



PINEAPPLE AND SELECTED MEDICINAL PLANTS AS POTENTIAL NATURAL INTERVENTIONS AGAINST ARSENIC TOXICITY: MECHANISMS AND BIOLOGICAL EFFECTS

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ABSTRACT

Arsenic toxicity is associated with oxidative stress, mitochondrial dysfunction, lipid peroxidation, DNA damage, inflammatory signalling as well as injury to hepatic, neural, renal and cardiovascular tissues. Medicinal plants are potentially able to abrogate arsenic toxicity based on their antioxidant, metal-chelating, anti-inflammatory, anti-apoptotic potentials, and organoprotective properties. These medicinal plants including *Ananas comosus*, *Allium sativum*, *Terminalia arjuna*, *Camellia sinensis* contain diverse phytochemicals that provide a plausible biochemical basis for their abrogative effects on arsenic toxicity. This review evaluates the mechanistic basis of arsenic-induced systemic toxicity and critically examines the potential of selected medicinal plants and phytochemicals against arsenic toxicity and predicts *Ananas comosus* as a potential dietary or nutraceutical adjunct against arsenic toxicity due to the presence of bromelain, phenolic compounds, flavonoids, carotenoids and vitamin C with reported antioxidant and anti-inflammatory activities. *Allium sativum* has presented anti-inflammatory and hepatoprotective properties following arsenic exposure. Anti-inflammatory, anti-apoptotic and cardio-protective effects are reported for *Camellia sinensis* following arsenic exposure. *Terminalia arjuna* abrogated arsenic-induced liver and testicular injury. Phytochemicals such as allicin, ellagic acid, melatonin, arjunolic acid, epigallocatechin-3-gallate, silibinin, quercetin, and silymarin have been reported to abrogate arsenic-induced systemic toxicity. Therefore, it is suggested that Pineapple (*Ananas comosus*) and its phytochemicals may abrogate arsenic toxicity by eliciting other effects distinct from reducing oxidative injury, supporting endogenous antioxidant systems and modulating inflammatory pathways following direct arsenic-pineapple experiments. Thus, pineapple is a promising candidate for further investigation as an adjunctive food-based intervention by conducting standardized dose-response studies, toxicological assessment, and pharmacokinetic characterization.

Keywords: *Ananas comosus*, Arsenic toxicity, Medicinal plants, Multi-organ toxicity, Organ protection, Phytochemicals

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INTRODUCTION

Contamination of environmental components by deleterious metalloids and heavy metals has emerged as an important public health challenge worldwide [1, 2]. This challenge has persisted owing to rapid localization of industries, industrialization, urbanization, mining processes, agricultural intensification, and inordinate disposal of industrial wastes [3, 4]. Metals and metalloids are persistent environmental contaminants that can accumulate in biological systems and exert toxic effects, depending on their chemical form and exposure level [1, 5]. Among these environmental toxicants, arsenic has emerged as one of the most important contaminants because of its widespread occurrence, persistence, bioaccumulation, and systemic toxicity [4, 6]. The inorganic forms, particularly arsenate [As(V)] and arsenite [As(III)], have

considerable toxicity and are carcinogenic to humans [7, 8]. Humans get exposed to arsenic by drinking contaminated water, by making contact with industrial emissions, food sources, pesticides, and inhalation of arsenic-containing dust particles [4, 9]. Arsenic exposure stimulates excessive generation of reactive nitrogen species (RNS) and reactive oxygen species (ROS), leading to formation of malondialdehyde (MDA) or 4-hydroxynonenal (4-HNE), DNA damage, oxidation of proteins, inflammation, apoptosis, and tissue degeneration [7, 10, 11]. Arsenic-induced oxidative stress also interferes with cellular signaling pathways, antioxidant enzyme systems, and energy metabolism [12, 13].

Liver, kidney, brain, cardiovascular system, and nervous system are among the major organs vulnerable to arsenic toxicity [14, 15, 16]. Chronic arsenic exposure has been linked with severe

pathological conditions including hepatotoxicity, nephrotoxicity, neurotoxicity, cardiovascular disorders, endocrine dysfunction, reproductive abnormalities, diabetes mellitus, skin lesions, and carcinogenesis [3, 14, 16]. Currently, chelation therapy remains the conventional therapeutic strategy for managing arsenic poisoning as chelators, including dimercaptosuccinic acid (DMSA), dimercaprol, penicillamine, and dimercaptopropane sulfonate (DMPS) have been used to facilitate arsenic elimination from the body [17, 18, 19]. However, these agents are associated with several limitations including poor intracellular penetration, redistribution of arsenic to sensitive tissues, depletion of essential minerals, nephrotoxicity, hepatotoxicity, neurotoxicity, gastrointestinal disturbances, and poor therapeutic efficacy during chronic exposure [20, 21, 22]. These limitations have necessitated the search for safer and more effective alternative interventions.

Natural products and medicinal plants have received increasing attention as promising therapeutic agents against heavy metal toxicity because of their anti-inflammatory, antioxidant, metal-chelating, and anti-apoptotic attributes [23, 24]. Among these medicinal plants, pineapple (*Ananas comosus*) has emerged as a potential nutraceutical candidate against arsenic-induced systemic toxicity. Pineapple is a tropical fruit rich in bromelain, phenolic compounds, flavonoids, carotenoids, vitamins, minerals, and dietary antioxidants [25]. Grape seed proanthocyanidin extract has also been reported to alleviate arsenic-induced oxidative reproductive toxicity in male mice [26]. Pineapple has been investigated for several biological activities, while nutritional and medicinal-plant interventions have also been explored as potential approaches to mitigating arsenic-associated toxicity [24, 25, 27]. However, the findings of Desai et al. [25] provide experimental support for the possibility that pineapple may influence arsenic burden and associated tissue injury.

It is worth mentioning that the antioxidant phytochemicals present in medicinal plants may attenuate oxidative stress induced by arsenic, thereby restoring endogenous defenses by antioxidants, preserving mitochondrial integrity, and suppressing inflammatory signaling pathways [12, 28, 29]. This review critically evaluates the mechanisms by which arsenic causes damage to biological systems and highlights the therapeutic potential of pineapple and other medicinal plants as natural interventions against arsenic-mediated organ and systemic damage. The review also discusses current chelation therapies, limitations of conventional treatment approaches, and future prospects of pineapple-derived nutraceuticals in the detoxification of arsenic.

