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Plant-derived natural compounds in the treatment of arsenic-induced toxicity

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ABSTRACT

Arsenic toxicity, imposed mainly by arsenic-contaminated groundwater, is considered a critical threat to global communal health, as there is no specific and proven conventional therapy for chronic arsenic toxicity, *i.e.*, arsenicosis, which is an insidious global public health menace affecting 50 countries. Alternative options should, therefore, be explored for the mitigation of arsenicosis. Literature survey reveals several natural compounds from plants possess significant protective efficacy against arsenic toxicity in chiefly preclinical and few clinical investigations. The studies on the ameliorative effects of plant-derived natural compounds against arsenic toxicity published in the last 25 years are collated. Forty-eight plant-based natural compounds possess alleviative effects on experimental arsenic-induced toxicity in animals, six of which have been reported to be clinically effective in humans. A potential nutraceutical or therapeutic candidate against arsenicosis for humans may thus be developed with the help of recent advancements in research in this area, along with the currently available treatments.

KEYWORDS: Arsenic toxicity; Arsenicosis; Natural compounds; Vitamins

1. Introduction

Arsenic is a metalloid element that is ubiquitously found on the earth. From the rocks and sediment, it is found on soil and groundwater as a result of their weathering and subsequent accumulation. Different anthropogenic events such as mining are also moving it to the soil and groundwater[1]. It is a systemic mammalian toxin and non-essential in terms of physiology. The main way that people are exposed to arsenic is through tainted drinking water; skin absorption and inhalation are the secondary routes[2]. Humans exposed to arsenic at work and who regularly drink water contaminated with arsenic over a long period experience irreversible carcinogenesis in the majority of body parts and organs, as well as morbid complications of the nervous system, hepatic, renal, respiratory, cardiovascular, gastrointestinal, reproductive (including teratogenesis), and neurological systems[3-5]. According to the United States Environmental Protection Agency, the World Health Organization (WHO), and the International Agency for Research on Cancer, arsenic is firmly established as a human carcinogen. The WHO recommends a 10 g/L limit or parts per billion (ppb) for arsenic in drinking water, above which it may hasten toxic effects of arsenic on the body. Chronic arsenic toxicity syndrome, or arsenicosis, is a serious public health threat that affects 50 countries, particularly India, Pakistan, Bangladesh, Iran, Myanmar, the Czech Republic, China, Taiwan, Thailand, Vietnam, Egypt, Argentina, and Chile; where arsenic contents in groundwater are several times higher than the previously recommended level[5].

The detrimental effects of arsenic on the body and common treatments thereof were well documented[4]. Chelation therapy, or the administration of metal complexing or chelating agents for arsenic toxicity, may be regarded as the recommended form of treatment for symptomatic and systemic relief as well as metabolic arsenic elimination from the body by forming a complex with arsenic, thereby reducing the risk of developing cancer and other future health risks. To treat acute and subchronic arsenic poisoning, chelating agents such as dimercaptosuccinic acid, *D*-penicillamine, and dimercaptopropane succinate are currently used. However, their

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clinical efficacy for the long-term management of chronic arsenic toxicity, or arsenicosis, has not yet been proven[4,6,7]. Complexing agents might not be appropriate for ongoing, high-dose arsenicosis therapy in humans. There is currently no long-term treatment regimen for patients with common arsenicosis that has been clinically proven effective. Therefore, it seems rather obvious that unconventional solutions are required to prevent arsenic toxicity.

Several harmful health issues have been linked to prolonged and continuous arsenic exposure. Therefore, unconventional strategies to prevent arsenic-induced chronic toxicity are required. Experimental toxicity caused by toxic elements, heavy metals, or metalloids is reduced by aromatic, medicinal, and herbal plants[8-11]. It is currently urgently necessary to explore safe and effective herbal-based treatments for arsenicosis. Due to their safety and efficacy profile, as well as their relative affordability, the use of medicinal plants and their constituents, appears to be a viable option. The higher plant-derived natural compounds (phytochemicals) may typically be consumed as a dietary ingredient or supplement, physiologically received by the body innately and producing less or no adverse effects, which may outweigh the adverse effects of the typical chelation remedy. A number of natural compounds isolated from the higher plants provided significant protection against experimentally induced arsenic toxicity, particularly in animals. The goal of this review is to compile relevant natural compounds that have shown promising ameliorative effects on arsenic toxicity in preclinical and clinical trials from the academic literature.

