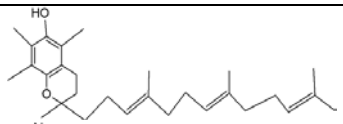
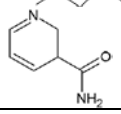
Vitamin E (Tocopherol)		Vitamin	FW: 424.658	Antioxidant
Vitamin B 3 (Niacin)		$C_6H_8N_2O$ Vitamin	FW: 124.140	Helps to cure anaemia

Table 3: Minerals in curry leaves

Name of the compound	Nature	Medicinal use
Calcium	Minerals	Helps to avoid osteoporosis
Iron	Minerals	Enough quantity of iron is there to cure anaemia
Phosphorous	Minerals	Phosphorus is an important constituent in every body tissue
Magnesium	Minerals	Necessary cofactor for many enzymes
Copper	Minerals	Necessary cofactor for many enzymes
Manganese	Minerals	Necessary cofactor for many enzymes
Zinc	Minerals	Necessary cofactor for many enzymes
Chromium	Minerals	Chromium slows the loss of calcium, so it may help prevent bone loss in women during menopause
Chloride	Minerals	An essential electrolyte located in all body fluids responsible for maintaining acid/base balance, transmitting nerve impulses and regulating fluid in and out of cells

Thus, they are toxic or poisonous for living organisms. Heavy metals tend to bioaccumulation and hence they are dangerous. An increase in the concentration of any chemical in a biological organism over time, compared to the chemical's concentration in the environment is termed as bioaccumulation**.** Compounds when taken up and stored faster than they are broken down (metabolized) or removed (excreted) in a living body, they accumulate therein. Heavy metals can enter a water supply by industrial and consumer waste. Acidic rain may break down soils and release heavy metals into water bodies like streams, lakes, rivers, and groundwater from where they may enter water supply [3]. Heavy metals may enter living system if present in high concentration in air near emission sources or may enter the food chain due to their bioaccumulative tendency.

Heavy metals in industries

Industries like metallurgy, paint, batteries, toys, crayons, cosmetics, fashion use heavy metals. Workers, who work in these industries, get regularly exposed to heavy metals.

Cadmium

Cadmium occurs naturally within the raw ores of metals like zinc and lead**.** During refining of zinc (or occasionally lead), cadmium is produced as an inevitable by-product. Once collected cadmium is easy to recycle. Cadmium is most significantly used in nickel/cadmium batteries, as rechargeable or secondary power sources exhibiting high output, long life, low maintenance and high tolerance to physical and electrical stress. Coatings of cadmium provide good protection from corrosion, particularly in high stress environments such as marine and aerospace applications where high safety or reliability is required. The coating is corroded only if damaged. Cadmium is also used in pigments, stabilizers for PVC, in alloys and electronic compounds. Cadmium is often found to be present as an impurity in several products, including phosphate fertilizers, detergents and refined petroleum products. Cadmium has a very long half-life in the body (10 to 30 y) and can build up over a long time. Over 80% of the body burden resides in the kidneys [7, 8].

Lead

In spite of declining lead prices**,** secondary production of lead has increased steadily because lead is one of most recycled non-ferrous metals. It is used in the manufacturing, construction and chemical industries. The physical and chemical property of metal lead makes it suitable for being used in those industries. It is malleable and ductile and hence can be easily shaped. Any operation in which battery plates, lead scrap, or oxide is handled may be a significant source of lead exposure. An additional source of lead exposure for workers can be airborne dispersion of lead dust (which settles on equipment, floors and other surfaces) via cross-drafts, pedestrian and vehicular traffic, and dry sweeping. Children also get badly exposed to lead metal and are prone to lead poisoning. Toys, plastic bathtubs, crayons, paints etc. contain lead. If lead pots are handled carelessly, lead exposure can occur. Lead fumes from lead pots, torching, burning or other operations where a flame contacts lead, or lead is heated above the melting point, may also be sources of lead exposure [3]. Lead has eight broad categories of industrial use: batteries, petrol additives (no longer allowed in some developed countries), rolled and extruded products, alloys, pigments and compounds, cable sheathing, shot and ammunition. Cosmetics like lipstick and nail colors may contain large amount of lead. Lead accumulated in bone marrow may lie dormant for years, and cause symptoms of toxicity later in life during situations which mobilizes stores of lead in bones i.e., in pregnancy, lactation, osteoporosis, and hyperthyroidism and hyperparathyroidism [9].

Mercury

Mercury is indirectly discharged into the atmosphere due to its World-wide mining. Mercury is widely used in industrial processes and in various products (e. g. batteries, lamps and thermometers). Mercury is also widely used by the pharmaceutical industry and in dentistry as an amalgam for fillings. The main sources of mercury emissions are from the manufacture of chlorine in mercury cells, non-ferrous metal production, coal combustion and crematoria. The five major sources of emitters of mercury in the environment are coal-fired power plants, cement kilns, chlor alkali plants, trash incinerators and gold mining [10].

Arsenic

The metallic form of arsenic is used in making batteries and cables. When added in small amounts, it improves the hardness of lead and copper alloys. Arsenic compounds also have potential uses in a range of products i.e., glass, Wood preservatives, electronics etc. Arsenic trioxide is used to help the formation of glass and as a colorant. Arsenic trioxide and pentoxide are used for the industrial treatment of wood against fungal decay and insect attack. Gallium arsenide is used to grow crystals in the manufacture of semiconductors. Arsenic is also present as an impurity in coal and oil-based products such as petrol, diesel fuel and motor oil. Half-life of arsenic is short in the body (weeks) but its effects can be seen years after exposure [11, 12].

