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A Review

Insights on the assessment of the potential of phytochemical chelating, protective, and detoxifying properties in managing chronic arsenic toxicity

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Arsenic exposure, a global issue originating from polluted groundwater, is a significant health threat due to its environmental and human health effects. This exposure leads to numerous illnesses (insulin resistance, cancer, bronchitis, asthma, neurodegenerative disorders, liver and kidney dysfunction, hypertension, and cardiovascular diseases), posing significant risks to overall health and economic and social welfare, particularly in underdeveloped nations. Arsenic-related health issues are caused by many factors, including the formation of reactive oxygen species, oxidative damage, inflammation, DNA damage, proteinopathies, apoptosis, and dysregulation of cell signaling pathways. Chelation therapy is the most common method for detoxifying arsenic, but it has been linked to harmful effects such as hepatotoxicity and neurotoxicity. Indigenous plant-based drugs have been shown to effectively relieve arsenic-mediated toxicity without causing adverse effects. These phytochemicals aid in the elimination of As from biological systems, making them more effective than the conventional therapeutic agents. This review provides an overview of the toxic effects of arsenic and discusses available therapeutic strategies, emphasizing the protective and detoxifying activities of phytochemicals and herbal drugs against arsenic. This information could help to identify new prophylactic and therapeutic formulations against arsenic-induced toxicity.

Keywords: Anti-apoptotic, Anti-inflammatory, Antioxidant, Arsenic exposure, Chelating agent, Phytochemicals

Arsenic (As) is an element present in soil, water, food, and the environment. Drinking water is one of the most important ways to expose to As[1,2]. Many health problems have arisen from arsenic exposure. Acute As exposure can damage the nervous and cardiovascular systems, resulting in symptoms that include nausea, vomiting, and abdominal discomfort. It can also produce neurological effects, such as light-headedness, lethargy, convulsions, and delirium. The long-term health risks associated with arsenic exposure were significant. Skin, lung, liver, bladder, and kidney malignancies can occur in extreme conditions[3-5]. This results in DNA changes and damage to the major organ systems through necrotic and apoptotic cell death (Figs 1 & 2). Patients' quality of life is negatively affected by numerous physical issues that arise from emotional, behavioral, and neurological clinical presentations. The skin is severely affected by As accumulation, resulting in hyperpigmentation. When exposed to high quantities of metalloids, arsenic can accumulate in keratin-rich tissues such as the epidermis, nails, and hair. Accordingly, the International Agency for Research on Cancer[2] has classified As as a Class I human carcinogen. As poisoning instances have suddenly increased at a pandemic rate, major concerns have been raised in several countries, especially Bangladesh, China, India, Pakistan, Chile, and Taiwan, where excessive groundwater As levels have been reported to be a worrying condition[5]. However, the precise mechanisms by which As causes cancer are not completely understood[6]. Metabolic reprogramming encompasses alterations in various metabolic pathways including glycolysis, glutaminolysis, de novo fatty acid synthesis, and fatty acid oxidation[7]. According to Pavlova and Thompson[8] (2016), cancer cells exhibit a collective occurrence of these pathways, which serve to enhance the uptake of vital nutrients, prioritize the distribution of nutrients to metabolic pathways, and promote tumor

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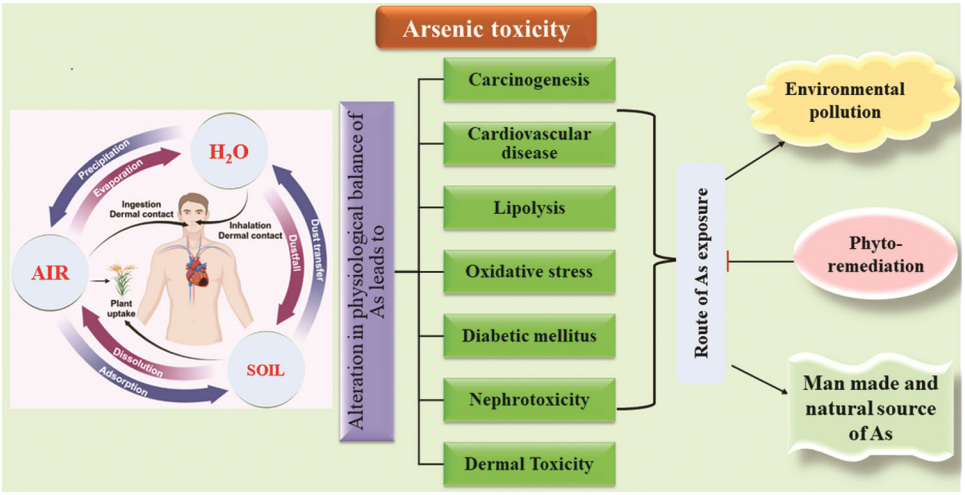

Fig. 1 — Source and route of exposure to arsenic, as well as its associated health problems

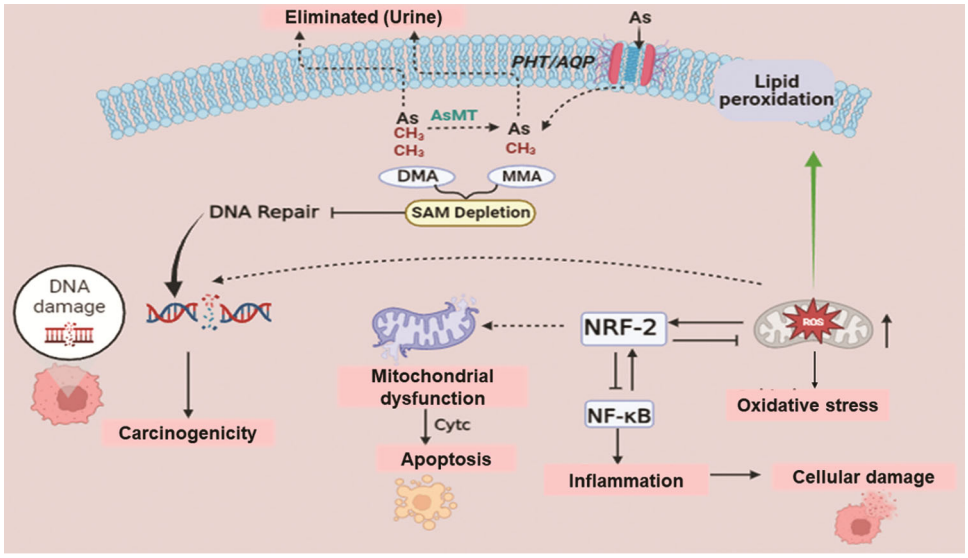

Fig. 2 — Elucidation of molecular pathways underlying arsenic poisoning, Dimethylamine (DMA); monomethy-larsonic acid (MMA); S-Adenosylmethionine (SAM); Nuclear factor kappa B (NF-κB); nuclear transcription factor erythroid 2 (NRF-2); Cytochrome c (Cytc) and (PHT/AQP) Phosphate transporter/aquaporin-1

