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Review Article

Diseases Induced by Heavy Metal Exposure and their Ameliorative Phytochemicals: A Review

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ABSTRACT

Indiscriminate disposal of refuse and industrial effluents have continued to introduce toxic chemicals into our environment. Most of these toxic wastes, particularly the heavy metals are colourless, hence, the silent access which they often gain into the human body via food and water. This has increasingly posed deleterious effects on public health globally in the twenty-first century. Relevant publications were primarily sourced from Science Direct (a major contributor to the Scopus database) using "heavy metals; toxicity; amelioration; herbs, treatment" as keywords. This article gives an overview of health risk factors, the pathogenic health effects of common heavy metals and the sustainable route to their amelioration using natural products with heavy metal chelating potential in different animal models. The incorporation of these herbs in diets and the direct therapeutic applications of crude plant extracts, fractions and isolates enhance the human defense system against the various diseases which are usually associated with the consumption of heavy metal contaminated food and water.

Keywords: Amelioration, Antioxidant, Herbs, Heavy Metal, Phytochemicals, Toxicity.

Introduction

Several life-threatening diseases which afflict people today are as a result of gradual heavy metal accumulation via ingestion of contaminated food and water. This contamination is usually an offshoot of environmental pollution, the unwanted and unlawful entry of hazardous materials into our environment. Among the major contaminants in the environmental systems are the heavy metals which gain access into our environment through natural and human activities such as soil erosion and run-offs, mining and rock weathering, indiscriminate disposal of industrial effluents, sewage discharge, unguided use of pesticides, etc.[1] Although some of these metals are 'essential', however, above their permissible limits, such metals become harmful to the body. The WHO permissible limit for cadmium, chromium, copper, lead, manganese and nickel in drinking water are 0.003, 0.05, 2.00, 0.01, 0.50, and 0.02 mg/L, respectively.[2] Above these levels, these metals are no longer beneficial.

When aquatic animals ingest heavy metal-contaminated water, they naturally bio-accumulate the metals. Similarly, when plants are irrigated with such water, heavy metal accumulation occurs. The eventual consumption of these is dangerous as it consequently leads to the development of various life-threatening diseases such as cancer and organ damage among others.

The threat of heavy metal poisoning is higher for people in rural areas. Particularly, people in neglected parts of developing nations are more prone to such poisoning because of ignorance and lack of potable water supply.[3]

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Although, government agencies in many countries have paid relevant attention to this pollution challenge, it is not so in some rural areas in developing nations.[4] Hence, the amount of heavy metals which is ingested via food and water, and the quantity that has already accumulated in individuals are points of concern. It is important to eliminate these toxic elements from the body. Recent research has shown that these dangerous pollutants can be scavenged from the human body and their effects can be ameliorated using herbs and spices. Such abatement, detoxification and amelioration studies are herein reviewed. This review gives an overview of the dangers associated with exposure to heavy metals and it identifies some natural products which can be incorporated into diets for the purpose of heavy metal abatement/detoxification or treatment of health conditions resulting from heavy metal contamination.

Methodology

In this study, available publications relevant to heavy metal-induced diseases and their potential herbal ameliorators were reviewed. Publications were primarily sourced using the science direct search engine (a major contributor to the Scopus database) and google scholar search engine with the keywords "heavy metals; toxicity; amelioration; herbs, treatment". Manuscripts published between 2014 and 2019 as well as a few articles from earlier years were considered. Articles were eventually selected and used based on their clear relevance to the objectives of the work.

Risk Factors for Heavy Metal Poisoning

Several risk assessments studies have been carried out on different platforms and in different parts of the world with focus on soil, water, crop and food. [5, 6]

Industrial waste-water reuse and location of farms near mining sites seem to be major contributors to this risk.[5, 6]

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Food as a health risk factor

While water sometimes serves as a vehicle for the transportation of toxic metals into food, food remains a major avenue via which heavy metals gain access into the human body. Contaminated water will eventually lead to food contamination. Hence, food constitutes a health risk factor which has been investigated by several researchers with focus on metals such as Copper, Chromium, Zinc, Nickel, Lead, Arsenic, Cadmium and Manganese. These metals were recently found to be present in freshwater (82.9 – 226 µg/L dw) and in fishes therein (3.32 – 27.6 mg/kg dw).[7, 8] Although these findings indicate that heavy metal concentrations were within the safe limit, long-term accumulation of these heavy metals should be carefully prevented. This is especially necessary since there are cases in which heavy metal concentrations are above regulatory safety levels in fishes and crustaceans which are commonly consumed.[9] Atomic absorption Spectroscopy (AAS) was recently used to determine the concentration of Lead ions in *Rastrelliger kanarguta*, *Haplochromis nigrescens* and *Sargocenton rubrum*. The results were above the Australian regulatory safety level. However, acceptable carcinogen level was found in three other examined species of fishes with the crabs containing the highest concentrations of the investigated heavy metals.[9]