Heavy metals and workers' health *Cadmium*

Cadmium was discovered by German scientist as a by-product of the zinc refining process during the year 1817. Cadmium is an extremely toxic metal commonly found in industrial workplaces, particularly

where any ore is being processed or smelted. Due to its low permissible exposure limit (PEL), overexposures may occur even in situations where trace quantities of cadmium are found in the parent ore or smelter dust. Cadmium emits a characteristic brown fume (CdO) upon heating, which is relatively non-irritating, and thus does not alarm the exposed individual. Exposures to cadmium are addressed in specific standards for the general industry, shipyard employment, construction industry, and the agricultural industry. Hazards are present in every work environment; being unaware of them, especially when dealing with cadmium, can have critical, even fatal, consequences. Cadmium hazards may be present in a number of operations and materials, such as paints, batteries, and phosphate fertilizers. Human activities, such as tobacco smoking, mining, smelting and refining of non-ferrous metals,fossil fuel combustion, incineration of municipal waste (especially cadmium-containing batteries and plastics), manufacture of phosphate fertilizers, and recycling of cadmium-plated steel scrap and electric and electronic waste[13]. Cadmium is a heavy metal that causes adverse health effects at very low exposure levels. Cadmium affects many organ systems and induces toxicity following acute and chronic exposures. The amount of cadmium exposed to determines the degree and severity of effects. Toxicity is also related to the form of cadmium (cadmium oxide, cadmium chloride), the particle size (fume or aerosol), length of exposure, and route of exposure (inhaled cadmium is more readily absorbed than ingested cadmium). Cigarette smoke is the biggest source of cadmium toxicity, which seems to affect the lungs, kidneys, bones, and immune system primarily. It may lead to lung cancer, prostate cancer and heart disease, and also causes yellow teeth and anemia. Cadmium also seems to contribute to autoimmune thyroid disease [14].

Acute toxicity

Inhalation of high levels of cadmium fumes or dust in industries may severely irritate respiratory tissue (e. g. nasopharyngeal or bronchial irritation). Symptoms such as fever and chest pain may appear and acute pneumonitis may occur. Pulmonary edema may develop due to extreme exposure to cadmium. Respiratory symptoms may linger for several weeks, and impairment of pulmonary function may be there for months. At lower levels of exposure, non-specific symptoms such as headache, chills, muscle aches, nausea, vomiting, and diarrhoea can occur [13]. Metal fume fever can also occur from inhalation of cadmium oxide fumes that are produced when cadmium metal and cadmium compounds are heated to high temperatures. Metal fume fever causes flu-like symptoms. The smaller cadmium particles in fumes are more potent toxicants than the larger particles in dusts.

Chronic toxicity

Cadmium primarily accumulates in the kidneys with smaller amounts accumulating in the liver and muscles with chronic exposure. Kidney damage is the critical health effect associated with long-term cadmium exposure. Cadmium damages the proximal tubules and is characterized by increased urinary excretion of low-molecular-weight proteins including β2-microglobulin or intracellular tubular enzymes (proteinuria). Cadmium may also affect glomerular function with long term exposures. Long-term inhalation of cadmium at low levels can lead to reduced lung function and emphysema. Bone disorders have been reported following chronic exposure to high levels of cadmium which include osteoporosis and osteomalacia (adult rickets) [13]. Several inorganic cadmium compounds are associated with malignancy. Occupational exposure to cadmium has been implicated in an increase of lung and prostate cancer. The International Agency for Research on Cancer (IARC) has determined that there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds. Cadmium binds to proteins within cells and interferes with enzymes requiring zinc and thus affects the organ systems [15]. Cadmium is very similar to zinc in structure and function and may replace zinc in many physiological and enzymatic functions. The zinc/cadmium ratio influences cadmium toxicity and storage. Zinc deficiency increases toxicity while adequate levels of zinc can reduce cadmium-related tissue damage [15]. The effects of cadmium induced oxidative stress are illustrated in fig. 1.

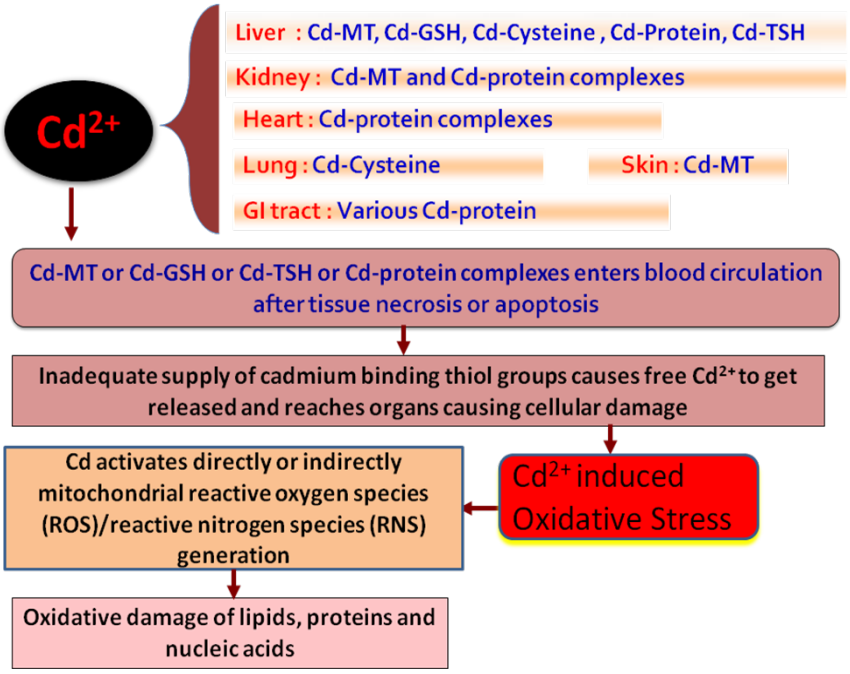


Fig. 1: Effects of cadmium induced oxidative stress

Lead

The most significant health exposure in battery manufacturing industry is inorganic lead dust. Lead gets absorbed into the body by inhalation and ingestion.

Generally the most important source of occupational lead absorption is inhalation of airborne lead. Once in the blood stream, lead is circulated throughout the body and stored in various soft organs and body tissues (e. g., kidney liver, brain, bone marrow, bones and teeth) [16, 17].

Acute toxicity

Lead adversely affects almost entire body systems, and causes forms of health impairment and disease which arise after periods of exposure as short as days or as long as several years. Lead is a potent, systemic poison, which when taken in large doses, can be fatal. Regular exposure to lead may cause a condition affecting the brain called acute encephalopathy associated with seizures, coma, and eventually death from cardio respiratory arrest. Short term occupational exposures of this magnitude are not impossible. Similar forms of encephalopathy may also arise from extended, chronic exposure to low doses of lead. There is no sharp dividing line between rapidly developing acute effects of lead, and chronic effects which take longer to acquire [17].

Chronic toxicity

Lead poisoning is also known as plumbism, colica Pictonum, saturnism, Devon colic, or painter's colic. Severe damage to blood cells, nervous, urinary, and reproductive systems may result from chronic overexposure to lead. Some common symptoms of chronic overexposure to lead include loss of appetite, metallic taste in the mouth, anxiety, constipation, nausea, pallor, excessive tiredness, weakness, insomnia, headache, nervous irritability, muscle and joint pain or soreness, fine tremors, numbness, dizziness, hyperactivity and colic. In lead colic there may be severe abdominal pain [18].