transformation. Recently, extensive research has been conducted to determinethe significance of metabolic reprogramming in the onset and progression of various malignancies[9-12]. Furthermore, alterations in immune cell metabolism play a vital role in preserving the tumor microenvironment (TME) and determining tumor prognosis of tumors[13]. The effect of prolonged arsenic exposure on various metabolites, including glucose[14-16], lipids[17,18], and amino acids[15,19], has been substantiated by multiple experimental studies. However, this situation is more intricate in living organisms, as studies have shown that exposure to As leads to a decrease in the expression of glycolytic genes in rodent livers. In addition, studies have shown that exposure to As alters the process of lipid deposition by preventing the breakdown of fat in human renal tubular epithelial cells[20] and activating the serine-glycine one-carbon pathway in BEAS-2B cells[21]. Because of its widespread acceptability, few side effects, and variable methods of action, there is an increasing need for the safe and efficient treatment of arsenic poisoning. Owing to their many benefits and general acceptance, the use of plant and phytoconstituent derivatives for the treatment of human disorders is becoming increasingly popular. Chelation treatment, a method used by chemotherapeutic agents to treat arsenic poisoning (Fig. 1), is hampered by numerous adverse effects that limit its clinical efficacy.

This review explores the harmful effects of As and its health implications and suggests various plant-based interventions focusing on chelation and the protective properties of phytochemicals and herbal products against As. This study aimed to identify new preventive and treatment strategies for As-induced toxicity and highlight the potential of plant-based medicines containing phytoconstituents as alternatives to chemotherapeutic agents.

Physicochemical properties of the Arsenic

Arsenic, with an atomic number of 33, is classified as a metalloid because of its metallic and non-metallic properties. It belongs to group VA in the modern periodic table and includes phosphorus, nitrogen, and arsenic. Arsenic can exist naturally in its oxidation states of +5, +3, 0 (arsenic), and -3 (arsine). Common oxidation states of inorganic arsenic in aquatic environments are arsenate, arsenite, and their corresponding salts. Additionally, inorganic arsenic can be converted into organic arsenic by methylation, which is carried out by fungi, bacteria, and yeast. The resulting organic arsenic compounds include dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), and gaseous derivatives of arsine. Arsenic is a silver-grey crystalline metal with low thermal conductivity in its elemental state,which displays its physicochemical properties[22].

Modes of human exposure

Natural resource

As is a metalloid widely distributed in the atmosphere, living organisms, geological formulations, and water. It is primarily associated with sulfide minerals such as enargite, cobaltite, loellingite, realgar, orpiment, mispickel, niccolite, and tennantite. As emissions into the atmosphere include ocean volcanoes, oil and wood burning, and forest fires. The concentration of As in freshwater and seawater fluctuates between 0.15 µg/L and 0.45 µg/L, and 0.09 µg/L and 24 µg/L, respectively. Epidemiological studies have identified As contamination in groundwater as a significant health risk in most developing countries. Natural processes contribute to the widespread dispersal of As in aquatic ecosystems. As pollution is a global event, with increasing evidence establishing a steady increase in As concentrations in water bodies, food, and soils worldwide[5] (Fig. 1).

Arsenic in drinking water

Approximately 200 million people worldwide, most of whom reside in southern Asia, have As in their drinking water. Many people are exposed to As, which is frequently detected in drinking water and groundwater. Recently discovered As-rich groundwater sites have primarily been reported in Asian countries. Groundwater samples from multiple locations were used to produce a hazard and risk map that revealed elevated As levels in the Indus Basin. Consequently, preliminary mitigation actions were initiated in the impacted areas. People are exposed to higher levels of As in their drinking water because many countries other than the US have groundwater with higher levels of metals. As use has been linked to numerous ailments including organ poisoning, diabetes, cancer, heart disease, skin blemishes, and neurological effects[5] (Figs 1 & 2).

Arsenic metabolism

The gradual conversion of As (V) to As (III) occurred following exposure to inorganic arsenic. Pentavalent organic arsenicals, monomethylarsonic acid and dimethylarsinic acid, are catalyzed by a methyltransferase to catalyze the oxidative biomethylation of As III, which is generated by these two (2) electron reductions or from external sources. Following arsenic metabolism, the body eliminates these waste products throughurine[23,24]. However, under pathological conditions, SAM depletion causes As (III) aggregation, affecting cellular homeostasis, including oxidative balance, inflammation, carcinogenicity, apoptosis, and genetic and epigenetic processes. This disrupted homeostasis leads to cellular damage and ultimately cell death[23,24] (Fig. 1). In addition, studies have indicated that As photo oxidation is a potentially significant mechanism that controls the speciation of inorganic As in aquatic system[25].

As poisoning

Drinking As-contaminated water can lead to acute and chronic poisoning. No specific symptoms of acute As poisoning were observed. Non-specific symptoms of chronic poisoning include weariness, colitis, reflex loss, weight loss, weakness, anorexia, gastritis, hair loss, and anorexia. Experimental evidence has implicated prolonged As poisoning in the pathogenesis of diseases such as cardiovascular disease, atherosclerosis, hypertension, hyperkeratosis, disturbance in the nervous and peripheral vascular system, hyperpigmentation, circulatory disorders, and hepatic and kidney disorders[26] (Fig. 1). The body systems of humans and other animals can detoxify inorganic pentavalent and trivalent As compounds. Detoxification was performed by adding a methyl

group to the inorganic As and converting it to methylated (organic) As. Methylated arsenic has a low affinity for tissues. After three or four days, arsenicals are excreted *via* the urine[27,28]. As is genotoxic because it prevents repair of damaged DNA. Therefore, they are considered carcinogenic. As uptake through contaminated air can lead to lung cancer pathogenesis. Furthermore, oral ingestion of As causes renal, bladder, skin, and liver cancer[29,30]. Similarly, epigenetic alterations are among the most studied mechanisms of As poisoning. Experimental studies have provided evidence of As-induced epigenomic alterations in healthy individuals[31] (Figs 1 & 2).