Many are also exposed to heavy metals through staple foods such as rice. In particular, a notable correlation exists among dietary patterns, cadmium intake and kidney disease.[10] Traditional dietary pattern in the south was found to greatly increase chronic kidney disease compared to modern dietary pattern in China. Hence paying close attention to the dietary pattern cannot be overemphasized. Very importantly, heavy metal presence has been established in 37 imported rice patronized in Saudi Arabia.[11] Only cadmium fell within the acceptable regulatory limit in unwashed rice. The level of lead and chromium were reduced by soaking/rinsing with water while the arsenic level remained above the safety limit in all investigated brands. The reason for the persistence of arsenic in rice is worthy of research attention. This becomes even more important as toxic metals such as arsenic and lead have continued to put certain rice consumers in great risks of carcinogenesis.[12]

Soil and water as health risk factors

Several heavy metals such as arsenic, cadmium, chromium, copper, lead, etc. are common in water and they are dangerous to the environment and to human health. Particularly, cadmium concentration which is beyond WHO permissible limit was detected in groundwater from UP, India.[13] Similarly, the concentration of cobalt and cadmium in soil from the same region were also beyond the safe limit.[14]

Once the soil is contaminated, the people of the land are not entirely free from the contamination.[15, 16] This explains the reason why another study in the same region found toxic metals (lead, cadmium and mercury) in the breast milk of nursing mothers.[17] This calls for urgent environmental protection policies in that particular region.

Air as a risk factor

The air is an extremely risky medium through which heavy metals penetrate biological systems.[18] Heavy metals may exist in the atmosphere as a composite of aerosols or particulate matter. Depending on the size, they have the tendency to enter the lungs and penetrate sensitive organs. A correlation has been established between the number of patients diagnosed with chronic health conditions (such as hypertension, asthma, diabetes, non-lung cancer and angina) and the quality of air in Ontario Canada.[19] The use of health services among the studied group increased with increased exposure to air pollution. Exposure to air pollution may be associated with certain occupations. Such occupational exposure to mercury which may not be easily detected has been known to cause respiratory failure in the recent past.[20] Several recent incidences of heavy metal exposure across various locations in the world are presented in Table 1.

Effect of Co-exposure

While individual exposures (contamination with a single metal ion) have been reported to have deleterious effects on the human body, combined exposure (co-exposure) has been shown to be more fatal.[29, 30, 31] Compared with the toxicity of each metal ion, Lead/Arsenic, and Lead/Arsenic/Mercury co-exposure caused a significant increase in oxidative stress in the blood while Mercury/Arsenic and Lead/Arsenic/Mercury caused greater hepatotoxicity.[31]

A similar synergy also exists between molybdenum and cadmium where kidney antioxidant indices such as glutathione reductase (GR) and ceruloplasmin reduced significantly in co-metal treated groups compared to the single metal treated groups.[32] Similarly, comparing the nephrotoxicity of lead and cadmium, co-exposure to the individual metals caused a more severe decline in renal function.[33]

Heavy metal-induced diseases

Heavy metal intoxication usually leads to the depletion of cellular antioxidants and a subsequent increase in the generation of excessive ROS leading primarily to oxidative stress. This subsequently induces several other life-threatening health conditions such as organ damage. The extent of damage is usually a function of the intensity of metal contamination.

Kidney damage

The kidney is a filtration organ that removes toxins and regulates fluid in the body. Increasing occurrence of chronic kidney disease with consequential effect on mortality rate has continued to be a global challenge.[33] The kidneys are a target of heavy metals because of their general involvement in metabolism and their detoxification role in the body. During reabsorption, the kidneys accumulate divalent heavy metals which eventually cause tubular dysfunctions.[34]

Table 1: Recent Incidences of Exposure to Heavy Metals at Different Locations

Metal	Recent Incidence/Location	Route of Exposure	Effect	Reference
Lead	Drinking water crisis, Michigan, USA.	Water	Elevated level of lead in the blood	21
	Zamfara, Nigeria.	Gold deposits, pond.	Death	22
Mercury	Mercury intoxication/ Riverine area, State of Pará, Brazilian Amazon	Fish	Irritability, dizziness, memory loss and more	23
	Burkina Faso	Occupational exposure	Elevated mercury level in urine	24
Cadmium	United States	Food such as rice, potato and wheat.	Cardiovascular disease	25
	Abuja, Nigeria	Air	Elevated blood Cd levels	26
Arsenic	Italy	Drinking water	Lung cancer, cardiovascular diseases, mortality	27
	India	Drinking water	High risk of cancer	28

The contribution of heavy metals to renal toxicity has been investigated and established by several researchers. Although heavy metal concentrations are sometimes within safe limits and the effects unnoticeable, Avallone *et al*. reported that there is a damaging effect of cadmium on the kidney upon long term exposure [29] and a rise in chromium concentration with time has been said to have a positive relationship with renal damage.[35] Farmers sometimes get exposed to heavy metal during pesticide application. A major component of certain pesticides is sodium arsenate. The nephrotoxic impact of arsenic has been investigated using Wistar rats.[36] The result calls for caution among farmers as it showed that chronic inhalation of arsenate containing pesticides poses a deleterious effect even at low concentration. This is in strong agreement with findings from some other studies.[37] Certain forms of metals are more easily absorbed in the kidneys than others. After a successful comparative analysis of three varying chemical forms of mercury in the kidneys of mice, Liu *et al*. observed that $HgCl_2$ and CH_3Hg are more nephrotoxic than α and β forms of HgS.[38] In a similar study, Apaydin *et al*. verified the deleterious effect of two agents of nephrotoxicity ($HgCl_2$ and $Pb(NO_3)_2$) at a low dosage and confirmed that $HgCl_2$ is more toxic.[39] Worthy of note is the observation which led El-safty *et al*. to raise a caution that this toxic effect of mercury chloride can aggravate kidney damage when combined with cigarette smoking.[40]