Chemistry, sources and toxicokinetics of arsenic

Arsenic exists in several oxidation states, including As(V), As(III), As(0) and As(-III), although As(V) and As(III) are the predominant environmentally relevant inorganic forms [4, 6]. As(III) is generally regarded to be more toxic than As(V) because it is highly specific to sulfhydryl-containing proteins and enzymes [8]. Inorganic arsenic is generally considered more toxic and carcinogenic than many organic arsenic species [7]. During metabolism, inorganic arsenic undergoes methylation to generate dimethylarsinic acid (DMA) and monomethylarsonic acid (MMA). Arsenic methylation has historically been regarded as a detoxification mechanism; however, several methylated metabolites retain substantial toxicity and may contribute to cellular and DNA damage [6, 30].

Human exposure to arsenic occurs through natural sources including volcanic eruptions, geothermal activities, weathering of arsenic-containing rocks, and groundwater contamination [4]. Human get exposed to arsenic through anthropogenic sources including mining, smelting, pesticide application, industrial discharge, fossil fuel combustion, wood preservatives, herbicides, and electronic waste disposal [31]. In addition to polluted water as risk factor for exposure to arsenic, in many developing countries [9]; arsenic-contaminated crops, seafood, and vegetables also contribute significantly to dietary exposure [6].

Absorption of arsenic is linked with the gastrointestinal tract (GIT), respiratory tract, and skin [6]. Following absorption, arsenic binds to erythrocytes and gets distributed to vital body organs including the kidney, heart, brain, liver, and lungs [32]. The liver plays a major role in arsenic biotransformation through methylation reactions involving glutathione and methyltransferase enzymes [13]. The primary urinary metabolites of arsenic include MMA and DMA. However, accumulation of arsenic metabolites in tissues contributes significantly to systemic toxicity, oxidative damage, and organ dysfunction [30].

Mechanisms of arsenic-induced systemic toxicity

1. Arsenic-induced oxidative stress and reactive species generation

Oxidative stress is reported as the basic underlying mechanism for arsenic-induced toxicity [7, 10]. In the context of this review (as shown in Figure 1), arsenic exposure stimulates the generation of reactive oxygen and nitrogen species, including superoxide anion, hydrogen peroxide, hydroxyl radicals, peroxynitrite and nitric oxide [11]. To promote the generation of ROS, arsenic intoxication induces mitochondrial dysfunction, activates NADPH oxidase activity, depletes glutathione reserves, inhibits antioxidant enzymes, and disrupts the

electron transport chain (ETC) [12, 33]. Hence, excessive ROS generation by arsenic overwhelms endogenous antioxidants, thereby results in oxidation of lipids, DNA, proteins, and cellular membranes [5].

2. Mitochondrial dysfunction induced by arsenic exposure

Mitochondria are major targets of arsenic toxicity because arsenic can impair components of the ETC, including complexes I (NADH dehydrogenase) and II (succinate dehydrogenase), disrupt oxidative phosphorylation, reduce ATP synthesis, and induce mitochondrial swelling [34, 35]. Arsenic also interferes with pyruvate dehydrogenase activity and promotes cytochrome c release, thereby triggering apoptosis [36]. Depletion of mitochondrial reduced glutathione (GSH) level due to reduced activity of reductase enzyme and increased level of oxidized glutathione (GSSG) increases the susceptibility of cells, organs and systems to oxidative stress-mediated injury and cellular necrosis [37].

3. Lipid peroxidation and DNA damage following arsenic intoxication

Excessive ROS generated during arsenic exposure promotes lipid peroxidation, leading to membrane destabilization and cellular injury [33] as shown in Figure 2. Levels of MDA, 4-HNE, and thiobarbituric acid reactive substances (TBARS) are elevated during arsenic toxicity [10]. Arsenic also interferes with DNA repair, induces chromosomal abnormalities, and promotes carcinogenesis [38, 39, 40].

4. Arsenic-induced alteration of inflammatory signaling pathways

Arsenic activates inflammatory pathways, including activator protein-1 (AP-1), c-Jun-N- terminal kinase (JNK), nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B), p38 mitogen-activated protein kinase (p38 MAPK), and phosphatidylinositol 3-kinase (PI3K/Akt) signaling cascades [41]. Activation of these signaling pathways stimulates cytokine production, inflammatory responses, apoptosis, and tissue injury [3]. Figure 3 provides an overview of the process by which arsenic activation stimulates signaling cascades/pathways.

5. Arsenic-induced multi-organ toxicity

The liver, an important site of arsenic metabolism, is a major targeted of arsenic toxicity [5, 42, 43]. Chronic arsenic exposure causes hepatocellular degeneration, necrosis, fibrosis, cirrhosis, steatosis, and hepatocellular carcinoma [38]. As reported, elevated levels of MDA, 4-HNE, and depletion of reduced glutathione levels with

corresponding reductions in the activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) significantly contribute to hepatic oxidative injury [10, 33]. Arsenic and its metabolites can affect the central nervous system, including regions involved in dopaminergic signaling [14]. Neurotoxicity by arsenic causes oxidative stress, mitochondrial dysfunction, neuroinflammation, neuronal apoptosis, neurotransmitter imbalance [44, 45]. In addition, arsenic exposure has also been associated with altered acetylcholinesterase activity and other neurotoxic effects [14, 44, 46], while broader evidence links arsenic exposure with mechanisms relevant to neurodegenerative disorders, including oxidative stress, mitochondrial dysfunction and neuronal injury [14, 44].