Oxidative stress

As toxicity is primarily caused by oxidative stress, which activates pro-inflammatory proteins such as NF-κB. This leads to increased concentrations of glutathione disulfide, protein carbonylation, oxidative stress, and malondialdehyde (MDA), a hallmark of lipid peroxidation. The brain's ability to store As intensifies its toxicity to neurons, affecting mental health, as well as cognitive and intellectual function. Long-term exposure to As can lead to significant declines in IQ and memory. The three most extensively studied pathways of As-induced neurotoxicity are inflammation, oxidative stress, and defective mitochondria (Figs 1 & 2). Rats exposed to As showed decreased rota-rod performance, grip strength, and locomotor activity. Oral sodium arsenite treatment in female rats resulted in gliosis, nuclear pyknosis, oxidative stress, increased anxiety, and motor incoordination[32]. Various concentrations of As trioxide affect oxidative stress, heat shock protein reactions, and minor histological alterations in chicken brain tissues[33].

Neurotoxicity

Numerous neurological disorders are significantly more likely to occur when exposed to As because of molecular mechanisms including cytotoxicity, DNA damage, increased reactive oxygen species (ROS) generation, and chromosomal abnormalities (Figs 1 & 2). Epidemiological research has shown that As can accumulate significantly in the brain[34-38], which is potentially intensified by the ability of the brain to collect significant amounts of As. As exposure has been linked to an increased occurrence of neurological behavioral disorders owing to its propensity to penetrate the blood-brain barrier. Asalso negatively affects mental health, cognitive function, and intellectual performance. As exposure induces neurotoxicity through two mechanisms: interference with communication between the neurological and skeletal systems and the generation of oxidative stress. The first factor results in compromised integrity of the neuroskeletal system, which, in turn, causes a decrease in the efficiency of nerve conduction. This leads to peripheral neuropathy and neuropathic pain. During the oxidative stress stage, the production of lipid peroxides occurs, which in turn activates the NF-kB and AP-1 signalling pathways and increases the levels of antioxidant enzymes. Eventually, this leads to neuronal loss and damage[22,38] (Fig. 3). Previous studies have highlighted the harmful effects of Ason mental health, cognitive function, and intellectual abilities. Children exposed to As over an extended period experienced a

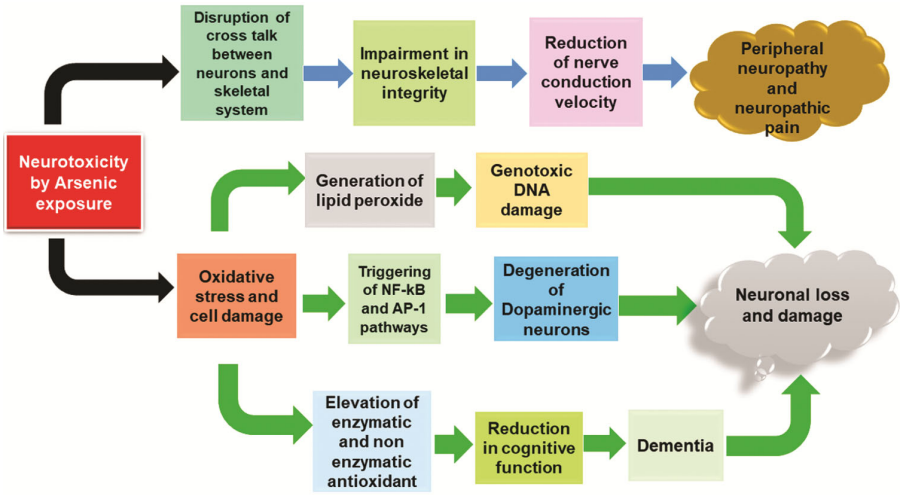

Fig. 3 — Neurotoxicity mechanisms resulting from arsenic exposure Nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1)

significant decline in their intelligence quotient and memory function, even at doses below 10 µg/L[34]. As-induced neurotoxicity has been confirmed to cause altered neurotransmitter concentrations, decreased synaptic plasticity, signaling, neurogenesis, altered sensory function, peripheral nerve neuropathy, and reduced conduction velocity[35-38]. These results implied that arsenic-induced neuronal damage is further amplified by the ability of the brain to collect large amounts of As.

Hepatotoxicity

Liver is an important organ for toxic substances because of its role in xenobiotic detoxification and metabolism. Fatoki *et al*. (2019)[32] reported that As at low, medium, and high doses of sodium arsenate may have potent hepatotoxic potential. Exposure of Wistar rats to arsenic for 4, 8, and 12 weeks significantly increased the plasma activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (γ-GT), markers of hepatotoxicity. The upregulation of plasma AST and ALT activity is a sensitive marker of hepatocyte cytoplasmic and/or mitochondrial membrane damage. As exposure has also been linked to upregulation of ALP activity in plasma and liver cancer patients. These studies suggest that As can compromise hepatic structural and functional integrity. Hepatic histological examinations revealed that various dose regimens of As disrupted normal cytoarchitecture, degenerated cytoplasmic contents, collapsed central vein, and enlarged hepatic sinusoids, indicating major liver damage[32]. The study found that As significantly inhibited mitochondrial biogenesis in hepatotoxicity[34-38], down-regulating expression levels of p-AMPK α/AMPK α, PGC-1 α, NRF1, NRF2, TFAM, TFB1M, TFB2M, and COX-IV[14]. However, As treatment increased mitophagy and pro-apoptotic indices, while reducing the anti-apoptosis index[20]. It was concluded that As-induced hepatotoxicity may be a combination of impaired mitochondrial biosynthesis, mitophagy, and mitochondria-dependent apoptosis (Fig. 4).

Nephrotoxicity

Hepatocytes are primarily responsible for metabolizing As, whereas renal cells are the primary means by which As is eliminated from the body. According to previous research, drinking water contaminated with As increases the risk of renal problems because As V is transformed into As III in the kidneys. Increased inflammation and a lower glomerular filtration rate (eGFR) have been associated with drinking water contaminated with As. An ineffective filtration process by the kidneys is indicated by elevated levels of blood urea and creatinine. Low excretion resulting from renal diseases