Liver damage

Just like the kidneys, the liver, which is also an excretory organ, has been negatively affected by heavy metal contamination. This is primarily because of the role played by the liver in the elimination of toxic substances from the body. Generally, most metals that are nephrotoxic have also been found to be hepatotoxic.[41] Hence, most studies simultaneously investigate the response of these excretory organs to heavy metal contamination. The liver gets damaged when lipid peroxidation results in oxidative damage in hepatic cells.[30] Apart from histopathological studies and lipid peroxidation biomarkers such as malonedialdehyde (MDA), other parameters which indicate liver damage include antioxidant enzymes[42] and cytokines.[43] It has been experimentally established that heavy metals such as Lead exhibit immense negative effect on the liver [44] and several other examples are captured in Table 2.

Brain damage/Cognitive Impairment

Frequent exposure to heavy metals at higher concentrations or even at low doses for a long period does not only affect excretory organs such as the kidneys and the liver but also the human brain. Several factors, particularly exposure to heavy metals have been identified to be responsible for this impairment which is characterized by the malfunctioning of the cognitive and behavioural facets of human lives.[45]

Certain metals are essential elements in the human body. However, they become toxic when the concentration is elevated. A good example is cobalt. A recent study investigated the physiological effect of this metal by subjecting goldfish to cobalt (II) chloride treatment in aquarium water and varying the concentrations for four days. The levels of lipid peroxides in the brain doubled after an exposure to up to 150 mg/L Co^{2+} while the activities of SOD, catalase and antioxidant enzymes were significantly suppressed.[46] This is similar to the effect of lead on the brain of infantile rat where cholesterol metabolism and increased amyloid-beta accumulation were observed in the cortex.[47] Amyloid-beta accumulation has been known to contribute to the pathogenesis of Alzheimer's disease. Furthermore, a notable relationship has been established between cadmium exposure and attention problems in children between 7 and 16 years of age.[48] This relationship strongly agrees with a recent report which directly associate childhood cadmium poisoning to low intelligent quotient (IQ) in ten-year-old Bangladeshi boys and erratic behaviour in the girls.[49] Lead has never been known to be friendly to the brain. According to a survey of blood samples from 125 adults, it was established that the elevation of the concentrations of lead and cadmium generates poor working memory.[50] This conclusion seems to subsist for many more heavy metals as shown by a comparative investigation of six metals *viz* Copper, Lead, Aluminium, Zinc, Manganese, and Cadmium in 183 patients diagnosed with cognitive impairment and 90 healthy individuals in the same age bracket. The concentrations of these metals were higher in cognitively impaired individuals than in the healthy ones and the intensity of the disorder was proportional to the concentrations of the metals. Amongst the metals, Al and Cu exhibited the strongest correlation with disease progression.[51]

Cancer

Heavy metals have also been known to induce carcinogenesis.[52] They do this by increasing the generation of reactive oxygen species (ROS), causing DNA (Deoxyribonucleic acid) damage and by interfering with the expression of tumour suppression genes.[52] For instance, prostate cancer occurs when arsenic attacks micro ribonucleic acid-143 (microRNA-143) whose job is to inhibit certain proteins such as L1M kinase 1 (LIMK1) and thus mitigate prostate cancer.[53] A recent study which was carried out on drinking water in Iowa revealed a dose-dependent association between arsenic concentration and prostate cancer.[54]

While some metals cause deleterious effects at high concentration, some others are extremely dangerous even at low concentrations. Such is the case of cadmium which causes serious damage to lung cells at low concentrations as shown by a study which established a direct correlation between DNA damage, induction of mutation and intracellular cadmium concentration.[55]

Since low concentrations of heavy metals could be that toxic, efforts should be directed at preventing the accumulation of such metals in the human body. The generally high prevalence of thyroid cancer in volcanic areas inspired a recent study which revealed multiple fold increases in the concentration of heavy metals such as Chromium, Copper, Iron, Manganese, Nickel, Lead, Zinc and Thungsten. This observation provided an explanation for the increased occurrence of thyroid carcinogenesis in volcanic areas. It also shows that certain cancers are environmentally induced and can be wisely prevented.[56]

Testicular damage

Another heavy metal-induced disease which is worthy of note is testicular damage. Some toxic metals have been known to cause testicular inflammation as well as oligospermia.[57] Oligospermia is a fertility situation which is characterized by low sperm count. Different heavy metals which have been known to facilitate testicular damage include cadmium [58, 59] and mercury.[60] These metals can alter certain oxidative stress parameters, the weight of the testes and its morphology, thus lowering the chances of fertility in men.