2. Methodology

2.1. Inclusion criteria

By using keywords and key phrases like 'arsenic toxicity amelioration/prevention/obviation/protection/alleviation/abrogation by plant-derived natural compounds (common or chemical names)' in various combinations, internet-based analysis of scientific literature was carried out by various online bibliographic databases, including Google, Scholar Google, PubMed, Toxnet, Wiley, and Science Direct. In this review, the experimental research articles published in English over the past 25 years that could be found online were evaluated. The preclinical and clinical research on natural phytocompounds that can prevent sub-acute and chronic arsenic toxicity was carefully chosen.

2.2. Exclusion criteria

English language articles were the only ones taken into consideration. Pre-prints that were hosted on specific web portals but were not peer-reviewed were not included. Natural compounds not obtained from plants or mixtures with other substances were kept out of the current endeavor. The current scope of compilation and review did not cover the environmental remediation effects of the natural compounds in removing arsenic and its compounds from the environment (water, soil, *etc*.).

3. Preclinical and clinical studies on natural compounds in the treatment of arsenic-induced toxicity

3.1. Preclinical studies

Forty-eight higher plant-derived natural compounds have been reported to possess alleviative effects against experimental arsenic-induced toxicity in animal systems, mostly in rodents. The details have been enumerated in Table 1. Among them, five are vitamins namely ascorbic acid (vitamin C), α-tocopherol (vitamin E), riboflavin (vitamin B_2), folic acid (vitamin B_9), and all-*trans* retinoic acid (vitamin A acid).

Apart from the cells/cell lines, the most common intact animal models were rodents like rats and mice. The commonly reported parameters include hematological (serum) and major organ (liver, brain, kidney, lung, gonads, *etc*.) biochemistry profiles *i.e.*, biomarkers principally indicating antioxidant status. Moreover, tissue histopathological examination of these vital organs was performed and arsenic contents of exposed tissues were estimated in a few studies. Arsenic trioxide (As_2O_3) and sodium arsenite ($NaAsO_2$) were generally utilized as toxicants whereas sodium arsenate (Na_3AsO_4) was the least used.

3.2. Clinical studies

There are twelve clinical studies involving six plant-obtained natural compounds, which were performed in Bangladesh and India (Table 2).

4. Discussion

Heavy metal toxicity poses a serious alarm to the environment and its inhabitants on a global scale. Indiscriminate industrialization and urbanization have degraded the environment's quality by introducing various pollutants that are upsetting stable ecosystems and having a pernicious and irreversible effect on both plants and animals, including people. Due to their environmental pervasiveness and biomagnification, toxic heavy metals are regarded as a serious silent threat to the population and livestock due to their long-term toxicity. Even after sincere endeavors, it still seems impossible to completely arrest the toxicity caused by heavy metals/metalloids[131-133]. Arsenic, a cardinal toxicant among all toxic heavy metals, led to various detrimental consequences on multiple organs as well as the overall health of cells affecting the overall life quality of underprivileged humans.

Table 1. Plant-derived natural compounds with arsenic toxicity reversal potential.