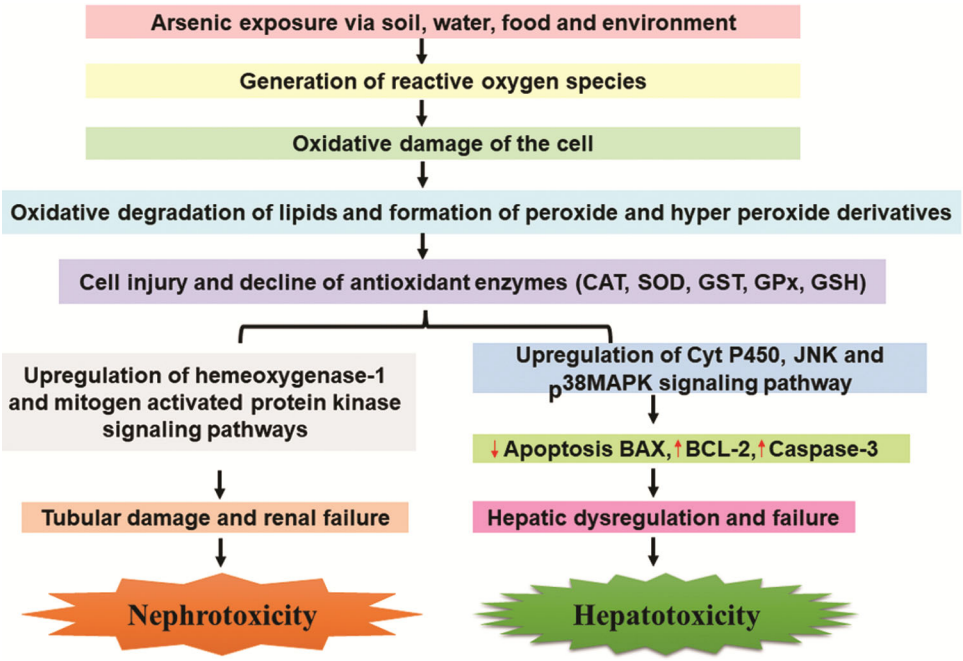

Fig. 4 — Mechanisms of hepatorenal toxicity caused by arsenic exposure Superoxide dismutase (SOD); B-cell lymphoma-2 (BCL-2); Glutathione (GSH); BCL-2 associated protein X (BAX); Catalase (CAT); glutathione peroxidase (GP_X); glutathione S-transferase (GST) and (p^{38} MAPK) p^{38} mitogen-activated protein kinase

and low GFR causes high blood urea concentrations[36]. As-induced renal injury was linked to oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis, as evidenced by the upregulation of HO-1, SOD, and MAPK[20,34,35] (Fig. 4).

Cardiovascular toxicity

As poisoning leads to cardiovascular diseases because it elevates the levels of soluble intercellular and vascular cell adhesion molecules and biomarkers of cardiovascular disturbance (Fig. 5). Exposure also leads to the formation of oxidized lipids that generate oxidative disorders and elevation of reactive oxygen species/reactive nitrogen species (ROS/RNS), nicotinamide adenine dinucleotide (NADH) oxidase, p38 mitogen-activated protein kinase (p38MAPK), intracellular glutathione disulfide (GSSH) levels, endo-epithelial injury, heme oxygenase-1 (HO-1), interleukin IL-6, calcium sensitization, myosine phosphorylation, cardiac output, decreased activity of endothelial nitric oxide synthase (eNOS), and antioxidant defense mechanisms (Fig. 5). Furthermore, research has demonstrated a substantial correlation between cardiovascular disease and modest elevations in blood pressure, suggesting that exposure to As during pregnancy may have an impact on blood pressure[37].

Protective mechanisms of phytocompounds in arsenic toxicity

As exposure can lead to organ damage, organ failure, and various health issues[38]. Plants contain bioactive molecules known as phytochemicals, including glycosides, carotenoids, phenols, flavonoids, alkaloids, terpenoids, and saponins[39-62]. They have been investigated for their ability to reduce metal and metalloid toxicity, owing to their antioxidant and chelating properties. It has been discovered that phytochemical antioxidants can counteract the oxidative damage caused by As. Diverse substituents at C3 can promote different patterns of modification and oxidation of the core structure of flavonoids. Similar to 3′,4′-dihydroxyflavone, *in vitro* research has demonstrated that hydroxy substitution of the flavone quercetin can trigger the NQO1 enzyme. NQO1 and inducible nitric oxide synthase are strongly induced by other phytochemicals including 5,7-dihydroxyflavone and 5,7-dimethoxyflavone. For methoxy and hydroxy substitutions at different parent ring locations, antioxidant activity increased[39].

Antioxidant

Antioxidant phytochemicals can reduce the harmful effects of As, which is a significant toxicological mechanism[40]. Essential organs exposed to arsenic-induced oxidative stress were less affected by plant extracts and phytochemicals. Polyphenolic substances possess significant free radical scavenging abilities, and antioxidant defense is the inhibition or postponement of the oxidation of oxidizing agents in live cells. Catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GR), glutathione

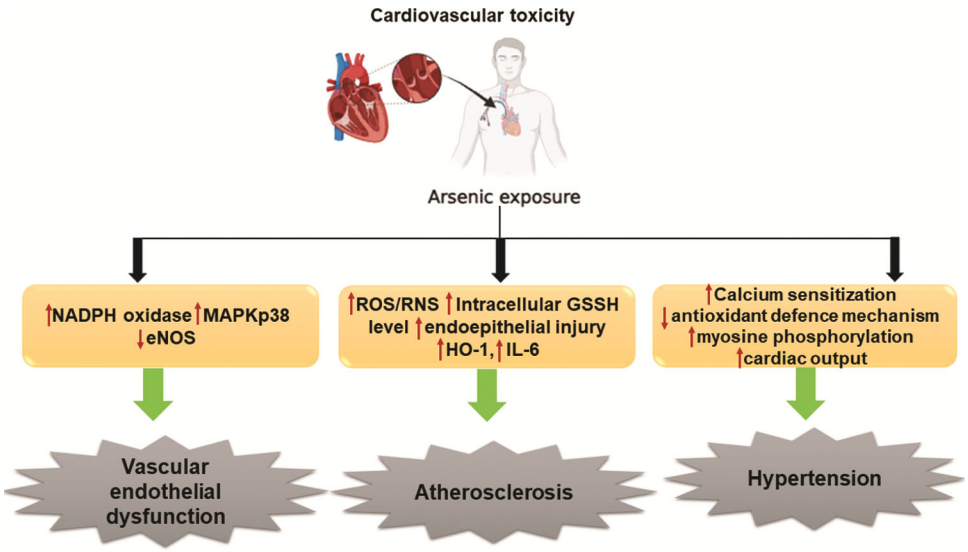

Fig. 5 — Pathological mechanisms underlying arsenic-induced cardiovascular toxicity Nicotinamide adenine dinucleotide phosphate (NADPH); p^{38} mitogen-activated protein kinases ($MAPKp^{38}$); endothelial nitric oxide synthase (eNOS); reactive oxygen/nitrogen species (ROS/RNS);Glutathione Disulfide (GSSH); Heme oxygenase-1 (HO-1) and Interleukin-6 (IL-6)

S-transferase (GST), and superoxide dismutase (SOD) are examples of enzymatic antioxidants. While peroxide is destroyed by CAT and GP_X, SOD catalyzes the dismutation of reactive superoxide anions to O_2 and H_2O_2[41]. Glutathione metabolism is intimately related to GPx, an enzyme that protects cells against the harm caused by free radicals. Non-enzymatic antioxidant defense of the extracellular environment is attributed to vitamins E and C, transferrin, ceruloplasmin, albumin, bilirubin, and β-carotene. Phytochemicals can lower prooxidant levels by lipid peroxidation, lower ROS levels, and alter the expression of antioxidant enzymes. The nuclear transcription factor erythroid 2-related factor (Nrf-2) can be depleted and the levels of antioxidant enzymes can be lowered by persistent oxidative stress (Fig. 2). An effective method for repairing oxidative damage caused by As exposure is to use phytochemicals with antioxidant qualities that can replenish enzyme levels or scavenge oxidative species with extra chelation or anti-inflammatory effects[42].