One of the most severe manifestations of lead poisoning is damage to the central nervous system and the brain (encephalopathy). The most severe, often fatal, form of encephalopathy may be preceded by vomiting, feeling of dullness progressing to drowsiness and stupor, poor memory, restlessness, irritability, tremor, and convulsions. It may arise suddenly with the onset of seizures, followed by coma, and death. Some other symptoms may include muscular weakness as well. This weakness may culminate to paralysis which is often observed as a characteristic "wrist drop" or "foot drop". It is a manifestation of a disease affecting the nervous system, called peripheral neuropathy [17, 18].

Chronic overexposure to lead also results in kidney disease often. It may lead to renal failure, kidney dialysis or even death. Both men and women suffer from impairment of the reproductive systems due to chronic overexposure to lead. Overexposure to lead may result in decreased sex drive, impotence, and sterility in men. Lead inhibits the activities of the heme synthesizing enzymes and thus inhibits heme synthesis (fig. 2). The enzyme d-aminolevulinic acid dehydratase (ALAD), (fig. 2.) one of the prime enzyme of heme synthesis is most adversely effected by lead [19, 20].

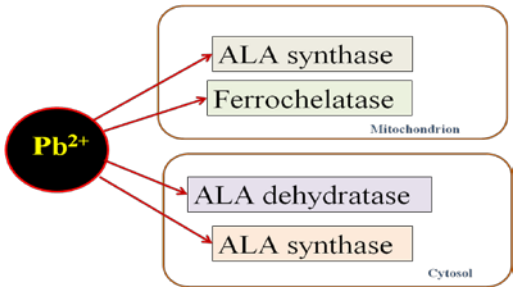


Fig. 2: Lead inhibits the activities of the heme synthesizing enzymes

Mercury

Almost half of atmospheric mercury comes from human-generated sources such as coal plants. An estimated two-thirds of human-generated mercury comes from stationary combustion, mostly of coal. Other important human-generated sources include gold production, non-ferrous metal production, cement production, waste disposal, human crematoria, caustic soda production, pig iron and steel production, mercury production (mostly for batteries), and biomass burning [21]. Workers at small independent gold mining operation are at higher risk of mercury poisoning because of crude processing methods. Mercury and many of its chemical compounds, especially organomercury compounds, can be readily absorbed through direct contact with bare, or in some cases (such as dimethylmercury) insufficiently protected, skin. Mercury and its compounds are commonly used in chemical laboratories, hospitals, dental clinics, and facilities involved in the production of items such as fluorescent light bulbs, batteries, and explosives. Common symptoms of mercury poisoning include peripheral neuropathy (presenting as paresthesia or itching, burning or pain), skin discoloration (pink cheeks, fingertips and toes), swelling, and desquamation (shedding of skin). Mercury is thought to inactivate S-adenosyl-methionine, which is necessary for catecholamine catabolism by catechol-o-methyl transferase. Due to the body's inability to degrade catecholamines (e. g. Epinephrine) a person suffering from mercury poisoning may experience profuse sweating, tachycardia (persistently faster-than-normal heart beat), increased salivation, and hypertension (high blood pressure). Affected person may show red cheeks, nose and lips, loss of hair, teeth, and nails, transient rashes, hypotonia (muscle weakness), and increased sensitivity to light.

Other symptoms may include kidney dysfunction (e. g. Fanconi syndrome) or neuropsychiatric symptoms such as emotional lability, memory impairment, or insomnia. Thus, the clinical presentation may resemble pheochromocytoma or Kawasaki disease [21,22]. Occupational exposure to mercury containing compounds i.e., adhesives, tattoos, batteries, cosmetics, fungicides, plastics, paints, mercury amalgam filling, pesticides etc. presents a significant health risk to individuals. Dentists, painters, fisherman, electricians, pharmaceutical/laboratories workers, farmers, factory workers, miners, chemists and beauticians are just some of the professions chronically exposed to mercury compounds. Kishi *et al.* (1993) have found that smelter workers exposed to inorganic mercury compounds continue to experience neurological symptoms like tremors, headaches, slurred speech-senile symptoms and diminished mental capacities eighteen years after the cessation of mercury exposure [23].

Arsenic

Inorganic arsenicals, such as the trioxide, a by-product of smelting of ore containing copper, lead, and zinc, are more toxic than the organic. Humans get exposure to arsenic mainly from food, air, and water. Arsenic may contaminate drinking water from pesticide containing arsenic, mineral deposits, disposed arsenical chemicals. Arsenic contamination in drinking water is the prime cause of arsenic toxicity around the globe [24]. The minimum lethal dose is 100-200 mg of arsenic trioxide. Exposure to a toxic dose initially produces a dry burning sensation in the mouth and throat and a constricted feeling in the throat. This is followed by severe abdominal pain, cramping, diarrhea, and vomiting. The diarrhea begins with "rice water" stools progressing to a bloody discharge. Stools and breath may have a garlicky odor. Vertigo develops, followed by delirium, coma, and often convulsions. Circulatory collapse with hepatic and renal failure ensues. Myocardial toxicity involves broadening of the QRS, flattening of the T waves, and ST depression. In acute exposure to the gaseous form, inhalation of toxic amounts of arsine gas results in headache, malaise, weakness, dizziness, and dyspnea accompanied by gastrointestinal distress. The effect is not immediate but is typically delayed by 2-24 h. usually, hemolysis occurs 4-6 h after the onset of symptoms and dark red urine is noticed. Jaundice develops 24-48 h later. Patients present to the emergency department with severe jaundice, anemia, and hemoglobinuria (ie, black water urine). On admission, the patient may have fever, tachycardia, and tachypnea. Acute oliguric renal failure occurs because concentration of arsenic in the proximal tubules and binding to proteins of tubular epithelium damages the tubules. Treatment involves hemodialysis and the use of BAL (Dimercaprol) [24]. Arsine was identified in 1775 [25]. The first reported fatality from arsine inhalation was in 1815 when a German chemist died after inhaling the gas in his laboratory. Workers in the metallurgy industry are at a risk of repeated exposure to arsine gas. The action of acid on metal ore contaminated with arsenic causes release of arsine gas. Arsenic-containing dust emitted from smelters is another source [25]. Exposure of bare skin to inorganic arsenic can result in skin hyper pigmentation or an eczematous dermatitis

[24]. Peripheral vascular involvement may occur, with acrocyanosis and the appearance of a Raynaud-like picture. In addition, a sensorimotor distal neuropathy may occur that presents like Guillain-Barré syndrome, and sideroblastic anemia—a state of ineffective erythropoiesis characterized by a significant number of erythroid precursors containing mitochondria with stainable iron granules—also may be noted. Although a similar hematopoietic picture is seen in lead toxicity, the mechanism producing the anemia is not believed to be the same. Leucopenia is a common finding in arsenic poisoning [25].