The kidney, often involved in arsenic excretion, is also highly susceptible to arsenic toxicity [16]. Arsenic-induced nephrotoxicity is characterized by proteinuria, albuminuria, reduced glomerular filtration rate, tubular necrosis, oxidative stress, and inflammation [47]. β 2-microglobulin, kidney injury molecule-1 (KIM-1), creatinine, N-acetyl- β -D-glycosaminidase (NAG), and blood urea nitrogen are commonly elevated during renal injury caused by arsenic [48]. Arsenic exposure initiates oxidative stress and inflammatory signaling which promote endothelial dysfunction, hypertension, atherosclerosis, ischemic heart disease, and vascular inflammation [3]. In addition, lipid oxidation, vascular adhesion molecule expression, nitric oxide imbalance, and cardiovascular injury are also observed [49].

Chelation therapy for arsenic toxicity and its limitations

Chelation therapy against arsenic involves the administration of ligands capable of binding arsenic and facilitating its elimination from the body [19]. Common arsenic chelators include dimercaptosuccinic acid (DMSA), dimercaprol (BAL), penicillamine, and dimercaptopropene sulfonate (DMPS) [17, 18, 19]. Chelating agents function by forming stable complexes with arsenic, thereby enhancing urinary excretion and reducing systemic accumulation [21, 22]. Although chelation therapy can reduce arsenic burden, several limitations restrict its clinical effectiveness [50]. Chelation remains an important clinical approach for significant arsenic poisoning, although its efficacy, timing, tissue distribution and adverse-effect profile impose important limitations [18, 20]. Some chelators may also redistribute arsenic to sensitive tissues such as the brain and kidneys, thereby exacerbating organ injury [17, 50].

Furthermore, common adverse effects associated with chelation therapy include nephrotoxicity, hepatotoxicity, gastrointestinal disturbances, mineral depletion, anaemia, hypertension,

neurological dysfunction, and allergic reactions [21, 22, 51]. Moreover, chronic chelation may interfere with essential trace metal homeostasis, thereby impairing normal physiological functions [19]. These limitations have encouraged the search for safer adjunctive therapies with antioxidant and cytoprotective properties, particularly plant-derived phytochemicals capable of attenuating oxidative stress and inflammation associated with arsenic toxicity [12, 24, 27].

Potential mechanisms and therapeutic prospects of pineapple and other medicinal plants

Medicinal plants possess potential to abrogate heavy metal toxicity based on their antioxidant, metal-chelating, anti-inflammatory, and anti-apoptotic potentials [23, 24]. Medicinal plants contain vitamins, dietary fibre, carbohydrates, minerals and diverse antioxidant phytochemicals, including phenolic compounds, flavonoids, carotenoids and bromelain. These constituents provide a plausible biochemical basis for the antioxidant, anti-inflammatory and cytoprotective activities attributed to pineapple and its various parts. In the context of arsenic toxicity, such properties are particularly relevant because arsenic-induced cellular injury is strongly associated with excessive generation of reactive oxygen and nitrogen species, depletion of endogenous antioxidant defenses, lipid peroxidation, mitochondrial dysfunction, inflammatory signaling, DNA damage and apoptosis [11, 23, 24, 25]. Importantly, however, the extent to which these activities translate into protection against arsenic toxicity remains dependent on the plant part, preparation, dose, exposure model and experimental system.

Arsenic exposure is known to increase reactive oxygen species and reactive nitrogen species while disrupting glutathione-dependent and enzymatic antioxidant systems, thereby promoting lipid, protein and DNA oxidation [7, 10, 11, 12]. Evidence from arsenic-exposed experimental systems demonstrates the importance of maintaining glutathione and antioxidant enzymes during arsenic intoxication [12, 33, 37], while studies of other medicinal plants demonstrate that phytochemical-rich preparations can reverse or attenuate arsenic-associated oxidative disturbances [52, 53]. These observations provide mechanistic support for investigating pineapple as an antioxidant-rich dietary intervention, although direct confirmation of each antioxidant effect specifically in arsenic-exposed animals remains limited.

i. Direct evidence for *Ananas comosus* in arsenic toxicity

Ananas comosus (pineapple), a member of the family Bromeliaceae, is widely cultivated in tropical and

subtropical regions and is consumed extensively because of its nutritional composition and potential health-promoting properties. The antioxidant capacity of pineapple represents one of its most biologically plausible mechanisms against arsenic-associated oxidative injury. Phenolic compounds, flavonoids, vitamin C and other antioxidant constituents can potentially participate in free-radical scavenging and maintenance of cellular redox balance [23, 25]. A particularly relevant direct observation is provided by Desai et al. [25], who investigated the heavy-metal-chelating potential of *Ananas comosus* fruit in arsenic-intoxicated rats. Their findings provide important experimental support for the possibility that pineapple may influence arsenic burden and associated tissue injury. Nevertheless, the chelating potential of pineapple should not be equated with the established pharmacological activity of conventional arsenic chelators. Polyphenols and related plant constituents may interact with metals through hydroxyl, carbonyl and other functional groups, but the strength, specificity, bioavailability and physiological relevance of such interactions require further investigation [17, 18, 21, 23, 24]. Therefore, pineapple may be more appropriately regarded at present as a potential adjunctive food-derived intervention rather than a substitute for clinically established chelation therapy.

ii. Anti-inflammatory effects

Arsenic-induced oxidative stress can activate inflammatory signaling and promote the release of mediators that contribute to tissue injury, endothelial dysfunction and cellular degeneration [3, 41]. Bromelain and other bioactive constituents of pineapple have been associated with anti-inflammatory effects, providing a rationale for investigating whether pineapple preparations can attenuate inflammation accompanying arsenic exposure [24, 25]. Evidence from other medicinal plants further supports the relevance of inflammation-modulating phytochemicals in arsenic toxicity [54, 55, 56]. Allicin from garlic has been reported to counter arsenic trioxide-induced hepatotoxicity, with involvement of the Nrf2-related antioxidant response [54], whereas Epigallocatechin-3-gallate (EGCG) from *Camellia sinensis* has demonstrated anti-inflammatory and anti-apoptotic effects in arsenic-exposed experimental models [55, 56].