Name	Experimental model/cell line	Organ(s)/system involved	References
Rutin	Rat	Body (general), brain	[12]
β-Carotene	Mice	Liver, kidney	[13]
Leutin	Mice	Testes, liver	[14-16]
Diallyl trisulphide	Rat	Blood	[17]
Silibinin	Rat	Kidney, liver	[18-20]
Naringenin	Mice	Liver, kidney	[21]
	Rat	Liver, kidney, brain	[22,23]
Genistein	Rat	Heart	[24]
	Mice	Brain	[25]
Ascorbic acid	Rat	Liver, kidney, blood	[26,27]
	Mice	Testes	[28]
α-Tocopherol	Mice	Liver, kidney	[29,30]
	Goat	Blood	[31]
Ascorbic acid + α-tocopherol	Rats, mice	Testes, brain, kidney	[32-38]
Curcumin	Mice	Liver	[39,40]
	Rat	Liver, brain	[41-43]
	Human lymphocytes	-	[44]
	Rat PC12 cells	-	[45,46]
Quercetin	Rat	Liver, brain, testes	[47-49]
Resveratrol	Cat	Liver, brain, lung, kidney	[50-53]
	Rat	Lung, liver	[54,55]
	Mice	Heart	[56]
All-*trans* retinoic acid	Rat	Uterus	[57]
Arjunolic acid	Mice	Liver, heart, brain, kidney, testes	[58-62]
Biochanin A	Rats	Liver, kidney, heart	[63]
Epigallocatechin-3-gallate	Mice, rats, human H9C2 cells	Liver, heart, testes	[64-67]
Oleuropein	Mice	Blood, liver, kidney, brain	[68]
Ellagic acid	Rats	Liver, testes	[69,70]
Silymarin	Hamster CHO-K1 cells	-	[71]
Silymarin + naringenin	Rats	Liver	[72]
Lentinan	Mice	Liver	[73]
Betulinic acid	Rats	Kidney	[74]
Diallyl disulphide	Human hepatic carcinoma (HepG2) cells	-	[75]
D-pinitol	Rat PC12 cells	-	[46,76]
Allicin	Rats	Liver	[77]
Oxymatrine	Rats	Liver	[78]
Sulforaphane	Mice	Liver, lungs	[79,80]
	Rats	Liver	[81]
Hydroxytyrosol	Rats	Brain	[82]
Eriodictyol	Rats	Liver	[83]
D-pinitol + curcumin	Rat PC12 cells	-	[46]
Andrographolide	Mice	Liver	[84]
	Human cardiomyocyte (H9C2) cells	-	[85]
Myricetin	Rats	Heart	[86]
Thymoquinone	Rats	Kidney, brain, liver	[87-90]
Lycopene	Human neuroblastoma (SH-SY5Y) cells	-	[91]
	Mice	Kidney	[92]
Sinapic acid	Rats	Blood, liver	[93]
Caffeic acid	Mice	Blood, testes	[94]
Ferulic acid	Rats	Blood, heart	[95]
Ferulic acid + ellagic acid	Mice	Testes	[96]
Betaine	Rats	Blood, kidney	[97]
Gallic acid	Rats	Blood, kidney, liver	[98]
	Human hepatic carcinoma (HepG2) cells	-	[99]
β-Glucogallin	Murine macrophage (RAW264.7) cells	-	[100]
Tannic acid	Rats	Blood, kidney	[101]
Chrysin	Rats	Blood, liver, kidney	[102,103]
Crocetin	Rats	Blood, heart	[104]
Folic acid	Mice	SWV/Fnn embryo fibroblasts	[105]
	Zebra fish (*Danio rerio*)	Embryo	[106]
	Mice	Body (general), liver, brain	[107]
Eugenol	Rats	Blood, liver	[108]
	Human peripheral blood lymphocytes	-	[109]
Riboflavin	Mice	Testes	[110]
	Rats	Testes	[111]
Hesperidin	Rats	Brain, heart, liver, testes, kidney	[112,113]
α-Lipoic acid	Rats	Liver, blood, testes	[114-116]
α-Lipoic acid + ascorbic acid	Mice	Liver, brain	[117]
Hesperidin + α-lipoic acid	Mice	Liver, kidney, testes	[118]
Chlorogenic acid	Mice	Testes, kidney, brain, liver	[119-123]

Table 2. Plant-derived natural compounds with clinical arsenic toxicity reversal effects.

Name	Subject/Region	References
Vitamin A	Bangladeshi arsenicosis patients	[124,125]
Vitamin C		[124-126]
Vitamin E		[124-127]
Riboflavin, pyridoxine, folic acid and vitamins A, C and E		[128]
Folic acid	Bangladeshi arsenicosis patients	[129]
	Indian arsenicosis patients	[130]

Arsenic and arsenicals are well-known poison and their toxicity had also been chronicled. Recently, groundwater arsenic toxicity is regarded as a pandemic-like grave public health concern. It causes multi-organ dysfunctions based on age, organ, demographic and exposure-related factors[4,6]. The treatment of arsenicosis-induced disorders remains a great challenge because of the want for efficacious therapeutic recourses. Adverse effects overrule the pharmacological implications of chelation therapy. Aside from keeping away from arsenic-contaminated drinking groundwater and occupational arsenic exposure; chelation therapy with certain symptomatic supportive treatments has generally been practiced for the management of arsenic toxicity. To date, there is no evidence-supported specified therapeutic approach for the battle against long-term arsenic toxicity (arsenicosis) in distressed humans. Therapeutic recourses recommended are dietary, multi-vitamin, and beneficial mineral supplements and antioxidant treatment[1,5,7,131]. However, currently, there is considerable argument about advocation of any alternative medicine like dietary, medicinal, and aromatic plants, natural products, or antioxidants in the treatment of arsenicosis[1,2].

Historically, herbs and herbal products had a wholesome influence on prevention and cure of different disorders with little or no untoward effects. There is sufficient evidence on the effectiveness of higher plant-derived constituents against arsenic toxicity.

The present literature unveiled that the 48 natural phytocompounds (Table 1, Supplementary Figure 1) with effective antioxidant properties showed ameliorative effects against arsenic toxicity by multimodal fortification of prevalent endogenous antioxidative defense mechanisms which led to mitigation of arsenic-imposed cellular and genetic toxicity. In addition to multimodal attenuation of oxidative stress, these compounds modulate molecular pathways (Nrf2, NF-κB, *etc*.) related to membrane and organelle functions, DNA functions, energy metabolism, inflammation, autophagy, and apoptosis. Co-administration of ascorbic acid and α-tocopherol had a notable ameliorative effect in a number of preclinical studies by modulating oxidative stress and apoptosis, suggesting its potential in clinical regimens. Ascorbic acid, α-tocopherol, and quercetin were also employed as standard/reference antitoxic compounds in similar studies when conducted with medicinal plant extracts[8].