Heavy metal poisonings have many similarities, making clinical distinctions between them difficult at times. Arsenic is more likely than other heavy metals to produce significant gastro enteric pathogenesis when ingested. Inhalation of arsine gas produces clinical features whose onset is dependent on the degree of exposure. The initial complaints may be headache, malaise, weakness, dizziness, and dyspnea. Later, the features are the same as those seen in inorganic arsenic ingestion [23-25].

Free radicals

A free radical can be defined as any atom (e. g. oxygen, nitrogen) which has at least a single unpaired electron in the outermost shell, and that can exist independently [26]. As a covalent bond is broken, a free radical is generated and one electron remains with each newly formed atom [26]. Free radicals are highly reactive and this is due to the presence of unpaired electron(s). Any free radical involving oxygen is referred to as reactive oxygen species (ROS). Oxygen centred free radicals contain two unpaired electrons in the outer most shell. Free radicals steal an electron from a surrounding compound or molecule and a new free radical is generated. The newly formed radical then wants to return to its ground state by stealing electrons with antiparallel spins from cellular structures or molecules. The most pronounced oxygen-containing free radicals in many disease states are hydroxyl radical, superoxide anion radical, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. Thus, the chain reaction goes on and can be "thousand of events long." [26].

The electron transport chain (ETC), in the inner mitochondrial membrane, uses oxygen to generate energy in the form of adenosine triphosphate (ATP). The terminal electron acceptor in ETC is Oxygen. Studies suggest that anywhere from 2 to 5% of the total oxygen intake have the ability to form the highly damaging superoxide radical via electron escape [26, 27]. Electrons appear to escape from the ETC at the ubiquinone-cytochrome c level [28]. Free radicals are generated continuously in the cells as a by product of enzymatic and nonenzymatic reactions. Enzymatic reactions, which are involved in the electron transport chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system, serve as source of free radicals. Free radicals can also be formed in nonenzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions [29].

Reactive oxygen species

Reactive Oxygen Species (ROS) like superoxide anion free radical, hydrogen peroxide and hydroxyl radical, are associated with cell damage. The ROS are most abundant and significant among the different free radicals [29]. ROS are produced as by products of normal cellular metabolism and the most significant site of ROS production is the mitochondria. These ROS are highly reactive entities and can bring about damage to all kinds of molecules in the body. Over production of ROS may lead to marked damage of biologically important molecules i.e., carbohydrates, proteins, lipids and even DNA. Recent works have revealed that ROS that are also generated by specialized plasma membrane oxidases in normal physiological signalling by growth factors and cytokines. There is evidence for ligand-induced generation of ROS and that several signalling pathways are activated by ROS [29, 30].

Oxidative stress

A balance between free radicals and antioxidants is necessary for proper physiological function [30]. Increased generation of ROS depletes cells' intrinsic antioxidant defences, and results in a condition known as "oxidative stress". Oxidative stress is the condition when the available supplies of the body's antioxidants are insufficient to handle or neutralize free radicals of different types. The consequence is massive damage due to oxidation of different components of the cells.

Cells under oxidative stress display various dysfunctions due to damages caused by ROS to carbohydrates, lipids, proteins and DNA. Consequently, it is suggested that metal-induced oxidative stress in cells is an important factor responsible for the toxic effects of heavy metals. Several studies suggest that antioxidant supplementation following heavy metal exposure reduces the risk and consequent symptoms of heavy metal induced oxidative stress diseases. Antioxidant molecules donate electron and neutralize free radicals (fig. 3). In order to prove the importance of using antioxidants in heavy metal poisoning further studies are required [30-32].

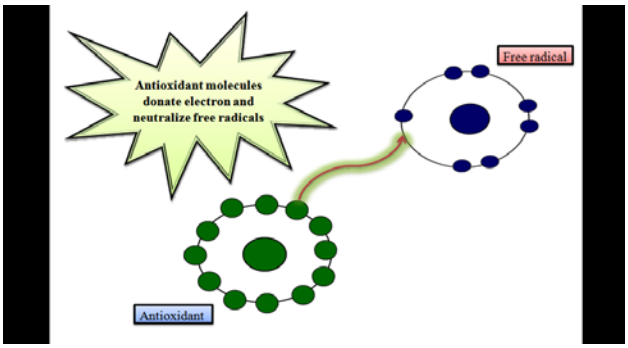


Fig. 3: Antioxidant molecules donate electron and neutralize free radicals

Heavy metals induce oxidative stress

Global industrialization has dramatically increased the overall 'load' of heavy metal toxins in the environment. Our societies are dependent upon industries for development, advancement and proper functioning. Industrial advancements and commercial processes have actively mined refined, manufactured, burned and manipulated heavy metals and their compounds. Heavy metal contaminations are abundant in our drinking water, air and soil due to our increased use of these compounds in our daily life. Mechanisms for this stress are not as clear and as easily understood as are the mechanisms for redox-active metal-induced oxidative stress, which has been studied by many scientists [33, 34]. Redox-active metals like iron, copper etc. as well as redox-inactive metals like lead, cadmium etc. may cause an increase in production of reactive oxygen species (ROS) such as hydroxyl radical (HO.), superoxide radical (O_2.-) or hydrogen peroxide (H_2O_2) [35]. Studies reveal generation of ROS by heavy metal exposure in protozoan [35]. It was found that all metals generate ROS, mainly superoxide and peroxides [35] (fig. 4).

Fenton like reactions of metals:

$M(n)+O_2^{\cdot-} \rightarrow M(n-1)+O_2$

$2\,O_2^{\cdot-}+2\,H+H_2O_2+O_2$

$M(n-1)+H_2O_2 \rightarrow M(n)+HO^{\cdot}+OH^-$

The heavy metals like lead, mercury and cadmium, all have electron-sharing affinities that can result in formation of covalent attachments [35]. One of the proposed mechanisms for metal-induced oxidative stress is their role in the generation of ROS and their effect on the antioxidant defense system [35, 36]. ROS and RCS generated by heavy metals damage lipids, proteins and DNA (fig. 5).