iii. Antioxidant and redox-modulating effects

Arsenic can impair mitochondrial respiration, alter membrane integrity, promote mitochondrial reactive oxygen species formation and compromise cellular energy metabolism [11, 13, 34]. Consequently, preservation of mitochondrial function represents a potentially important target for plant-derived

interventions. Studies using isolated rat liver mitochondria have demonstrated direct arsenic-induced impairment of mitochondrial function [34], whereas ellagic acid has been shown to protect mitochondria against arsenic toxicity, particularly through preservation of complex II activity [35]. Thus, antioxidant-rich medicinal plants could potentially protect mitochondrial structures by limiting oxidative damage. However, the specific ability of whole pineapple preparations to preserve mitochondrial membrane potential, respiratory-chain activity or ATP production during arsenic exposure has not yet been sufficiently demonstrated. Accordingly, mitochondrial protection by pineapple should currently be regarded as a plausible mechanistic hypothesis requiring direct experimental confirmation rather than an established effect.

iv. Neuroprotective potential

Arsenic-induced neurotoxicity involves oxidative stress, disruption of neuronal signaling, altered calcium homeostasis, mitochondrial dysfunction and apoptosis, which can ultimately contribute to cognitive and neurological abnormalities [14, 44, 45]. Phytochemicals from medicinal plants have demonstrated protective effects against these processes. Melatonin, for example, attenuated arsenite-induced neuronal apoptosis through mechanisms involving mitochondrial and endoplasmic-reticulum pathways [57], while hydroxytyrosol, a phenolic compound associated with *Olea europaea*, protected against oxidative stress-mediated arsenic neurotoxicity [58]. Similarly, phytochemical-mediated attenuation of heavy-metal neurotoxicity has been proposed to involve restoration of redox balance and preservation of neuronal function [23]. Pineapple contains antioxidant constituents capable of contributing to such mechanisms; however, direct evidence that whole pineapple or a standardized pineapple preparation prevents arsenic-induced neurodegeneration, cholinergic dysfunction or tau-related pathology remains insufficient. Thus, neuroprotective effects of pineapple should be presented as a potential consequence of its antioxidant and anti-inflammatory phytochemical composition, rather than as a conclusively demonstrated arsenic-specific effect.

v. Hepatoprotective potential

Hepatic protection represents one of the more plausible applications of pineapple in arsenic toxicity because the liver is an important target of arsenic accumulation and metabolism. Chronic arsenic exposure can produce hepatic oxidative stress, mitochondrial dysfunction, altered antioxidant defenses, inflammatory responses and hepatocellular injury [38, 42]. The direct study by Desai et al. [25] provides important evidence linking

Ananas comosus administration with responses relevant to arsenic intoxication. Additional evidence from other medicinal plants strengthens the mechanistic argument. Arjunolic acid, associated with *Terminalia arjuna*, has demonstrated protection against arsenic-induced hepatic and testicular oxidative injury [52, 59], while silymarin and naringenin have been investigated for their ability to reduce arsenic-induced hepatic damage [60]. Allicin from *Allium sativum* has also demonstrated hepatoprotective activity against arsenic trioxide, with involvement of antioxidant signaling mechanisms [54]. Collectively, these findings indicate that plant-derived antioxidants may mitigate arsenic-induced hepatic injury through restoration of redox homeostasis, suppression of oxidative damage and modulation of cellular defense pathways. For pineapple specifically, further studies should establish whether these effects are attributable to bromelain, phenolic compounds, flavonoids, vitamin C, or interactions among multiple constituents.

vi. Nephroprotective and cardioprotective potential

Arsenic-associated nephrotoxicity involves oxidative stress, inflammation, disruption of renal antioxidant systems and tubular injury [16, 47, 48]. Similarly, arsenic-induced cardiovascular toxicity has been associated with oxidative stress, endothelial dysfunction, altered nitric oxide signaling and vascular inflammation [3, 46, 49]. Evidence from medicinal plants supports the possibility that antioxidant and anti-inflammatory constituents can attenuate these processes. Arjunolic acid has demonstrated protective activity against arsenic-induced nephrotoxicity in experimental animals [61], while EGCG from *Camellia sinensis* has demonstrated protective activity against arsenic-induced cardiotoxicity [55]. Quercetin and silymarin have likewise shown protective effects against arsenite-induced oxidative stress in cellular models [62]. Nevertheless, evidence specifically demonstrating pineapple-mediated nephroprotection or cardioprotection during arsenic exposure remains comparatively limited and should therefore be described as a promising area for further investigation.

vii. Modulation of apoptosis and cell survival

Persistent arsenic exposure can promote mitochondrial dysfunction, oxidative DNA damage and activation of cell-death pathways [34, 36, 40]. Experimental studies with other plant-derived compounds have demonstrated attenuation of arsenic-associated apoptosis. Melatonin reduced arsenite-induced neuronal apoptosis [57], silibinin attenuated arsenic-induced renal oxidative stress, inflammation and apoptosis [43, 61], while EGCG inhibited arsenic-induced inflammation and

apoptosis through suppression of oxidative stress [56]. These findings suggest that antioxidant and anti-inflammatory phytochemicals can influence cell-survival pathways indirectly by reducing the upstream oxidative and inflammatory signals that activate apoptosis. For pineapple, the presence of bromelain, phenolics, flavonoids and other antioxidant constituents provides a reasonable mechanistic basis for this hypothesis, but direct evidence for regulation of specific apoptotic proteins or caspases by pineapple in arsenic-exposed tissues is still needed.

viii. Glutathione homeostasis and arsenic detoxification

Arsenic can interact with sulfhydryl-containing proteins and disturb cellular thiol homeostasis, while chronic exposure may alter glutathione availability and redox balance [7, 13, 37]. Maintenance of reduced glutathione and antioxidant enzyme activity is therefore central to cellular resistance against arsenic-induced injury. Medicinal plants and their constituents may support this defense system through direct antioxidant activity, stimulation of endogenous antioxidant responses and reduction of oxidative consumption of glutathione. Pineapple may potentially operate through related mechanisms because of its antioxidant-rich phytochemical composition; however, the precise effects of individual pineapple constituents on arsenic biotransformation, glutathione conjugation, arsenic transport and urinary elimination remain to be established.

ix. Future research directions

Oxidative stress, mitochondrial dysfunction, inflammation, lipid peroxidation, DNA damage, and apoptosis are caused by arsenic-induced systemic toxicity. Conventional chelation therapy can reduce arsenic burden but its effectiveness is limited by poor tissue penetration, toxicity, redistribution of arsenic, and adverse effects. Medicinal plants contain several phytochemicals with notable potential to mitigate systemic toxicity induced by arsenic. Thus, further studies should isolate and characterize the biologically active phytochemicals in medicinal plants, carry out omics-based studies and gene expression profiling, to aid functional food and nutraceutical development. Standardized preparations of medicinal plants, characterization of active constituents, arsenic-exposure animal models, dose-response studies, pharmacokinetics/bioavailability, mechanistic studies, toxicity/safety, and controlled clinical studies are required before definitive therapeutic claims can be made.