Anti-inflammatory

Oxidative stress and inflammation are the two major factors that contribute to the pathogenesis of As[40]. Nrf-2 and NF-κB play central roles in the regulation of oxidative stress and inflammation and thus are targets for developing agents against oxidative stress-and inflammation-related diseases[43]. Depletion of Nrf-2expression in the cellular environment inhibits the NF-κB pathway and enhances the production of proinflammatory cytokines. Persistent elevated levels of ROS/RNS might also result in the release of NF-κB-mediated proinflammatory cytokines (IL-1β, IL-8, and IL-6) release[49]. Chronic exposure to As has been linked to elevated levels of proinflammatory cytokines and NF-κB expression in different target organs[44]. Various phytochemicals, particularly polyphenolic compounds, exhibit potent anti-inflammatory effects. A few polyphenolic compounds, such as rutin, quercetin, and curcumin are known to alleviate As-induced upregulation of proinflammatorymarkers[38-62]. Thus, phytochemicals with anti-inflammatory properties may be useful in limiting As-induced inflammatory changes in tissues[45] (Figs 2 & 5).

Anti-apoptotic

Chronic As exposure through contaminated drinking water leads to immunosuppression and cytokine secretion, particularly in mitochondria. These cytokines, including TNF-α, IL-1β, and IL-6, generate free radicals through mitochondrial respiratory chain reaction[46]. Oxidative stress and inflammation can cause mitochondrial dysfunction and affect cellular homeostasis. Mitochondrial reactive oxygen species (ROS) cause membrane disruption, cytochrome c release, apoptosome aggregation, caspase-3 activation, and apoptotic cell damage. NF-κB activation and proinflammatory cytokines further exacerbate this damage. Several phytochemicals, terpenoids, flavonoids, and stilbenoids have been reported to mitigate this apoptotic cascade[38-62] (Fig. 6).

Chelating agents

As can be eradicated from the body by employing ligands to create a compound that facilitates the removal of As from body systems (As ligand). The term used to describe this method is "chelation therapy," and substances that form complexes are known as chelating agents. Chelation can lead to the removal of toxic and essential metals or cause there distribution of toxic metals into other tissues or organs. Chelation inhibits the interaction between As and biological targets, such as proteins, and promotes its excretion from the body. Chelating ligands exhibit many sites at which they can establish coordination bonds with As. Chelation treatment, including As, is still a commonly utilized detoxifying procedure in poisoning cases. However, this strategy has been associated with several unfavorable outcomes such as liver damage, neurotoxic effects, and additional negative consequences[47,48]. Side effects include fever, nausea, headache, vomiting, hypertension, gastrointestinal distress, myalgia, injection site pain, and burning sensation. According to Kosnett (2013)[49], the most popular As chelators are D-penicillamine, Dimercaprol, Unithiol (DMPS), and dimercaptosuccinic acid (DMSA). If administered immediately (within minutes or hours), the chelators DMPS, DMSA, BAL, and D-penicillamine are moderately efficient in treating acute As intoxication. Chelation during long-term Aspoisoning expedites the removal of poisons and reduces tissue deterioration. The efficacy of several treatments in reducing the morbidity and mortality rates associated with chronic As poisoning remains unclear. Most chelators are inappropriate for treating chronic As toxicity because of their numerous side effects and drawbacks. According to Susan *et al*. (2019)[48], novel methods are