Cardiovascular

The association between exposure of humans to heavy metals and cardiovascular diseases has been slightly investigated. Particularly, the presence of cadmium in the blood may initiate oxidative stress and heart conditions such as hypertension.[61] Apart from cadmium, another metal with potential for provoking cardiovascular diseases is lead.[61, 62] These metals cause cardiovascular diseases via an oxidative stress-related pathway and should be avoided.[62]

Herbal ameliorators of heavy metal-induced diseases

Heavy metals have been widely identified as the generators of reactive oxygen species (ROS) in the body. Conversely, herbal extracts, fractions and isolates have continued to offer significant protection against oxidative stress-induced diseases such as cancer.[63] As heavy metals generate these reactive species, the phytochemicals in plants offer protection to the body by scavenging for the ROS or chelating the heavy metals which induce the release of ROS, thus preventing a chain of diseases or ameliorating the effects of the health conditions which have already been developed.

Herbal ameliorators of kidney damage

Several herbs have proved to be efficient in the management of kidney dysfunction. Such herbs include *Zingiber officinale* whose extract was recently found to be suitable for the protection of the kidneys against mercury chloride intoxication.[41] Grape skin or purple carrot extracts are also known to work against cadmium intoxication in the kidney of

rats via tissue regeneration[64] while *Sedum sarmentosum* Bunge extract exerts its protective effect by suppressing M1-macrophage polarization amongst other examples.

Herbal ameliorators of liver damage

Antioxidant extracts have been known to offer protection to the liver.[65, 66, 67] Hence, several attempts have been made at protecting the liver from the influence of toxic metals using different varieties of phytochemicals. Joshi *et al*. found the ginger extract to be suitable for the protection of the liver against mercury chloride intoxication.[41] The extract offered protection by preventing oxidative degradation and up-regulating antioxidant enzymes. Although turmeric has also been found to be useful in ameliorating arsenic poisoning, the ginger extract was more effective as shown by a unique methodology. The concentration of arsenic in the urine, faeces and hair of the experimental calves were used to quantify the effectiveness of each herb in removing arsenic from the body.[68] Interestingly, turmeric and ginger contain some proteins which prevent arsenic from attacking thiol/dithiol containing proteins. This is in addition to the metal chelating potential of the extracts.[68] More studies are however required to ascertain the basis for the variation in this chelating potential. Such could include chromatographic isolation and functional group analysis of identified active isolates.

Generally, the presence of toxic metallic ions in the human body usually leads to elevated lipid peroxidation biomarkers and lower antioxidant enzymes. The more effective the plant extract, the more these parameters are reversed. Hence, apart from monitoring the ability of an extract to push these unwanted metallic ions into faeces and urine, these other parameters *viz* lipid peroxidation biomarkers, antioxidant enzymes and cytokines are studied to ascertain the effectiveness of various plants extracts.[68, 42, 43]

The use of *Nigella sativa* seeds as dietary supplements against lead acetate-induced oxidative damage in rabbits was successful. It decreased the lipid peroxidation biomarker (MDA) levels and restored other antioxidant parameters in the liver such as Glutathione (GHS) and Glutathione S Transferases (GST).[42] This is similar to the anti-hepatotoxicity exerted by fenugreek seed powder in male rats where hepatic tumor necrosis factor-α amongst others was reversed.[43] Furthermore, supplementing the feed of lead acetate poisoned rats with mushroom and *Garcinia cola* has been found to provide commendable hepatoprotective properties in different studies.[69, 30]

Aqueous extracts of *Carica papaya* roots also possess interesting ability to attenuate the effects of arsenic poisoning in rats.[70] The negative effects of arsenic on the antioxidant status and haematological parameters of the liver were corrected by this extract. Here, the ameliorative action was attributed to the high phenolic content which in turn informed the observed high antioxidant activity. The metal chelating potential of this *Carica papaya* root extract was higher than that of the vitamin C. Hence, a bioassay-guided fractionation or isolation of pure compounds from the extract may afford isolates with the better medicinal application. The protective effect of phytochemicals is clearly illustrated in the herbal component of An-Gong-Niu-Huang (AGNH), a medicinal formula which is administered to patients suffering from cerebral diseases in China.[71] Although Cinnabar (Hg_2S) and realgar (As_2S_2) which are constituents of AGNH induce oxidative stress and inflammatory damage, the herbs which include *Rhizoma coptidis, Radix scutellariae baicalensis, Fructus grandeniae, Radix curcumiae*, and *Borneoleum synthycticum* mitigated cinnabar and realgar-induced histopathological alterations and oxidative stress in the liver. The herbs down-regulated COX-2 (cyclooxygenase 2) and NOS (Nitric oxide synthase) enzymes as well as IL-1β (Interleukin 1 beta), TNF-α (Tumor necrosis factor-alpha), PGE 2 (prostaglandin E2) and NO (nitric oxide) proinflammatory regulators.