CONCLUSION

Natural antioxidant interventions have been investigated as potential adjunctive approaches to complement conventional management of arsenic toxicity. Pineapple and selected medicinal plants show promising antioxidant, anti-inflammatory and organ protective potential relevant to arsenic-induced systemic toxicity. However, direct evidence for pineapple-specific protection against arsenic toxicity remains limited, and most mechanistic interpretations are supported by indirect evidence from pineapple studies in other experimental models or from studies of other medicinal plants and isolated phytochemicals. These phytochemicals may attenuate arsenic-induced oxidative stress and consequent organ damage through mechanisms including reactive-species scavenging, preservation of mitochondrial integrity, modulation of inflammatory responses and restoration of endogenous antioxidant defenses. Thus, parts and by-products of medicinal plants may serve as promising nutraceutical candidates for mitigating arsenic-induced systemic toxicity. However, further mechanistic studies, clinical trials, and standardization protocols are important to provide more details on its safety and therapeutic efficacy and safety in humans.

REFERENCES

1. TCHOUNWOU, P.B., YEDJOU, C.G., PATLOLLA, A.K. & SUTTON, D.J. (2012). Heavy metals toxicity and the environment. *Molecular, clinical and environmental toxicology*, **3**: 133-164.
2. JAN, A.T., AZAM, M., SIDDIQUI, K., ALI, A., CHOI, I. & HAQ, Q.M.R. (2015). Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants. *International Journal of Molecular Sciences*, **16**(12): 29592-29630.
3. ELLINSWORTH, D.C. (2015). Arsenic, reactive oxygen, and endothelial dysfunction. *Journal of Pharmacology and Experimental Therapeutics*, **353**(3): 458-464.
4. JANG, Y.C., SOMANNA, Y. & KIM, H. (2016). Source, distribution, toxicity and remediation of arsenic in the environment: a review. *International Journal of Applied Environmental Sciences*, **11**: 973-977.
5. SHARMA, B., SINGH, S. & SIDDIQUI, N.J. (2014). Biomedical implications of heavy metals induced imbalances in redox systems. *BioMed Research International*, **2014**: 640754.
6. HUGHES, M.F., BECK, B.D., CHEN, Y., LEWIS, A.S. & THOMAS, D.J. (2011). Arsenic exposure and toxicology: a historical

- perspective. *Toxicological Sciences*, **123**(2): 305-332.
7. JOMOVA, K., JENISOVA, Z., FESZTEROVA, M., BAROS, S., LISKA, J., HUDECOVA, D., RHODES, C.J. & VALKO, M. (2011). Arsenic: toxicity, oxidative stress and human disease. *Journal of Applied Toxicology*, **31**(2): 95-107.
8. SINGH, N., GUPTA, V.K., KUMAR, A. & SHARMA, B. (2017). Synergistic effects of heavy metals and pesticides in living systems. *Frontiers in Chemistry*, **5**: 70.
9. PURI, A. & KUMAR, M. (2012). A review of permissible limits of drinking water. *Indian Journal of Occupational and Environmental Medicine*, **16**(1): 40-44.
10. FLORA, S.J.S., MITTAL, M. & MEHTA, A. (2008). Heavy metal induced oxidative stress and its possible reversal by chelation therapy. *Indian Journal of Medical Research*, **128**(4): 501-523.
11. BIRBEN, E., SAHINER, U.M., SACKESSEN, C., ERZURUM, S. & KALAYCI, O. (2012). Oxidative stress and antioxidant defense. *World Allergy Organization Journal*, **5**(1): 9-19.
12. FLORA, S.J.S., BHADAURIA, S., KANNAN, G. M. & SINGH, N. (2007). Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review. *Journal of Environmental Biology*, **28**(2): 333-347.
13. RUBINO, F. (2015). Toxicity of glutathione-binding metals: a review of targets and mechanisms. *Toxics*, **3**(1): 20-62.
14. TYLER, C.R. & ALLAN, A.M. (2014). The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. *Current Environmental Health Reports*, **1**(2): 132-147.
15. HEDAYATI, A. (2016). Liver as a target organ for eco-toxicological studies. *Journal of Coastal Zone Management*, **9**(1): 6-7.
16. ROBLES-OSORIO, M.L., SABATH-SILVA, E. & SABATH, E. (2015). Arsenic-mediated nephrotoxicity. *Renal Failure*, **37**(4): 542-547.
17. FLORA, S.J.S. & PACHAURI, V. (2010). Chelation in metal intoxication. *International Journal of Environmental Research and Public Health*, **7**(7): 2745-2788.
18. KOSNETT, M.J. (2013). The role of chelation in the treatment of arsenic and mercury poisoning. *Journal of Medical Toxicology*, **9**(4): 347-354.
19. AASETH, J., SKAUG, M.A., CAO, Y. & ANDERSEN, O. (2015). Chelation in metal intoxication: principles and paradigms. *Journal of Trace Elements in Medicine and Biology*, **31**: 260-266.
20. HEGDE, M.L., BHARATHI, P., SURAM, A., VENUGOPAL, C., JAGANNATHAN, R., PODDAR, P., SRINIVAS, P., SAMBAMURTI, K., RAO, K.S., SCANCAR, J., MESSORI, L., ZECCA, L. & ZATTA, P. (2009). Challenges associated with metal chelation therapy in Alzheimer's disease. *Journal of Alzheimer's Disease*, **17**(3): 457-468.
21. SEARS, M.E. (2013). Chelation: harnessing and enhancing heavy metal detoxification: a review. *The Scientific World Journal*, **2013**: 219840.
22. SMITH, S.W. (2013). The role of chelation in the treatment of other metal poisonings. *Journal of Medical Toxicology*, **9**(4): 355-369.
23. GUPTA, V.K., SINGH, S., AGRAWAL, A., SIDDIQI, N.J. & SHARMA, B. (2015). Phytochemicals mediated remediation of neurotoxicity induced by heavy metals. *Biochemistry Research International*, **2015**: 534769.
24. BHATTACHARYA, S. (2017). Medicinal plants and natural products in amelioration of arsenic toxicity: a short review. *Pharmaceutical Biology*, **55**(1): 349-354.
25. DESAI, V.T., GANATRA, T.H., JOSHI, U.H., DESAI, T.R. & TIRGAR, P.R. (2012). An investigation into the heavy metal chelating potential of *Ananas comosus* fruit in arsenic intoxicated rats. *Journal of Pharmacy Research*, **5**(8): 4084-4087.
26. LI, S.G., DING, Y.S., NIU, Q., XU, S.Z., PANG, L.J., MA, R.L., JING, M.X., FENG, G.L., LIU, J.M. & GUO, S.X. (2015). Grape seed proanthocyanidin extract alleviates arsenic-induced oxidative reproductive toxicity in male mice. *Biomedical and Environmental Sciences*, **28**(4): 272-280.
27. SHARMA, A. & FLORA, S.J.S. (2018). Nutritional management can assist a significant role in alleviation of arsenicosis. *Journal of Trace Elements in Medicine and Biology*, **45**: 11-20.
28. GHOSH, S., DUNGDUNG, S.R., CHOWDHURY, S.T., MANDAL, A.K., SARKAR, S., GHOSH, D. & DAS, N. (2011). Encapsulation of the flavonoid quercetin with an arsenic chelator into nano capsules enables the simultaneous delivery of hydrophobic and hydrophilic drugs with a synergistic effect against chronic arsenic accumulation and oxidative stress. *Free Radical Biology and Medicine*, **51**(10): 1893-1902.