Cadmium is biopersistent and, once absorbed by an organism, remains stored in the body for many years (over decades for humans) though it is eventually excreted. In humans exposure to lead can result in a wide range of biological effects depending on the

level and duration of exposure. High levels of exposure to either of the heavy metals may result in toxic biochemical effects in humans which in turn cause problems in the synthesis of haemoglobin, effects on the kidneys, gastrointestinal tract, joints and reproductive system, and acute or chronic damage to the nervous system [13, 37].

Mercury is a toxic substance which has no known function in human biochemistry or physiology and does not occur naturally in living organisms. Inorganic mercury poisoning is associated with tremors, gingivitis and/or minor psychological changes, together with spontaneous abortion and congenital malformation.

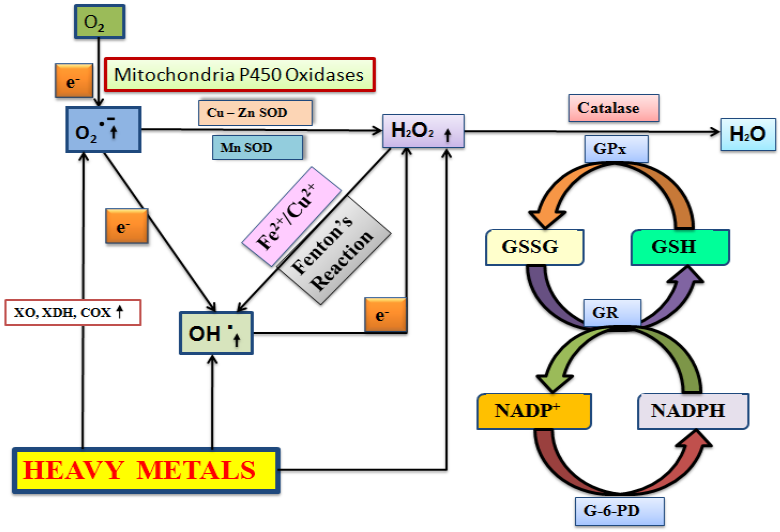


Fig. 4: Heavy metals generate reactive oxygen species (ROS)

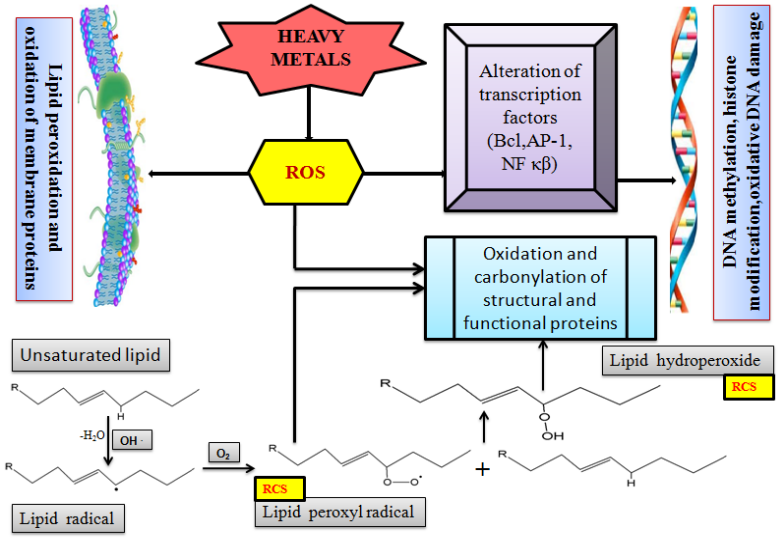


Fig. 5: Reactive oxygen species (ROS) and reactive carbon species (RCS) generated by heavy metals damage lipids, proteins and DNA

Monomethylmercury causes damage to the brain and the central nervous system, while foetal and postnatal exposure have given rise to abortion, congenital malformation and development changes in young children [38]. Arsenic and many of its compounds are potent poisons. Water supplies close to mines are mostly contaminated by these poisons. Arsenic through several mechanisms disrupts ATP production.

At the level of the tricarboxylic acid cycle, arsenic inhibits lipoic acid, which is a cofactor for pyruvate dehydrogenase. Arsenic competes with phosphate and thus it uncouples oxidative phosphorylation, thus inhibiting energy-linked reduction of NAD+, mitochondrial respiration and ATP synthesis. Hydrogen peroxide production is also enhanced by arsenic [39]. These metabolic interferences culminate to death due to multi-system organ failure, from necrotic cell death. Post mortem reveals brick-red-coloured mucosa, owing to severe haemorrhage. Elemental arsenic and arsenic compounds are classified as "toxic" and "dangerous for the environment" in the European Union underdirective 67/548/EEC. The International Agency for Research on Cancer (IARC) recognizes arsenic and arsenic compounds as group 1 carcinogens, and the EU lists arsenic trioxide, arsenic pentoxide and arsenate salts as category 1 carcinogens. Chronic arsenic toxicity have been reported in most States of India around the upper, middle and lower Ganga and Brahmaputra plain. Arsenic contamination has been found in the States of Bihar, Uttar Pradesh, Jharkhand, Assam, Chhattisgarh, Andhra Pradesh and West Bengal [40, 41].

Main complains

There are more than twenty various heavy metal toxins that can affect human health and each toxin produces different behavioral, physiological, and cognitive changes in an exposed individual. The extent to which a system, organ, tissue, or cell is affected by a heavy

metal toxin depends on the toxin itself and the individual's degree of exposure to the toxin. Each of these heavy metals accumulates within the body of an individual and its respective accumulation within the body leads to a decline in the mental, cognitive, and physical health of the individual. These accumulate primarily in the soft organs like brain, muscles, liver lungs, bones, kidneys, skin, reproductive organs and stomach [43].

Many arsenic compounds are readily absorbed through the GI tract in humans. The extent of absorption within the lungs is dependent upon the size of the arsenic compound and it is believed that much of the inhaled arsenic is later absorbed through the stomach after (respiratory) mucocillary clearance. After the absorption of arsenic compounds, the primary areas of deposition are the liver, kidneys, lung, spleen, aorta, and skin. Arsenic compounds are also easily deposited in the hair and nails [40, 41]. Acute exposure to arsenic compounds can cause nausea, anorexia, vomiting, abdominal pain, muscle cramps, diarrhea and burning of the mouth and throat. Garlic-like breath, malaise, and fatigue are also reported in individuals exposed to an acute dose of arsenic. Contact dermatitis, skin lesions and skin irritation are seen in individuals whom come into direct tactile contact with arsenic compounds [41]. Repeat exposure to arsenic compounds have been shown to lead to the development of peripheral neuropathy, encephalopathy, cardiovascular distress, peripheral vascular disease, EEG abnormalities, Raynaud's phenomenon, Black foot disease, acrocyanosis, increased vasopastic reactivity in the fingers, kidney and liver damage, hypertension, myocardial infarction, anemia and leucopenia [42, 43].