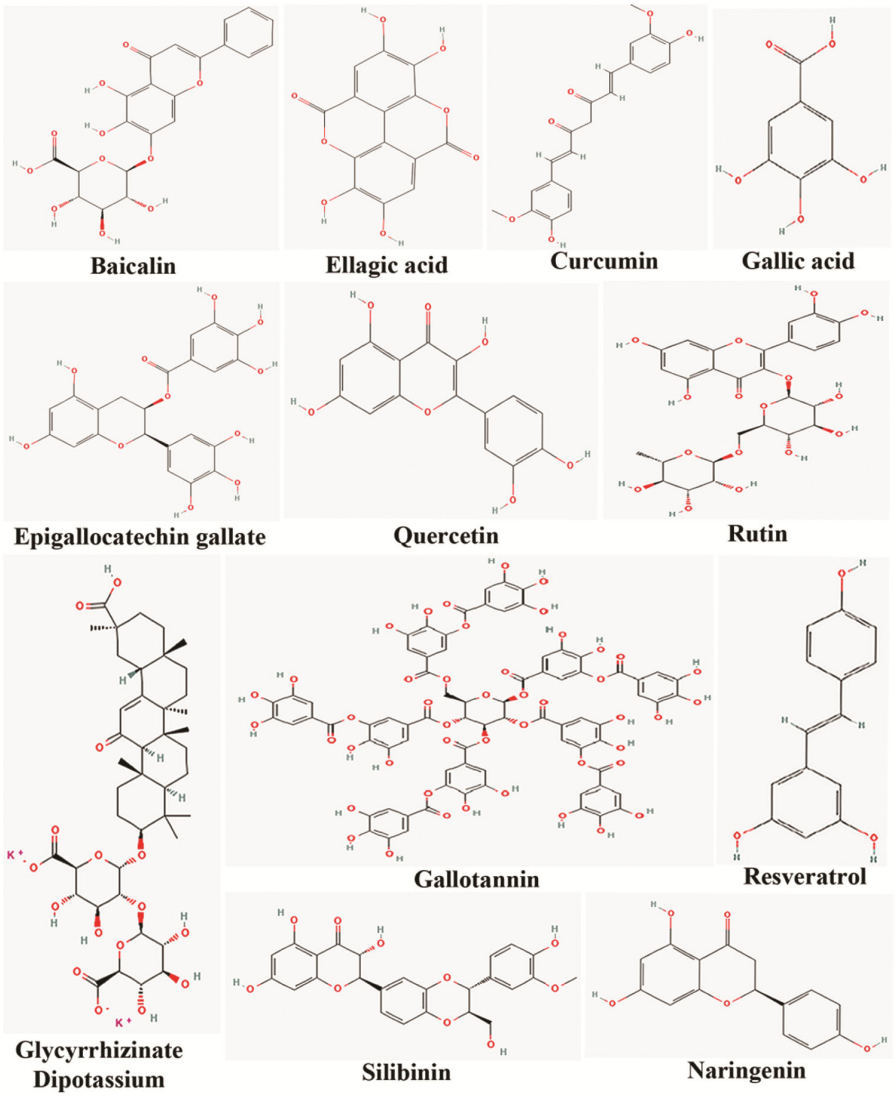

Fig. 6 — Promising phytochemical drug candidates for arsenic removal

required to remove metalloids from the body with the least number of negative effects. Current literature shows that most chelating agents have various side effects, making them ineffective for treating As-induced toxicity. The synthetic chelating agents[48] (meso-2,3-dimercaptosuccinic acid (DMSA), Monocyclohexyl DMSA (MchDMSA), lipoic acid, Monoisoamyl DMSA (MiADMSA), monomethyl DMSA (MmDMSA), and Zinc and N-acetyl cysteine (NAC)), their doses, and side effects are listed in (Fig. 7), indicating the need for new antidotes of plant origin that can detoxify heavy metals without side effects[48, 52-60].

Phyto-chemicals role in As toxicity

Flavonoids in green tea leaves have antioxidant and anti-inflammatory properties, as well as scavenging reactive oxygen species and chelating metal/metalloid ions. Phase II detoxifying enzymes, such as glutathione-S-transferase and CYP-mediated detoxification detoxify toxicants[48,50]. Taurine, quercetin[59], silymarin, rutin, and ECGC[56] protect against As-induced damage through their antioxidant and chelating abilities (Figs 6, 8, and 9). Naringenin[56], found in citrus and grapefruits, has been found to mitigate arsenic-induced hepatic and renal pathological changes in the rat liver and renal tissues. Silibinin (flavolignan) from *Silybum marianum* inhibits caspase-3-mediated tubular cell apoptosis and downregulates NADPH oxidase, iNOS, and NF-κB expression in renal tissues, thereby preserving the structure of the renal tissues in rats exposed to As. The major flavonoid in green tea, epigallocatechin-3-gallate (EGCG)[56], was found to reduce immunosuppression,

inflammation, and As-induced testicular toxicity in male Swiss mice. Naringenin[56], found in citrus and grape fruits, has been found to reduce As-induced hepatic and renal pathological changes in the rat liver and renal tissues. It also restored biomarkers of oxidative damage in the liver. EGCG reduced As-induced cardiotoxicity, testicular toxicity, immunosuppression, inflammation, and oxidative stress in rats by activating Nrf-2

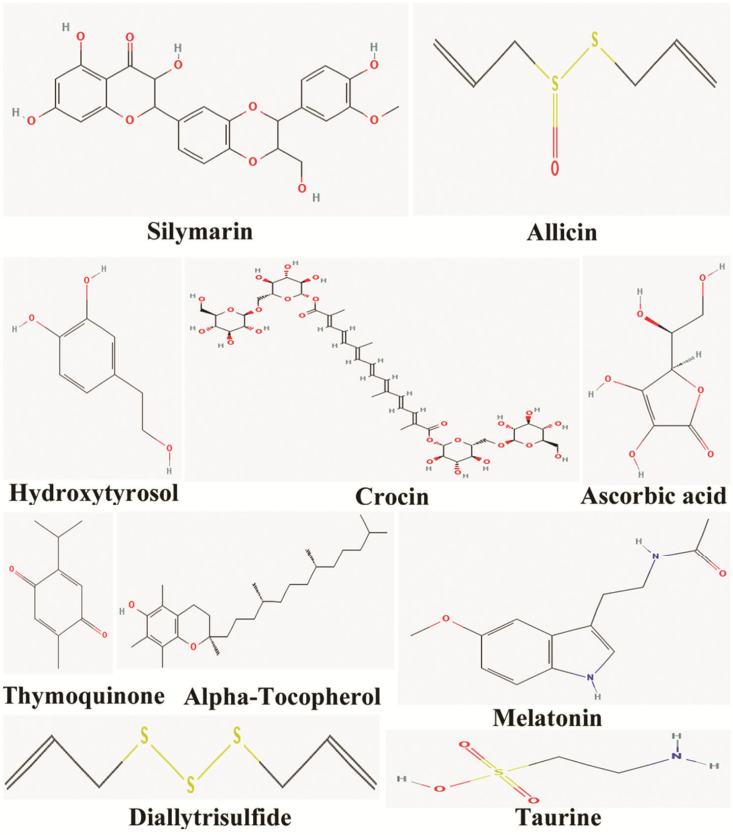

Fig. 7 — Plant-based, hormone, and amino acid alternatives as potential chelating agents for the removal of arsenic

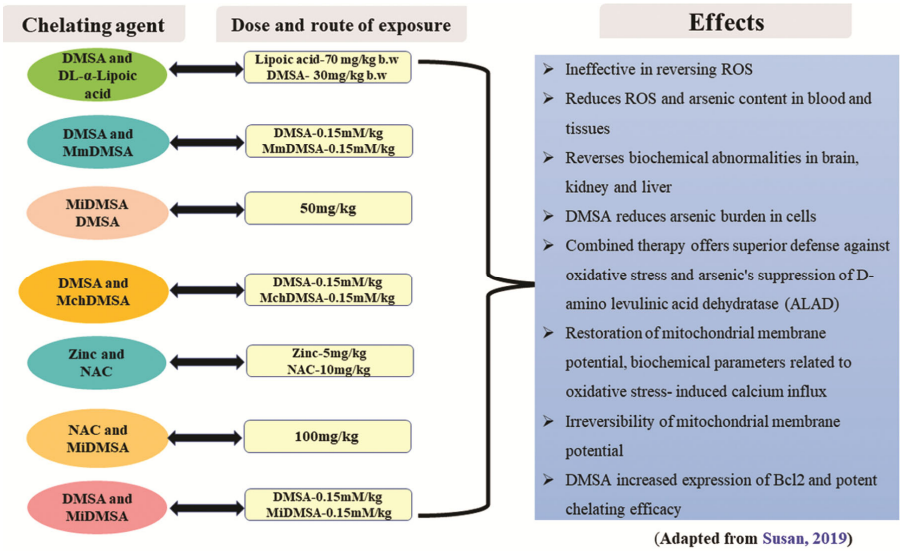

Fig. 8 — Therapeutic intervention against arsenic toxicity using synthetic chelatorsmeso-2,3-dimercaptosuccinic acid (DMSA); Monocyclohexyl DMSA (MchDMSA); Monoisoamyl DMSA (MiADMSA); monomethyl DMSA (MmDMSA); D-aminolevulinic acid dehydratase (ALAD); B-cell lymphoma 2 (Bcl2); Superoxide dismutase (SOD); Glutathione(GSH); Reactive oxygen species(ROS) and N-acetyl cysteine (NAC)