Acetone extracts of *Vernonia amygdalina* recently demonstrated the potential to treat cadmium-induced liver injury using a Wistar rat model. The degenerated hepatocytes and the observed inflammation were drastically reduced by the applied extract.[72] The application of Rosemary extract to cadmium poisoned rats also led to the restoration of all observed hepathological and histopathological changes.[73]

Herbal ameliorators of testicular damage

Testicular damage is a major unpleasant effect of heavy metals on the reproductive system in man and several studies about the effect of cadmium on the testes have been documented.

Generally, testicular damage is monitored by observing levels of cytokines, weight of testes, morphology and carrying out sperm analysis.[58] Fenugreek seed powder demonstrated the ability to antagonize cadmium-induced testicular damage mechanisms in male rats. The seed powder reversed the effects of cadmium on the testicular antioxidant systems, interleukin-4 and testicular tumor necrosis amongst others.[58] *Lycium barbarum* polysaccharides was also effective in ameliorating testes damage in rats. The polysaccharides could only effect a slight restoration of the morphology which was altered by cadmium poisoning. Again, changes in the oxidative stress parameters indicate that the observed amelioration of testicular damage occurred through the antioxidative pathway. *Mimosa pudica is* another plant which offers protection against cadmium-induced testicular damage.[57] Sperm analysis and histological findings revealed the protective and restorative effects of this plant on testes making the plant extract a bio-resource for compounds with activity against cadmium-provoked infertility. Mercury poisoning has also been known to affect sperm quality leading to a reduction in male reproductive efficiency. It is on this basis that Rizzeti *et al.* investigated the effectiveness of bioactive peptides from egg white in preventing testicular damage. The sperm number and its morphology were successfully restored by egg white hydrolysate.[60] Although the mechanism of this bioactivity is not yet ascertained, the impressive property of the egg white peptides is also suspected to have occurred via an antioxidant pathway.

Herbal ameliorators of brain damage/cognitive impairment

Several herbs have been explored for their possibility of alleviating the toxic effects of heavy metals on the brain. Such heavy metal effects on the brain include Alzheimers, a major type of dementia. Hussein *et al.* achieved this Alzheimer-like status for rats using a mixture of Aluminium, cadmium and fluoride and used the rats to investigate the neuroprotective effect of berberine.[74] Berberin improved cognitive behaviour in rats and protected them against metal-induced memory impairment via anti-inflammatory and antioxidant mechanisms. The saponin component of ginseng has also been reported to possess memory improving characteristics.[75] This significant memory improvement was achieved by regulation of amino acids metabolism, neurotransmitters, choline, kynurenine and sphingolipids.

Herbal Ameliorators of Cancer

Owing to the generally high cost of modern treatment and the accompanying side effects, a number of cancer patients now resort to the use of herbal medicine as a way out of their health challenge. Several herbal mixtures exist for cancer therapy. While some plant extracts with a high concentration of phenolics chelate metals which otherwise would lead to the generation of reactive oxygen species in the body, others kill cancer cells via different mechanisms. These herbs include the ethanol extract of sweet potato peels which has the potential to mitigate different types of cancer *viz* breast, colon, head and neck cancers amongst others.[63] Another herb is *Celastrusor biculatus* whose ethyl acetate extract possesses notable antitumor properties.[76] The activity is due to the presence of phytochemicals in the extracts. The extracts are sometimes partitioned into fractions via Solvent-solvent partitioning or column chromatography, thus achieving less complexity and better anticancer results.[63]

Herbal ameliorators of cardiovascular diseases

The heart is a delicate organ which must be guarded from toxic elements which present in different forms. Some interesting and protective effects of herbs on the heart have also been documented. Curry leaf possesses the ability to protect the heart of rats from cadmium-induced oxidative stress. The cadmium-induced damage which was confirmed by histological studies was ameliorated by pre-treatment of the experimental rats with an aqueous extract of curry leaf. This suggests that a curry-rich diet may be a good prescription for the prevention of heart diseases and its eventual failure.[77] Going

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beyond the use of crude/raw extracts, Zhang *et al.* studied the protective effect of a water-soluble polysaccharide from the root bark of *Aralia alata* on mercury-induced cardiovascular damage using a rat model. The polysaccharide offered protection by enhancing the rats' antioxidant status, suppressing pro-inflammatory mediators and by preventing neutrophil infiltration.[78] Similarly, the antioxidant potential of *Tinospora cordifolia* has been reported as the basis for the application of its methanol extract in the attenuation of cadmium-induced heart disease. The biochemical and histological alterations in the heart of the experimental rats were reversed by its inherent antioxidant phytochemicals.[79]

Other herbal amelioration of metal-induced health conditions which are also worthy of note include the ameliorative effect of *Curculigo orchoides* on Cr(VI)-induced oxidative damage[80] and the immunomodulatory effect of *Cymbopogan schoenanthus* (L.) on cadmium-induced oxidative stress.[81]

Pure natural product isolates in ameliorative application

The fore going review captures the application of extracts and fractions from plants for the amelioration of heavy metal-induced health conditions. However, comparative research into the ameliorative effects of pure compounds from bioactive plant extracts reveals fascinating advancement.