Other chronic effects of arsenic intoxication are skin abnormalities i.e., darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, torso, neurotoxic effects, chronic respiratory diseases like pharyngitits, laryngitis, pulmonary insufficiency, neurological disorders, dementia, cognitive impairment, hearing loss and cardiovascular disease [43]. Studies have shown there is a close association between rate of occurrence of cancer and inhaled and ingested arsenic. For medical test for arsenic toxicity, urine, hair and fingernails are used for screening.

Copper is absorbed through skin, gastrointestinal tract and lungs. The degree to which copper is absorbed in the gastrointestinal tract largely depends upon its chemical state and the presence of other compounds, like zinc. After being absorbed copper is distributed primarily to the liver, kidneys, spleen, heart, lungs, stomach, intestines, nails, and hair. Symptoms of acute copper toxicity are abdominal pain, diarrhea, vomiting, tachycardia and a persistent metallic taste in the mouth. Continued ingestion of copper compounds can cause cirrhosis of liver [44].

Copper toxicity causes Wilson's disease, a genetic disorder that causes an abnormal accumulation of copper in body tissue. Wilson's disease is fatal unless diagnosed in time. Symptoms of Wilson's disease include brain damage and progressive demylination, psychiatric disturbances i.e., depression, suicidal tendencies and aggressive behavior--hemolytic anemia, cirrhosis of the liver, motor dysfunction and corneal opacities. Medical tests for copper toxicity, blood, urine and hair are screened.

Lead enters body by inhalation or ingestion and is absorbed. Children absorb lead much more efficiently than adults do after exposure, and ingested lead is more readily absorbed in a fasting individual. Over 90% of inhaled lead is absorbed directly into the blood [45]. After being absorbed into the body, lead circulates in the blood stream and is distributed primarily in the soft tissues e. i., kidneys, brain and muscle and bone. Adults distribute about 95% of their total body lead to their bones, while children distribute about 73% of their total body lead to their bones [46]. High concentrations of lead can cause irreversible brain damage (encephalopathy), seizure, coma and death if not treated immediately. The Central Nervous System (CNS) becomes severely damaged at blood lead concentrations starting at 40 mcg/dL, causing a reduction in nerve conduction velocities and neuritis. Neuropsychological impairment has been shown to occur in individuals exposed to moderate levels of lead. Studies suggest that lead may cause fatigue, irritability, information processing difficulties, memory problems, a reduction in sensory and motor reaction times, impairment of decision making and lapses in concentration [47]. At high blood concentrations, lead has been shown to cause anemia, characterized by a reduction in hemoglobin levels, and erythropoiesis and a shortened life span of red blood cells [47, 48]. Lead is very detrimental to the cardiovascular system as well [49]. Occupationally exposed individuals tend to have higher blood pressure than normal controls, and are at an increased risk for cardiovascular disease, myocardial infarction, and stroke [50]. The renal tissues are targets of lead toxicity and prone to impairment at moderate to high levels of lead concentrations. Kidney disease, both acute and chronic nephropathy, is a characteristic of lead toxicity [51]. Morphological changes in the kidney epithelium increase in the excretion rates of many different compounds, reductions in glomerular filtration rate, progressive glomerular, arterial, and arteriolar sclerosis, and an altered plasma albumin ratio are the reported symptoms of lead toxicity [52]. Chronic nephropathy has lead to increased death rates among individuals occupationally exposed to lead [53]. Other signs/symptoms of lead toxicity include gastrointestinal disturbances-abdominal pain, cramps, constipation, anorexia and weight loss-immunosuppression, and slight hepatic impairment [51, 52]. Prenatal and postnatal development is compromised significantly by the presence of lead in the body. At blood lead concentrations of 80-100 mcg/dL, severe encephalopathy occurs. Those children who survive lead-induced encephalopathy typically suffer permanent brain damage marked by mental retardation and numerous behavioral impairments. These children also suffer slower neural conduction velocities, peripheral neuropathy, cognitive impairment, and personality disorders [53]. Numerous studies have implicated lead as a causal agent in the deterioration of cognitive functioning in children. Maternal blood lead concentrations and prenatal lead exposure appear to be strong predictors of cognitive performance in offspring. Prenatal exposure may also cause birth defects, miscarriage, spontaneous abortion and underdeveloped babies [47]. Young children exposed to lead may exhibit mental retardation, learning difficulties, shortened attention spans (ADHD), increased behavioral problems (aggressive behaviors) and reduced physical growth. Lead has been determined by many health experts to be a threat to developing children in our industrial societies. Medical test for lead toxicity blood, urine and hair are screened. Acute mercury toxicity may cause gastrointestinal disorders such as abdominal pain, vomiting, diarrhoea, and hemorrhage [54]. Repeated and prolonged exposure has been reported to result in severe disturbances in the central nervous system, gastrointestinal tract, kidneys, and liver. Reported dementia, colitis, and renal failure in individuals chronically poisoned due to the ingestion of an inorganic mercury containing laxative. Clinical complications in individuals due to exposure to mercury include corrosive bronchitis, interstitial pneumonitis, renal disorders, fatigue, insomnia, loss of memory, excitability, chest pains, impairment of pulmonary function and gingivitis. Chronic inhalation of inorganic mercury compounds has been reported to result in a reduction of sensory and motor nerve function, depression, visual and/or auditory hallucinations, muscular tremors, sleep disorders, alterations in autonomic function (heart rate, blood pressure, reflexes), impaired visuomotor coordination, speech disorders, dementia, coma and death have shown that a group of dentists exposed to mercury vapors occupationally perform significantly worse in neurobehavioral tests that measure motor speed, visual scanning, visuomotor coordination and concentration, verbal memory and visual memory. Adults experience symptoms including parasthesia, visual disorders, ataxia, fatigue, tremor, hearing disorders (deafness) and coma due to mercury poisoning [54]. Neuropathologic observations of exposed individuals have shown irreversible brain damage including neuronal necrosis, cerebral edema, gliosis and cerebral atrophy. Methyl mercury can pass through the placental barrier and produce many deleterious effects on the unborn fetus [54]. Children born to mercury poisoned mothers were of smaller total weight, had decreased brain weights at birth, had fewer nerve cells in the cerebral cortex, and experienced an abnormal pattern of neuronal migration. Mercury has recently been implicated as being a contributing factor to the increasing prevalence of autism in American children. Mercury poisoning has been reported to cause cerebral palsy, amyotrophic

lateral sclerosis, Parkinson's disease, psychosis, and chronic fatigue syndrome [54]. Overall we can summarise heavy metal induced adverse health effects as symptoms like decreased intelligence in children, nervous system disorders, immune dysfunction, depression, fatigue, muscle weakness and aches, anemia, skin rashes, high blood pressure, memory loss, diarrhea, nausea, metallic taste in mouth, irritability, tremors, cancer, hyperactivity, autism, behavioral disorders, headaches [54-56].