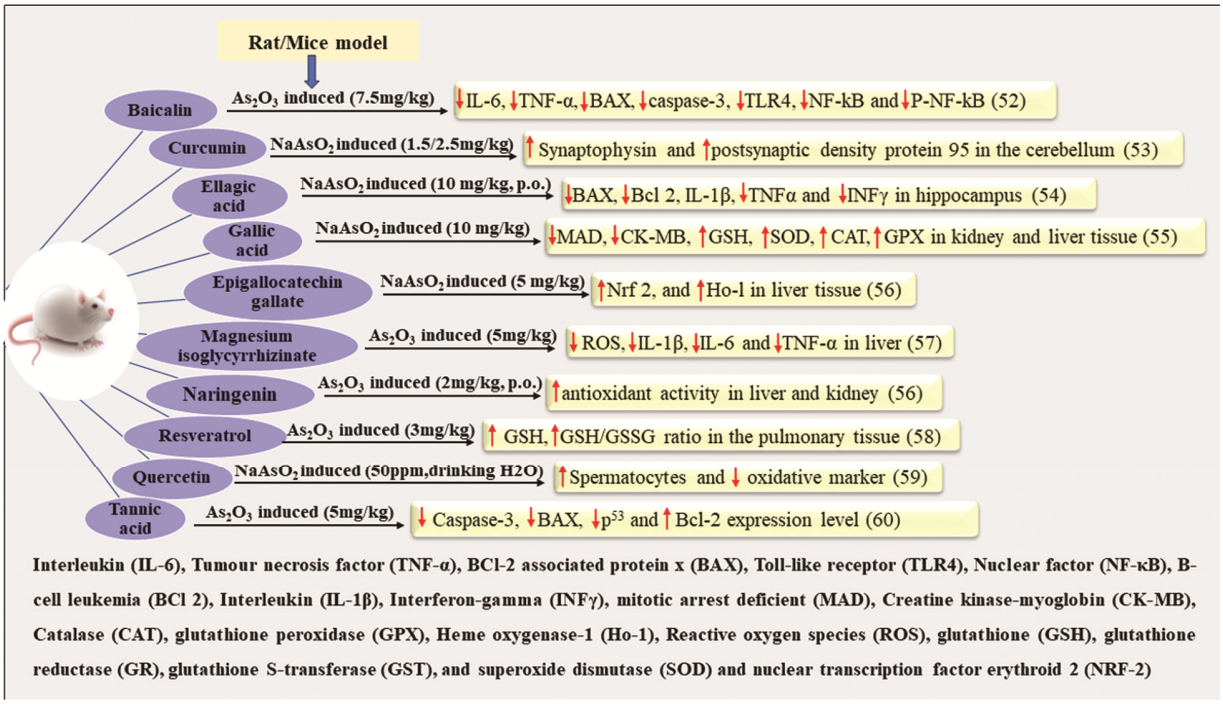

Fig. 9 — Plant based chelating agents utilized for the treatment of arsenic-mediated toxicity in rat and mice model

signaling and reducing oxidative stress (Figs 6 & 8). Resveratrol[58] can ameliorate cytotoxic chemotherapy-induced toxicity and oxidative stress by increasing GSH, CAT, and SOD levels. Cruciferous vegetables rich in sulforaphane and isothiocyanate have been found to reduce pulmonary toxicity by activating the Nrf-2 pathway[48,50,61]. Allicin and diallyl trisulfide from *Allium sativum* have been found to reverse dyslipidemia, proinflammatory changes, and hepatotoxicity in rats exposed to As. Silymarin, a polyphenolic flavonoid found in *Silybum marianum*, has been found to reverse As-induced conjugated diene formation, lipid peroxidation, decrease γ-glutamyl transpeptidase, and increase heat shock protein activities. Melatonin, which is found in vegetables, grains, and fruits, helpsto reduce oxidative stress in the brains of As-exposed animals by scavenging free radicals and enhancing glutathione peroxidase enzyme synthesis (Fig. 9). A study conducted in rats demonstrated that hydroxytyrosol effectively reverses As-mediated neurotoxicity by acting as an antioxidant[48,50]. Ascorbic acid and vitamin E were found to be effective in counteracting As-induced histopathological changes in rodents[50], with the therapeutic effect of vitamin E owingto its antioxidant properties, as α-tocopherol reduces membrane fluidity and lipid peroxidation (Fig. 7). Silymarin and naringenin, when administered at adose of 50 mg/kg, significantly altered GST, SOD, catalase, and thiobarbituric acid reactive substance levels inthe serum (Figs 6, 8, and 9). Taurine, a sulfur-containing aminoalkanoic acid found in meat, fish, and the body, can mitigate As-mediated toxicity by scavenging free radicals and protecting membranes from reactive oxygen-mediated damage by intercalating within the membrane bilayer[48,50]. Crocin, a diester of gentiobiose, reduces As toxicity and mitochondrial oxidative stress and damages mitochondrial membranes by lowering ROS, lipid peroxidation, and cytochrome c release (Fig. 8). The molecular modulation of curcumin contributes to its anticancer, antimicrobial, antioxidant, lipid-lowering, hypoglycemic, anti-inflammatory, and anti-aging properties (Figs 6 & 8). According to Khan (2022)[50], curcumin, a chain-breaking antioxidant, provides hydrogen from the phenolic moiety and exerts anti-inflammatory effects through molecular targets such as NF-κB, p38, HIF-1α, PPAR-γ, and PI3K/Akt. Its antioxidant action is induced by theactivatingofNrf-2, which may suppress synaptophysin and increase host factors related to inflammation. However, the antioxidant properties of ellagic acid, baicalin, and oleuropein have been found to reduce oxidative stress-mediated damage after As administration in rodent models. Curcumin[53] improves As-induced

genotoxicity, nephrotoxicity, hepatotoxicity, angiogenesis, dermatological disorders, reproductive toxicity, neurotoxicity, and immunotoxicity. A synergistic combination of curcumin and a chelating agent has been found to be effective in treating As toxicity, as reported in various studies[48,50]. Quercetin[59], a flavone substitute, can induce NQO1 enzyme activity, leading to a 12-fold increase in its specific activity. Tannic acid[60]reduced caspase-3, BAX, p53,and NF-κB expression and increased BCl-2, Nrf-2, and Keap-1 levels (Fig. 6). The phytochemical constituents in the extract of *Trichosanthes dioica, Hippohae rhamnoides, Syzygium* seeds, *Triticum aestivum, Tephrosia purpurea, Phyllanthus emblica*, grape seed proanthocyanidin extracts, *Alchornea laxiflora*, *Ipomea, Phyllanthus freternus, Terminalia arjuna* (bark), *Hibiscus sabdariffa* (flowers), *Peris longifolia* (leaves), *Withania somnifera* (root), and *Bauhinia variegata* (leaves) were found to significantly alter the lipid peroxidation and further scavenge free radicals and lead to genotoxicity and exhibit hepatoprotective and nephroprotective effects (Table 1)[38-62]. These plant extracts exert their effectiveness against As toxicity by either decreasing intracellular ROS, restoring antioxidant enzymes, GSH, and catalase levels to normal levels, or by restoring haematological and immunological parameters (Table 1)[48].