Thangarajan *et al.* studied the effect of morin **(I)**, a pentahydroxyflavone, on lead acetate-induced oxidative stress and sensorimotor impairment.[82] The lead intoxication effected cognitive dysfunction and anxiety-like behavior in experimental rats. However, morin antagonized the up-regulation of Bax and the down regulation of B-cell lymphoma 2 (Bcl-2) thus offering protection against lead toxicity. It was recently discovered that kolaviron **(II)**, a biflavonoid, does not affect cyclooxygenase activity in rats. It, however, prevents lipid peroxidation.[83] Similarly, Wen *et al.* observed that baicalin **(III)**, a trihydroxyflavone is a good candidate for the prevention of Cd-induced oxidative stress as it inhibited oxidative stress, chelated cadmium as expected and ameliorated hepatic cytotoxicity.[84]

The ameliorative functions of hydroxyflavones may directly vary with the number of hydroxyl groups present in each molecule as well as the position of the hydroxyl groups. This possibility is worthy of further investigation.

In a bioactivity guided isolation experiment, Pandey *et al.* evaluated the effect of different isolates from *W. somnifera* on Alzheimer's disease and arrived at withanone **(IV)** as the most active compound.[85] In addition to its earlier established anticancer property,[86] withanone corrected the cognitive impairment by a mechanism which inhibits amyloid β-42 and attenuating pro-inflammatory cytokines such as TNF-α, NO, IL-1β, and IL-6. Worthy of note is the fact that withanone did not stop at inhibiting acetylcholinesterase (AChE). It also modified Aβ processing thus correcting the foundational cause of the disease.

The protective effects of ginger extract and its active constituent – 6-gingerol **(V)** against $HgCl_2$ intoxication in the liver and in kidneys have been investigated.[41] Both the ginger extract and 6-gingerol offered protection by up-regulating antioxidant enzymes and preventing oxidative degradation in biological membranes. Although a lower amount of 6-gingerol (50 mg) compared to ginger (125 mg) were applied per kg p.o., 6-gingerol generally exhibited higher potency. For example, 6-gingerol achieved 71% restoration of the GSH while ginger gave 56.7%. Also, 6-gingerol effected 85.1% inhibition of lipid peroxidation while ginger achieved only 57.9% inhibition. Similar trends were also recorded in kidneys. This is in agreement with their earlier report in which curcumin **(VI)** (80 mg/kg) provided 85% protection while *Curcuma longa* extract (200 mg/kg) exerted 70% protection of the kidney against mercury chloride toxicity as shown by the kidney function test.[87] Structures of the various pure isolates (compounds) in the foregoing discussion are captured in Figure 1.

Following notable ameliorative studies by Flora *et al.* Sharma *et al*., Zeng *et al*., and Joshi *et al*. [87, 88, 89, 90] more recent studies on the amelioration of heavy metal toxicity using herbs are presented in Table 2.