Conventional treatments and their drawbacks

Heavy metal toxicity is a condition that often goes overlooked in medical diagnoses. Metal toxins have the ability to impair not just a single cell or tissue, but many of the body's systems that are responsible for our behavior, mental health, and proper physiological functioning that is necessary for a normal life. If undetected and remains undiagnosed, these metal toxins can cause severe pain and suffering for an effected individual. Fortunately, there are avenues that an affected individual can pursue to detoxify heavy metals already in their system. Free radicals being highly reactive attack and alter the chemical integrity of the structural and functional units of cell. Free radicals adversely alter lipids, proteins, and DNA and thus trigger a number of human diseases. Heavy metals induce the generation of these free radicals and thus bring about oxidative stress. Use of antioxidants can help to combat this heavy metal induced oxidative stress mediated damages in different cellular components. Synthetic antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole have recently been reported to be dangerous for human health. These chemicals have been found to have deleterious side effects. Thus, the search for effective, nontoxic natural compounds with antioxidative activity has been of prime concern for clinicians, researchers and health practitioners in recent years [58, 59]. Most popular and extensive treatment in practice for metal toxicity is chelation therapy. Chelation therapy involves intravenous (IV) administration of solution that chelates the metal and thus helps in its elimination. Two compounds that are used mostly in chelation therapy to remove heavy metals are EDTA and DMSA. These therapies are effective, but have been reported to be potentially harmful to many individuals. Side effects of chelation therapy includes fever, headache, nausea, stomach upset, vomiting, convulsions, reduced blood cell counts, decrease in blood pressure, cardiac arrhythmias, respiratory distress, and hypocalcemia. Other pathological conditions arising due to side effect of chelation therapy include kidney failure which may ultimately lead to death [55]. **C**helation of heavy metal toxins and their removal from living system may be brought about using natural herbal preparations which lack any kind of side effect and are thus safer. We have observed in our studies reduced concentration of heavy metals like lead and cadmium in liver, heart and kidney tissues of male Wistar rats when pre-treated with aqueous extract of curry leaves [2, 16, 30]. Thus we may think of including curry leaves in the group of those few potent nutritional substances those are used in oral chelation therapy which helps to detoxify heavy metals and help to remove them from the living system. Exposure to toxic metals is associated with many chronic diseases. Recent research has found that even low levels of lead, mercury, cadmium, aluminum and arsenic can cause a wide variety of health problems [47].

Complementary and alternative medicine (CAM), integrative medicine and curry leaves

Lots of people around the world still depend and trust on their traditional material medica (medicinal plants and other materials) for their day to day health care needs. It is also an observed fact that one fourth of all medical prescriptions are formulations based on substances derived from plants or plant-derived synthetic analogs, and according to the WHO, 80% of the world's population—primarily those of developing countries—trust on plant-derived medicines for their healthcare [57]. Modern drug development research aims to develop a patentable single compound or a magic bullet to treat specific pathogenic conditions. Complementary and alternative medicine is being accepted all over the globe and is well adapted by clinicians in for diagnosing a variety of pathological states. A big percent of adults all around the world has been reported to be using complementary and alternative medicine (CAM) [57, 58]. Clinicians are adapting CAM therapies, often combining them with conventional medical therapies using the new term "integrative medicine." National Center for Complementary and Alternative Medicine (NCCAM) is the agency that funds scientific research on complementary and alternative medicine has classified the new medicines as follows:

- Whole medical systems
- Mind-body medicine
- Biologically based practices
- Manipulative and body-based practices
- Energy medicine

Alternative medicine is gentle to the health and has almost no or very rare and mild side effects. Prime reason behind alternative medicine being less cytotoxic as safer is that they are derived from natural herbal sources and their mode of function is slow and gradual. We can say that most of the alternative medicines are derived from nature and hence are soothing to human system. On the other hand, conventional regular drugs lack the natural ingredients like dietary vitamin, minerals etc. Dietary supplements included in alternative medicine are selenium, glucosamine sulfate, S-Adenosyl-L-Methionine (SAMe) while some herbs used in CAM are ginseng, tulsi, arjuna, Curry, ginkgo and Echinacea. Herbs and supplements are administered in the form of teas, oils, syrups, powders, tablets or capsules. Curry leaf has an antioxidant and free radical scavenging activity [2, 58, 59]; Cocktail of various vitamins, minerals and phytochemicals in the leaf are the prime players; Phytochemical studies revealed the presence of flavonoids, polyphenols, alkaloids etc in the curry leaves. The reducing power, hydroxyl radicals scavenging activity of the leaves extract has also been observed [2]. Studies reveal that the aqueous extract of the leaves of *Murraya koenigi* do possess potent antioxidant activity that may have future therapeutic relevance. Curry leaves contain crystalline glycosides, carbazole alkaloids, koenigin, girinimbin, iso-mahanimbin, koenine, koenidine and koenimbine. Triterpenoid alkaloids cyclomahanimbine, tetrahydromahanimbine are also present in the leaves. Murrayastine, murrayaline, pyrayafoline carbazole alkaloids and many other chemicals have been isolated from *Murrya koenigii* leaves [59, 60, 61]. The major compounds obtained from the hydro-distillation were *E*-caryophyllene (21.4%), *α*-selinene (10.3%) and selin-11-en-4-*α*-ol (8.3%) and from the methylene chloride extract were *E*-caryophyllene (31.1%), *α*-selinene (15.2%) and *β*-selinene (8.1%) and from the ethyl acetate extract were *E*-caryophyllene (19.9%), *α*-selinene (15.2%) and *β*-selinene (5.7%). In addition, the hydro-distillation, methylene chloride extract and ethyl acetate extract showed anticancer activities against with IC_{50} KB-Oral cavity cancer 34.2, 7.3 and 27.2 *μ*g/ml. NCI-H187-small cell lung cancer 7.6, 8.5 and 18.3 *μ*g/ml. and MCF7-breast cancer inactive, 3.9 and 9.2 *μ*g/ml, respectively [60, 61].