29. DAS, B. & CHAUDHURI, K. (2014). Amelioration of sodium arsenite induced toxicity by diallyl disulfide, a bioactive component of garlic: the involvement of antioxidants and the chelate effect. *RSC Advances*, **4**(39): 20964-20973.
30. ROSEN, B.P., AJEES, A.A. & MCDERMOTT, T.R. (2011). Life and death with arsenic. *Bio Essays*, **33**(5): 350-357.
31. PATEL, K.S., PANDEY, P.K., MARTÍN-RAMOS, P., CORNS, W.T., VAROL, S., BHATTACHARYA, P. & ZHU, Y. (2023). A review on arsenic in the environment: contamination, mobility, sources, and exposure. *RSC Advances*, **13**(13): 8803-8821
32. CARBREY, J.M., SONG, L., ZHOU, Y., YOSHINAGA, M., ROJEK, A., WANG, Y., LIU, Y., LUJAN, H.L., DICARLO, S.E., NIELSEN, S., ROSEN, B.P., AGRE, P. & MUKHOPADHYAY, R. (2009). Reduced arsenic clearance and increased toxicity in aquaglyceroporin-9-null mice. *Proceedings of the National Academy of Sciences*, **106**(37): 15956-15960.
33. WANG, L., XU, Z.R., JIA, X.Y., JIANG, J.F. & HAN, X.Y. (2006). Effects of arsenic (AsIII) on lipid peroxidation, glutathione content and antioxidant enzymes in growing pigs. *Asian-Australasian Journal of Animal Sciences*, **19**(5): 727-733.
34. HOSSEINI, M. J., SHAKI, F., GHAZI-KHANSARI, M., & POURAHMAD, J. (2013). Toxicity of arsenic (III) on isolated liver mitochondria: a new mechanistic approach. *Iranian Journal of Pharmaceutical Research*, **12**(1): 119-136.
35. KESHTZAR, E., KHODAYAR, M.J., JAVADIPOUR, M., GHAFFARI, M.A., BOLDUC, D.L. & REZAEI, M. (2016). Ellagic acid protects against arsenic toxicity in isolated rat mitochondria possibly through the maintaining of complex II. *Human & Experimental Toxicology*, **35**(10): 1060-1072.
36. CHENG, T.J., WANG, Y.J., KAO, W.W., CHEN, R.J. & HO, Y.S. (2007). Protection against arsenic trioxide-induced autophagic cell death in U118 human glioma cells by use of lipoic acid. *Food and Chemical Toxicology*, **45**(6): 1027-1038.
37. HALL, M.N., NIEDZWIECKI, M., LIU, X., HARPER, K.N., ALAM, S., SLAVKOVICH, V., ILIEVSKI, V., LEVY, D., SIDDIQUE, A.B., PARVEZ, F., MEY, J.L., VAN GEEN, A., GRAZIANO, J. & GAMBLE, M.V. (2013). Chronic arsenic exposure and blood glutathione and glutathione disulfide concentrations in Bangladeshi adults. *Environmental Health Perspectives*, **121**(9): 1068-1074.
38. CHEN, H., LI, S.F., LIU, J., DIWAN, B.A., BARRETT, J.C. & WAALKES, M.P. (2004). Chronic inorganic arsenic exposure induces hepatic global and individual gene hypomethylation: implications for arsenic hepatocarcinogenesis. *Carcinogenesis*, **25**(9): 1779-1786.
39. CHANDA, S., DASGUPTA, U.B., GUHAMAZUMDER, D., GUPTA, M., CHAUDHURI, U., LAHIRI, S., DAS, S., GHOSH, N. & CHATTERJEE, D. (2006). DNA hypermethylation of promoter of gene p53 and p16 in arsenic-exposed people with and without malignancy. *Toxicological Sciences*, **89**(2): 431-437.
40. MUENYI, C.S., LJUNGMAN, M. & STATES, J. C. (2015). Arsenic disruption of DNA damage responses: potential role in carcinogenesis and chemotherapy. *Biomolecules*, **5**(4): 2184-2193.
41. CHEN, Q.Y. & COSTA, M. (2018). PI3K/Akt/mTOR signaling pathway and the biphasic effect of arsenic in carcinogenesis. *Molecular Pharmacology*, **94**(1): 784-792.
42. MAJUMDAR, K.K. (2017). Chronic arsenic poisoning and hepatotoxicity. *Journal of Comprehensive Health Specialties*, **5**(1): 1-7.
43. MUTHUMANI, M. & PRABU, S.M. (2012). Silibinin potentially protects arsenic-induced oxidative hepatic dysfunction in rats. *Toxicology Mechanisms and Methods*, **22**(4): 277-288.
44. HWANG, O. (2013). Role of oxidative stress in Parkinson's disease. *Experimental Neurobiology*, **22**(1): 11-17.
45. PACHAURI, V., MEHTA, A., MISHRA, D. & FLORA, S.J.S. (2013). Arsenic induced neuronal apoptosis in guinea pigs is Ca²⁺ dependent and abrogated by chelation therapy: role of voltage gated calcium channels. *Neurotoxicology*, **35**: 137-145.
46. GUPTA, V.K., KUMAR, A., YADAV, S.H., PANDEY, R. & SHARMA, B. (2017). Acetylcholinesterase as a biomarker of arsenic induced cardiotoxicity in mammals. *Science International Lahore*, **5**(4): 142-149.
47. SHAHID, F., RIZWAN, S., KHAN, M.W., KHAN, S.A., NAQSHBANDI, A. & YUSUFI, A.N.K. (2014). Studies on the effect of sodium arsenate on the enzymes of carbohydrate metabolism, brush border membrane, and oxidative stress in the rat kidney. *Environmental Toxicology and Pharmacology*, **37**(2): 592-599.