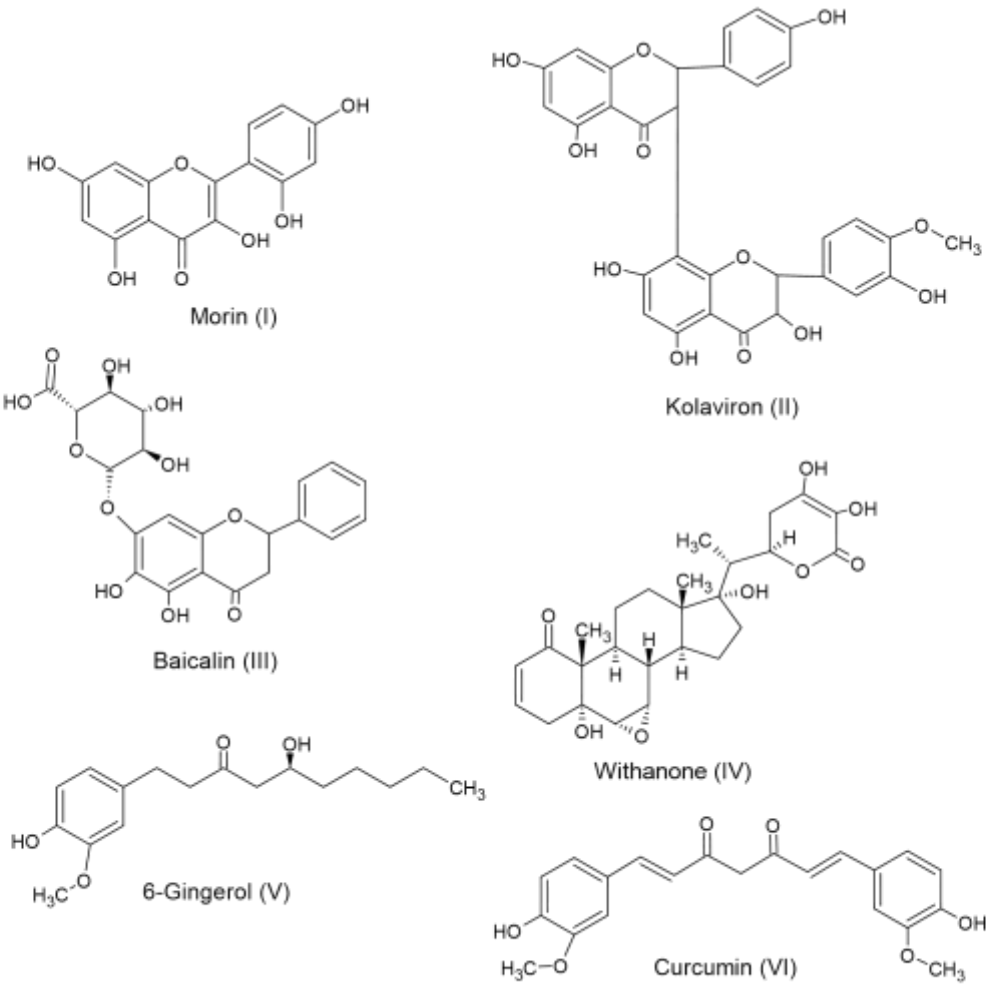

Figure 1: Pure compounds (Isolates) which ameliorate heavy metal induced diseases

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Table 2: Combating heavy metal toxicity with herbs - dosage and animal models

S/N	Ameliorator	Intoxication	Affected Organ	Dosage	Animal's used in the experimental model	Remark	Reference
1	Aqueous (a) Grape skin (b) purple carrot extract	Cadmium	kidneys	(a) 175/350mg/L (b) 400/800mg/L in drinking water	Wistar rat	Both extracts exhibited protective effect on the kidney via tissue regeneration and antioxidant activity. Grape skin, with the lower dosage concentration, showed greater potency	91
2	Egyptian purslane ethanol extract	Cadmium	kidneys/Liver	2 g/kg bw for 30 days	Sragues-Dawley rats	Oral administration of extracts reversed the pathological alterations observed in the liver and kidneys	92
3	*Tribulus terrestris* extract	Copper	Testes	10 mg/kg , po	Rats	The extract is a good candidate for the suppression of male fertility impairment and hypertension	43
4	Vitamin D3	Lead	Liver	Injection 1000 IU/kg for 3 days a week	Rat	Vitamin D offered hepatic protection by inhibiting oxidative stress and pro-inflammatory molecules. It restored hepatocyte calcium momeostatic molecules	93
5	Ginger	Cadmium	kidneys	100 and 200 mg/kg bw	Rat	Ginger is an effective drug for the restoration of kidney tissue damage and renal dysfunction	94
6	Polysaccharides isolated from *Peroploea augustifolia*	Cadmium	kidneys	250 mg/kg bw	Rat	This polysaccharide is a strong preventer of oxidative stress and cytotoxicity induced by cadmium in HEK 293 cells	95
7	Pigment-protein complex is isolated from *Phormidium versicolor*	Cadmium	Liver	50 mg/kg bw	Rat	This antioxidant complex prevented hystopathological alterations at low concentrations.	96
8	Chlorogenic acid or sunflower seed extract	Cadmium	Intestinal barrier	50 mg/kg bw	Sragues-Dawley rats	This acid reduces the expression of Divalent metal transporter 1. Hence, it is a promising compound which can be developed into a preventative drug for the management of cadmium-induced toxicity.	97
9	Ethanol extract of Leaf, Seed and fruit of *Datura metel* L.	.-	kidney	300 mg/kg bw (low) 600mg/kg bw (high) of leaf, seed and fruit for seven consecutive days	Male albino rat	While some parts of this plant could be employed as kidney function regulators, some parts exhibited negative effects.	98
10	Chicoric acid	Lead	Zebra fish/BV-2 microglial cells	2 - 20 µM for 48 hours	Zebra fish/BV-2 microglial cells	Lead (Pb)-induced malformation of zebra fish larvae was suppressed from 61% to 20%. Hence, this compound could be developed into commercial natural detoxifying agent.	99
11	*Spirolona maxima* and *Allium satuvum* (Garlic)	Lead	testes	500 mg/kg and 600 mg/kg daily for one	Albino rats	Although both were effective at restoring the antioxidant biomarkers and testosterone levels to normal, spirolina	100