The bioassay guided fractionation of the acetone extract of the fresh leaves of *Murraya koenigii* resulted in the isolation of three bioactive carbazole alkaloids, mahanimbine (1), murrayanol (2), and mahanine (3), as confirmed from their (1)H and (13)C NMR spectral data [62]. Major curry leaf flavonols included myricetin-3-galactoside, quercetin-O-pentohexoside, quercetin-3-diglucoside, quercetin-3-O-rutinoside, quercetin-3-glucoside, quercetin-3-acetylhexoside, quercetin-O-xylo-pentoside, kaempferol-O-glucoside, and kaempferol-aglucoside [53]. Fresh leaves contain yellow color 2.5 % volatile oil [63].

Curry leaves collected from different districts of the Gangetic plain of West Bengal, India has been found to have free radical scavenging activity [3] and antioxidant potential. Aqueous extract of curry leaves also possess antioxidant potential and has been found to provide protection against lead as well as cadmium induced oxidative stress mediated toxicity and damages in liver and heart [14,16, 30, 32] and against lead induced oxidative stress mediated

tissue damages [49] and other disorders [58]. Polyphenols of curry leaves and endogeneous antioxidant machinery acts together to combat heavy metal induced oxidative damages (fig. 6). Uses of plants as alternative medine are being studied in case of various diseases because of their high potency and lack of adverse side effects. *Murraya koenigii* has been found to possess hypoglycaemic potency as well [64].

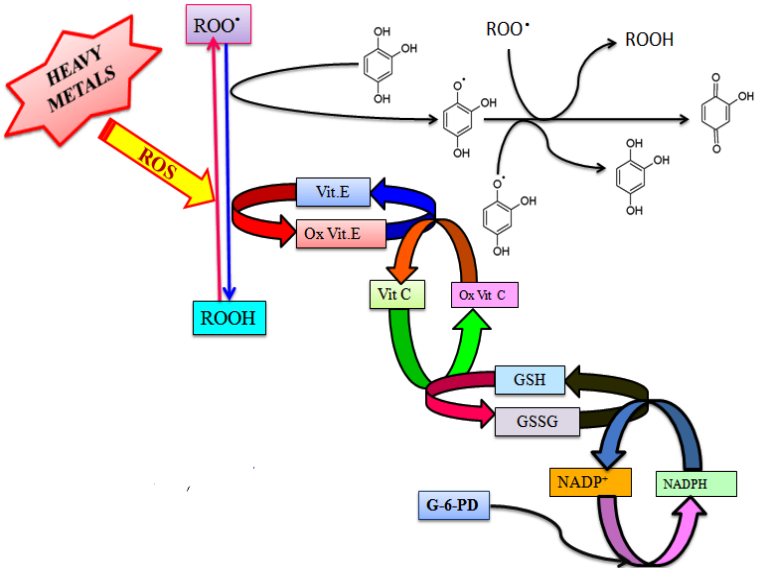


Fig. 6: Polyphenols of curry leaves and endogeneous antioxidant machinery together combats heavy metal induced oxidative damages

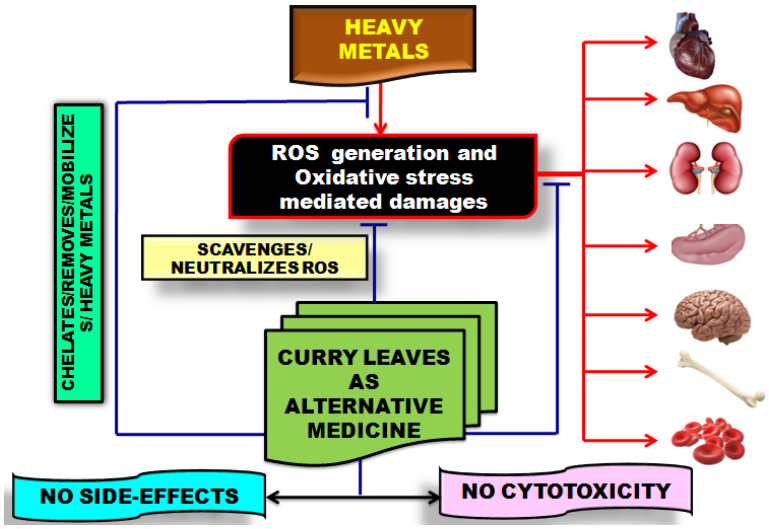


Fig. 7: Curry leaves as alternative medicine against heavy metal induced oxidative stress mediated damages in various tissues

CONCLUSION

Studies so far available on *Murraya koenigii* reveals that various ethnic groups, Vaidyas, Hakims and ayurvedic practitioners use curry leaves for cure of variety of ailments. There has been some effective studies in the present days for investigating the pharmacological potential of curry leaves. Heavy metals are persistent toxins in the environment. Many individuals get occupationally exposed to these heavy metal toxins daily. And on the other hand almost all of us get environmentally exposed to the heavy metals in the environment. Curry leaves have been found to protect against heavy metal induced oxidative damages in various *in vivo* and *in vitro* experimental models. It is interesting to note that crude organic extracts of leaves of *Murraya koenigii* have been screened for some pharmacological activities and found to possess antioxidant property and hence protective activity against heavy metal induced ailments. Curry leaves contain certain potent phytoconstituents which have the potential to scavenge ROS and boost the body's endogenous antioxidant system and thus can protect against metal-induced oxidative stress, damage and subsequent health hazards (fig. 7). These phyto-components present in curry leaves, so far reported, have no reported cytotoxic or adverse side effects, if not over consumed. Some specific or a perfect blend of potent phyto-constituent(s) from curry leaf can be adapted as alternative medicine or integrative medicine for preventing or treating or curing or protecting against heavy metal-induced oxidative stress related occupational health hazards. Curry leaves may have future therapeutic relevance in the prevention of heavy metal-induced pathogenicity in humans exposed occupationally or environmentally to this toxic heavy metal and may be used for development of new protective drugs of herbal origin with less cytotoxic effects.

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CONFLICT OF INTERESTS

The authors have no conflict of interest

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