Table 1 — Potential chelating properties of plant extracts in reducing the harmful effects of arsenic[48]

Sl. No	Chelating agent	Plant extract	Rat/Mice model	Dose/Route of exposure	Effects
1	*Bauhinia variegata*	Leaf/rhizome ethanolic extract	Swiss Albino mice	150 mg/kg for 15 days and 30 days	Upregulates liver function and antioxidant
2	*Alchornea laxiflora*		Wistar Albino rats	0.5, 1.0, 5, 10 mg/kg for 14 days	Reduces liver damage and its biochemical parameters
3	*Mentha piperita*		Swiss Albino mice	1 g/kg/day for 10 days prior to As treatment and 30 days after treatment	Remarkable alternation in antioxidant enzyme and liver biochemical parameters
4	*Phyllanthus emblica*		Male Swiss Albino mice	50 μg/g for 10 weeks	Decrease in apoptosis through inhibition of caspase-3, lipid peroxidation, organo-megaly and elevated mitochondrial membrane potential and antioxidant enzyme activity
5	*Curcuma aromatica*		Wistar strain albino rat	50 mg /kg	By altering the serum urea, creatinine, uric acid levels normal kidney function is restored
6	*Withania somnifera*		Charles Foster rats	200 mg/kg for 45 days	Detoxification of liver and kidney diseases
7	*Pteris longifolia*		Charles Foster rats	400 mg/kg for 45 days	Downregulation of liver and kidney toxicity
8	*Triticum aestivum*		Wistar Albino rats	200 and 400 mg/kg for 20 days	Decreases the level of ALT, AST, ALP and bilirubin
9	*Proanthocyanidin*	Grape seed extract	Kunming Mice	100- 400 mg/kg	Increase detoxification pathway like GST, HO-1, NQO1, Nrf2 and elevates reproductive toxicity
10	*Achyranthes aspera*	Aqueous whole plant extract	Swiss Male Albinomice	100 mg/kg to 200 mg/kg for 10 days	Inhibition of COX-2 restores the hematological and immunological parameters
11	*Ipomea aquatica*		Male Swiss Albinomice	100 mg/kg for 15 days	Reduction of intercellular ROS protein carbonylation and lipid peroxidation
12	*Allium sativum*	Garlic tuber extract	HepG2 cells	50 μM for 24 hrs asenic poisoning enhances lipid peroxidation	Downregulation of ROS generation, lipid peroxidation, cytotoxicity in HepG2 cells and antioxidant defense mechanism is restores
13	*Hippophae rhamnoides*	Ethanolic fruit extract	Swiss albino mice	500 mg/kg for 3 weeks	Toxicity of arsenic is reverted

(*Contd.*)

Table 1 — Potential chelating properties of plant extracts in reducing the harmful effects of arsenic[48] (*Contd.*)

Sl. No	Chelating agent	Plant extract	Rat/Mice model	Dose/Route of exposure	Effects
14	*Syzygium jambolanum*	Ethanolic seed extract	Swiss albino mice	20 mg/kg for 8 weeks in mice	Intracellular glucose level, GLUT4 and glucokinase is upregulated with decrease in ROS which mitigates arsenic induced hyperglycemia
15	*Nasturtium officinale*	Hydro alcoholic extract	Sprague Dawley rats	500 mg/kg for 28 days	Restore hematological parameters
16	*Tephrosia purpurea*		Wistar albino rats	500 mg/kg for 28 days	Reduction of haemorrhagic enteritis, Villi structure is protected and haemoglobin, leukocytes and erythrocytes levels are restored
17	*Moringa oleifera*	Seed powder	Male Swiss Albino mice	250 and 500 mg/kg	Antioxidant defense mechanism is restored
18	*Trichosanthes dioica*	Fruit extract	Wistar Rats	50,100 mg/kg for 20 days	Reduction of aminolaevulinic acid dehydratase (ALAD) activated and restore the level of antioxidant enzymes in liver and kidney tissues
19	*Hibiscus sabdariffa*	Crude ethanolic extract	Wistar Rats	0.25 – 0.1 mg/mL	Regulates lipid peroxidation (LPO) and effectively scavengers DPPH radicals
20	*Corchorus olitorius*	Crude aqueous extract of leaf	Wistar rats	50 mg/kg /day and 100 mg/kg /day	Prevents liver and kidney damage and its histological structure
21	*Terminalia arjuna*	Bark extract	Male Swiss Albino mice	20 mg/kg for 4 days	Inhibit testicular damages
22	*Emblica officinalis*	Ethyl acetate extract	BALB/c mice	500 mg/kg for 28 days	Degradation of oxidative stress

Conclusion

As poisoning is a severe issue that interferes with key cellular functions and causes several health complications. The principal treatment for As toxicity is chelation; however, this treatment has limitations. Therefore, it is essential to develop new countermeasures and treatment modalities that have fewer adverse effects. An alternative method for treating As poisoning involves the use of plant extracts and products, either as a preventive precaution or as an adjuvant or supplemental medication during chelation. Owing to oxidative stress, the anti-inflammatory and antioxidant properties of phytochemicals may reduce the toxicity caused by exposure to As. According to recent research, co-administration of phytochemicals during chelation therapy can lessen oxidative stress and other biochemical effects, in addition to lowering the body's As burden. However, low bioavailability, bio-distribution, and lack of human cohort data present challenges for the use of phytochemicals in the fight against As toxicity. New opportunities are emerging in the form of phytochemical combinations, increasing bioavailability and chelating compound efficacy against As toxicity. Clinical and preclinical research is needed to fully examine phytochemical interventions as potential preventive strategies against As-induced harm. Phytomedicine is a viable solution, for developing nations, offering ample opportunities to employ plant-based goods and therapeutics that canmitigate the harmful effects of As and protect against its toxicity.

Conflict of interest

All authors declare no conflict of interest.

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