48. CÁRDENAS-GONZÁLEZ, M., OSORIO-YÁÑEZ, C., GASPAR-RAMÍREZ, O., PAVKOVIĆ, M., OCHOA-MARTÍNEZ, A., LÓPEZ-VENTURA, D., MEDEIROS, M., BARBIER, O.C., PÉREZ-MALDONADO, I.N., SABBISSETTI, V.S., BONVENTRE, J.V. & VAIDYA, V.S. (2016). Environmental exposure to arsenic and chromium in children is associated with kidney injury molecule-1. *Environmental Research*, **150**: 653-662.
49. CHEN, Y., SANTELLA, R.M., KIBRIYA, M.G., WANG, Q., KAPPIL, M., VERRET, W.J., GRAZIANO, J.H. & AHSAN, H. (2007). Association between arsenic exposure from drinking water and plasma levels of soluble cell adhesion molecules. *Environmental Health Perspectives*, **115**(10): 1415-1420.
50. YADAV, A., MATHUR, R., SAMIM, M., LOMASH, V., KUSHWAHA, P., PATHAK, U., BABBAR, A.K., FLORA, S.J.S., MISHRA, A.K. & KAUSHIK, M.P. (2014). Nanoencapsulation of DMSA monoester for better therapeutic efficacy of the chelating agent against arsenic toxicity. *Nanomedicine*, **9**(4): 465-481.
51. FLORA, S.J.S. (2009). Metal poisoning: threat and management. *Al-Ameen Journal of Medical Sciences*, **2**(2): 4-26.
52. MANNA, P., SINHA, M., PAL, P. & SIL, P.C. (2007). Arjunolic acid, a triterpenoid saponin, ameliorates arsenic-induced cyto-toxicity in hepatocytes. *Chemico-Biological Interactions*, **170**(3): 187-200.
53. OGUN, M., OZCAN, A., KARAMAN, M., MERHAN, O., OZEN, H., KUKURT, A. & KARAPEHLIVAN, M. (2016). Oleuropein ameliorates arsenic induced oxidative stress in mice. *Journal of Trace Elements in Medicine and Biology*, **36**: 1-6.
54. YANG, D., LV, Z., ZHANG, H., LIU, B., JIANG, H., TAN, X., LU, J., BAIYUN, R., & ZHANG, Z. (2017). Activation of the Nrf2 signaling pathway involving KLF9 plays a critical role in allicin resisting against arsenic trioxide-induced hepatotoxicity in rats. *Biological Trace Element Research*, **176**(1): 192-200.
55. SUN, T.L., LIU, Z., QI, Z. J., HUANG, Y. P., GAO, X. Q., & ZHANG, Y. Y. (2016). (-)-Epigallocatechin-3-gallate (EGCG) attenuates arsenic-induced cardiotoxicity in rats. *Food and Chemical Toxicology*, **93**: 102-110.
56. YU, N. H., PEI, H., HUANG, Y. P. & LI, Y. F. (2017). (-)-Epigallocatechin-3-gallate inhibits arsenic-induced inflammation and apoptosis through suppression of oxidative stress in mice. *Cellular Physiology and Biochemistry*, **41**(5): 1788-1800.
57. LIN, A.M.Y., FANG, S.F., CHAO, P.L. & YANG, C.H. (2007). Melatonin attenuates arsenite-induced apoptosis in rat brain: involvement of mitochondrial and endoplasmic reticulum pathways and aggregation of α -synuclein. *Journal of Pineal Research*, **43**(2): 163-171.
58. SONI, M., PRAKASH, C., DABUR, R. & KUMAR, V. (2018). Protective effect of hydroxytyrosol against oxidative stress mediated by arsenic-induced neurotoxicity in rats. *Applied Biochemistry and Biotechnology*, **186**(1): 27-39.
59. MANNA, P., SINHA, M. & SIL, P.C. (2008). Protection of arsenic-induced testicular oxidative stress by arjunolic acid. *Free Redox Report*, **13**(2): 67-77.
60. JAIN, A., YADAV, A., BOZHKOVA, A. I., PADALKO, V.I. & FLORA, S.J.S. (2011). Therapeutic efficacy of silymarin and naringenin in reducing arsenic-induced hepatic damage in young rats. *Ecotoxicology and Environmental Safety*, **74**(4): 607-614.
61. SINHA, M., MANNA, P. & SIL, P.C. (2008). Arjunolic acid attenuates arsenic-induced nephrotoxicity. *Pathophysiology*, **15**(3): 147-156.
62. BONGIOVANNI, G.A., SORIA, E.A. & EYNARD, A.R. (2007). Effects of the plant flavonoids silymarin and quercetin on arsenite-induced oxidative stress in CHO-K1 cells. *Food and Chemical Toxicology*, **45**(6): 971-976.