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				month		provided better improvement of spermatogenesis after administering the ameliorators.	
12	Gallic acid (GA)	Chromium	Thyroid	20mg GA/kg b. wt	Albino rats	Gallic acid strongly influenced oxidative stress and showed thyroprotective tendencies by lowering the thyroid expression of iNOS, TNF-α, IL-6 and COX-2	101
13	Ginger	Mercury	Liver/Kidneys	Ginger (125 mg/kg, po) and compound 6-gingerol (50 mg/kg, po)	Rats	Both the extract and the isolate offered protection (by hindering oxidative degradation) after 3 days administration to HgCl2 poisoned rats.	41
14	*Tinospora cordifolia* stem methanol extract	Cadmium	Heart	100mg extract/ kg of bodyweight for 28 days	Male wistar rats	Induction of lipid peroxidation and protein carbonylation were reduced by the administration of the extract	79
15	Berberine	Cadmium (+ fluoride + Aluminium)	Brain (Alzheimer's Disease)	50 mg/kg /day 30 days after Cd+F+Al contamination	Rats	This herb is multipotent against the modelled Alzheimers-like disease via the antiinflammatory and the antioxidant pathways. Particularly, it inhibited the formation of the progenitors of amyloid-β plaques	74
16	Mushroom (*Pleurotustuberregium*)	Lead	Liver/kidneys	(90% of feed + 10% of mushroom → 30% of feed + 70% mushroom)	Wistar albino rats	*P. tuberregium* ameliorates lead toxicity in liver and kidney tissues with the tissues showing improvement with increasing mushroom content in the feed of Albino rats	69
17	*Garcinia Kola* Hekel	Lead	Liver	12 g/0.002 g feed to bitter cola powder fed to rats for 28 days	Wistar rats	Both coated and uncoated *G. kola* supplemented feed demonstrated strong ameliorative potential in experimental lead-poisoned rats	30
18	*Opuntia dillenii* (Ker Gawl.) Haw. (OD) fruit extract	Cadmium	Liver	0.2 ml of OD fruit extract (once daily) by gavage on days 16-22	Mice	Clear hepatoprotective effects were observed in OD treated mice	102
19	*Murraya koenigii* Chlorof orm Extract	Lead	Liver	50 mg/kg) once daily for 7 days	Male albino Swiss mice	Nearly 100% restoration of all hepatic function markers was achieved	103
20	*Moringa oleifera*	Cadmium	Liver/ kidneys	400 mg/kg *Moringa oleifera*	Rats	Cd intoxication caused elevated biochemical parameters which were restored by the moringa drug treatment	104

Synergistic amelioration of heavy metal-induced diseases using herbal combinations

Apart from isolating pure compounds with the aim of achieving better potency, herbal mixtures have also been co-administered in order to achieve better efficiency.[105] Rasool *et al.* studied the hepatoprotective effect of co-administration of *Silybum marianum* (S) and *Glycyr rhizaglabra* (G) extracts on male rats. Although each of G and S exhibited hepatoprotective effects when used alone, their co-administration (GS) achieved even better hepatic protection as shown by the observed changes in liver enzymes and different antioxidant indices.[106]

In another study, Biswas *et al.* compared the effectiveness of turmeric and ginger in the treatment of arsenic-poisoned rats.[69] Although turmeric displayed higher ability to mitigate the effects of arsenic toxicity, the synergy of the two herbs for improved amelioration was not investigated. However, Praveen *et al.* applied a combination of a polysaccharide from *Mormodica charantia* and curcumin from *Curcuma longa* to prevent As^{3+} degradation of SOD and catalase in the liver.[107] Hepatic tissue MDA and CD levels showed that the co-administration offered better antioxidant effect compared to single applications and the highest restoration of SOD/catalase was recorded in the co-administration experiments.

Underlying Mechanisms

Based on the fore-going review, the underlying mechanism by which phytochemicals ameliorate the effect of heavy metal intoxication can be summarized as follows:

i. Enhancement of the antioxidant defense system of the body by preventing the erosion of antioxidant enzymes such as GSH.[68]
ii. Prevention of the depletion of thiol-containing proteins/enzymes.[68]
iii. Chelation of heavy metals contaminants in the body to prevent the generation of ROS.[70]
iv. Down-regulation of inflammatory mediators such as TNF-α. [71, 72, 74]
v. Prevention of genetic/cytotoxic damage.[53, 55]

Conclusion and Future Trends

Oxidative stress is usually the immediate result of heavy metal contamination as reactive oxygen species (ROS) are generated. The generated ROS then attack various cell constituents such as the antioxidant enzyme GSH, thus lowering the intracellular antioxidant capacity of the cell. Unchecked reactive oxygen species damage important biomolecules such as the DNA, alters haematological parameters and inhibit vital enzymes, causing diverse organ dysfunctions.

Diverse sustainable herbs with antioxidant properties have been successfully employed in scavenging these dangerous radicals as a protective measure against organ damage and for ameliorative purposes.[108, 109] Particularly, spices such as ginger and turmeric are generally accepted since they are with less negative side effects and are therefore good candidates for nutraceutical development.

In the near future, supplement therapy will be employed to manage unavoidable heavy metal concentration in the body.[99, 93] Active extracts will be incorporated into foods to conveniently convey these supplements.[30]

While attempting to combat the unpleasant effects of heavy metal toxicity, new health challenges could emerge as a result of the toxicity of the applied herbs.[98] This calls for more intensive toxicological research which will assist in the establishment of right dosage for these herbal ameliorators.

The future of research in this direction is compelling. Intentional evaluation of the heavy metal content of local and imported food as well as a periodical air and water analysis in different countries of the world will lead to environmental protection acts which will eventually reduce the statistics of organ damage. There is also a need to investigate many more local herbal resources for their potential in serving preventive and ameliorative functions. Although the primary mechanism by which these reviewed herbs offer protection is the antioxidant and anti-inflammatory pathways, there is still a measure of uncertainty in some reported mechanisms of disease treatment. Careful isolation of bioactive compounds from plant extracts should precede biological tests as this will aid investigation into the detailed mechanism of action via which the phytochemicals exert their desired ameliorative properties.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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