The 48 natural products (phytochemicals or phytocompounds) tested have globally been established and consumed as medicinal foods or nutraceuticals and these have been reported as naturally occurring antioxidants as well. This implies the favorable effect of antioxidant treatment and firmly substantiates the advocacy of antioxidant supplementation for human victims. Furthermore, some are nutritionally essential *i.e.*, vitamins. Nonetheless, the observed preclinical benefits of such natural compounds require thorough clinical corroboration in arsenicosis patients.

Towards the journey of drug development exercise, application of novel drug delivery systems like nanotechnology; and preparation of semi-synthetic active analogs of lead compounds can improve their pharmacokinetic attributes as well as pharmacodynamic potential *e.g.*, specificity towards target arsenicals and therefore gross potentiality in the body as therapeutic candidates. The present data reveal that development of novel formulation or drug delivery systems like liposome and nanoencapsulation in the case of quercetin, nanoencapsulation for curcumin and andrographolide improved the ameliorative efficacy against arsenic toxicity compared with their regular administration to the animals.

Although most of these studies are preclinical, there are few yet noteworthy clinical studies on six preclinically proven natural compounds, conducted in Bangladesh and India - the most arsenic-affected region of the world. Improvement of symptoms of arsenicosis patients in Bangladesh has been reported to occur following the use of vitamins A, C, and E in two studies[124,125]. Vitamin E slightly improved arsenic-induced skin lesions in another study[127]. A combination of vitamins B group with vitamins C and E reduced the risk of arsenic-induced skin lesions in Bangladesh[128]. Studies conducted in Bangladesh and India reported folic acid (vitamin B_9) supplementation can reduce blood arsenic burden in humans with a symptomatic improvement of arsenicosis conditions[129,130]. Another recent study conducted in Bangladesh demonstrated vitamins C and E significantly improved arsenic-induced keratotic skin lesions in arsenicosis patients[126]. However, it is important to determine their effects on long-term arsenic toxicity. To the author's knowledge, other relevant clinical studies are presently underway in Bangladesh.

So far, the most investigated natural compounds in rodents and humans like vitamins and their combinations need further definitive exploitation at a clinical level. Other preclinically proven natural compounds should be forwarded to the clinical stage. These plant-derived natural compounds may facilitate the alleviation of arsenicosis-induced complications that result in disease reversal, or they may function as palliative or auxiliary therapeutic recourses in addition to the standard therapeutic approaches for arsenicosis.

Arsenic exists inorganically in the groundwater in its pentavalent and trivalent forms. Even though both forms of arsenic pose serious risks to human health, trivalent arsenic is regarded as being more toxic[3,8]. In the current studies under discussion, the active natural compounds ameliorated trivalent arsenical *i.e.*, arsenic trioxide or sodium arsenite-induced toxicity, implying their plausible prospect for groundwater arsenic toxicity management in humans.

5. Future perspective

Natural compounds from higher plants have the sustainable potential for the prevention and treatment of arsenic toxicity, as is clear from the explained preventive effects of the reported preclinical and clinical works. They primarily work by eliminating oxidative stress, controlling inflammation and modifying apoptosis pathways. Future clinical management of arsenicosis in humans may benefit from the development of therapeutic candidates that act through mechanisms other than chelation, such as modulation of oxidative/nitrosative stress, apoptosis, or detoxification. Further studies on the mechanism of the effects of natural compounds against arsenic toxicity and clinical trials are necessary for medical application of these compounds. The preclinically chosen active phytoconstituents should be forwarded to the clinical stage alone or together with currently available chelating agents. The preclinical and clinical research on vitamins is conducive to serving as relevant remedial evidence. The appropriate natural compounds in this case may promote synergism, aid in disease mitigation, and thus may act as adjuvant, complementary agents and help in reversing the complications of arsenicosis as the form of palliative or auxiliary regimen.

Natural product supplementation may thus be conceivably considered as the present-day sustainable alternative therapeutic option against arsenicosis toxicity along with currently available therapies like chelation, antioxidant, anti-inflammatory, and supportive benevolent treatments. The development of a potential nutraceutical or therapeutic candidate to treat chronic arsenic toxicity in humans may thus be made possible by thorough clinical as well as mechanistic probing in this area.

Conflict of interest statement

The author declares no conflict of interest.

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