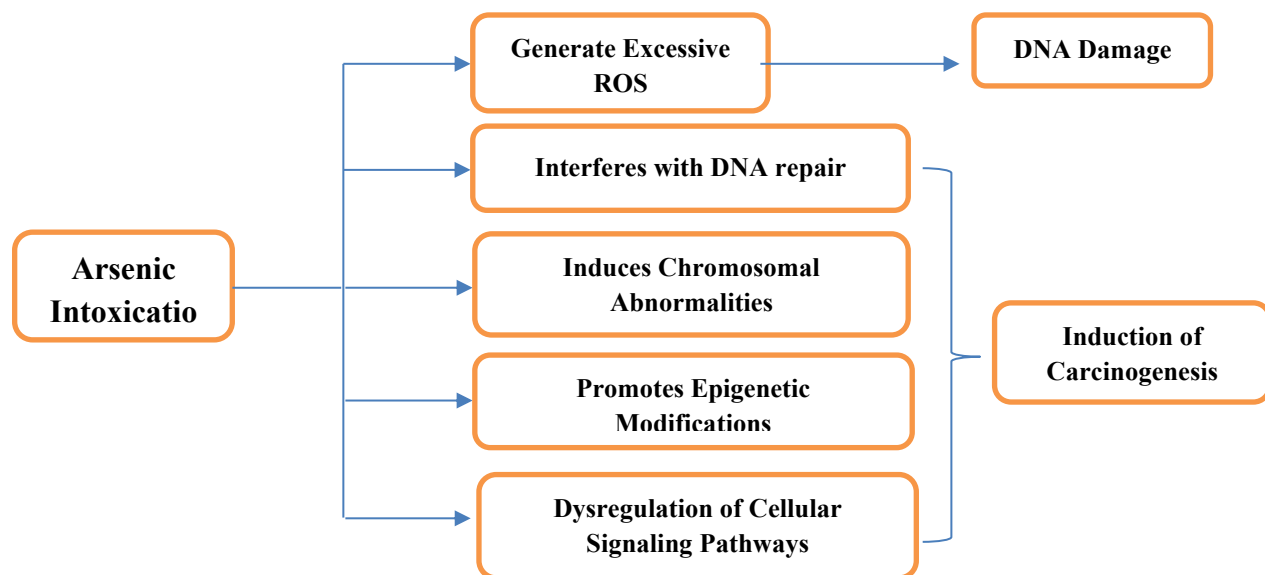


Figure 1: Effects of arsenic exposure on oxidative stress and mitochondrial dysfunction

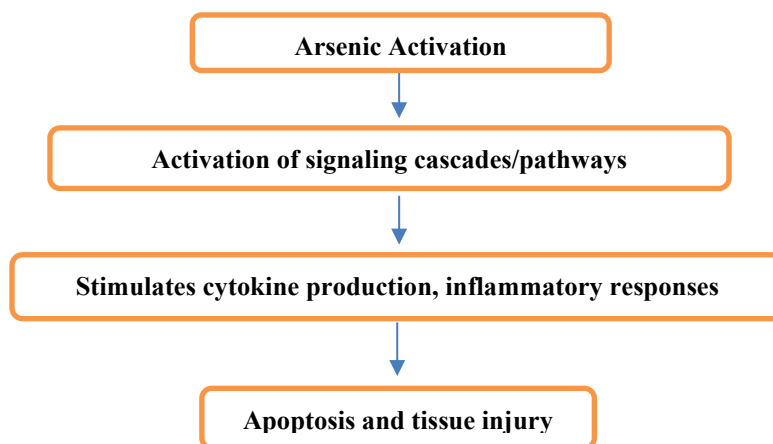


Figure 2: Effects of arsenic exposure on cellular integrity, DNA damage and carcinogenesis

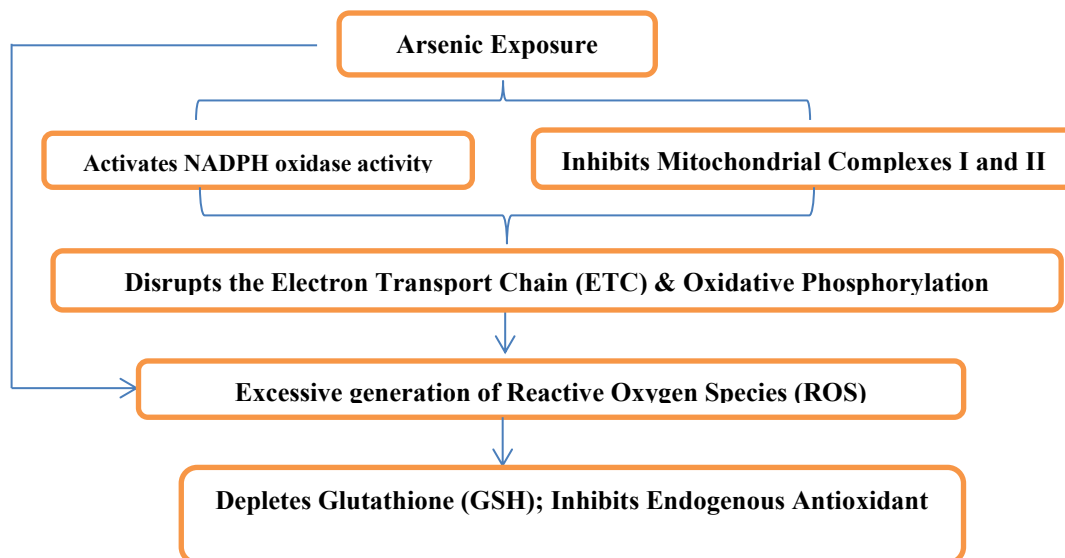


Figure 3: Arsenic-induced activation of intracellular signaling pathways is associated with inflammation and cell death