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Review Article

Role of Curcumin in the Prevention of Arsenicosis

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Summary

Though chronic arsenic toxicity is associated with various clinical symptoms, its medical treatment is unsatisfactory. Despite the magnitude of its potentially fatal toxicity, there is no effective therapy for this disease. Patients once affected may not recover, even after remediation of the arsenic-contaminated water. The need for an effective therapy for chronic arsenicosis is evident. Chelation therapy is thought to be the specific therapy for relief of systemic clinical manifestations and reduction of arsenic stores in the body, reducing subsequent cancer risk. Chelating agents like meso-2,3-dimercaptosuccinic acid (DMSA), sodium 2,3-dimercapto-1-propane sulfonic acid (DMPS) have been considered for treatment of chronic arsenic toxicity. However, their usefulness as a standard method of treatment is yet to be established. Anti oxidants and vitamins are also been tried by some researchers for the treatment of arsenicosis. Turmeric (Curcuma longa; an Indian spice) has been described in Ayurveda, as a treatment for inflammatory diseases. Oxidative stress to cellular DNA is considered as an important mechanism in arsenic induced toxicity including carcinogenesis. The exposure of arsenite(as trioxide) or arsenate has been shown to result in generation of reactive oxygen species (ROS) in laboratory animals and human cells A phytochemical curcumin, from turmeric appears to be a potent antioxidant and antimutagenic agent. DNA damage prevention with curcumin could be an effective strategy to combat arsenic toxicity.

Key words: :Arsenicosis, Curcumin, antioxidants, chelating agents.

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Introduction

Various disease manifestations are associated with chronic arsenic toxicity (arsenicosis). Over and above skin lesions like pigmentation, keratosis, and Bowen's disease, chronic arsenic toxicity produces protean systemic manifestations like weakness, chronic respiratory disease, peripheral neuropathy, liver fibrosis, peripheral vascular disease etc. Arsenicosis leads to irreversible damage in several vital organs and organ systems; it is also an established carcinogen. Important cancers associated with chronic arsenicosis are cancers of skin, lung, urinary bladder and liver.[1, 2] Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this disease; patients once affected may not recover, even after remediation of the arsenic-contaminated water. The need for an effective therapy for chronic arsenic toxicity is obvious. Chelation therapy for chronic arsenic toxicity is thought to be the specific therapy for relief of systemic clinical manifestations and reduction of arsenic stores in the body, reducing subsequent cancer risk. Chelating agents like meso-2,3-dimercaptosuccinic acid (DMSA), sodium 2,3-dimercapto-1-propane sulfonic acid (DMPS) have been considered as treatment for chronic arsenic toxicity.[3 4] However, their usefulness as a standard method of treatment is yet to be established. Anti oxidants and vitamins has also been tried by some workers for the treatment of arsenicosis[5, 6] but no authentic evidence on their efficacy in altering the natural history or symptom score of arsenicosis is available. Turmeric (Curcuma longa; an Indian spice) has been described in Ayurveda, as a treatment for inflammatory diseases and is referred by different names in different cultures. The active principle called curcumin, a polyphenol derived from the plant, or diferuloylmethane, a yellow pigment present in turmeric (curry powder) has been shown to exhibit numerous activities. Extensive research over the last half century has revealed several important functions of curcumin. It binds to a variety of proteins and inhibits the activity of various kinases. By modulating the activation of various transcription factors, curcumin regulates the expression of inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins. Curcumin also down regulates cyclin D1, cyclin E and MDM2; and up regulates p21, p27, and p53 genes. Mouse double minute 2 homolog (MDM2) is a protein that in humans is an important negative regulator of the p53 tumor suppressor gene. Cyclin D and cyclin E are members of the cyclin protein family that is involved in regulating cell cycle progression. Curcumin is a natural phenolic compound with impressive antioxidant properties. It is proved to exert its chemo preventive effects partly through the activation of nuclear factor (erythroid-2 related) factor 2 (Nrf2) and its antioxidant and phase II detoxifying enzymes. The potent Nrf2 activation capability might be valuable for

the protective effects of curcumin against arsenic intoxication especially arsenic induced hepatotoxicity and oxidative injuries. This provides a potential useful chemo preventive dietary component for human populations.[7]

Materials and Methods

An extensive systemic review of various studies was done to assess the role of Curcumin in the prevention of arsenicosis and role of Curcumin as an antioxidant and chelating agents from 2011 to 2016. This systematic review was conducted using electronic databases to report on long term effect of chronic arsenic toxicity after stoppage of drinking arsenic contaminated water on skin manifestations. To find relevant studies various databases was used including *PubMed*, and the *Cochrane Library*. All types of relevant studies were included like journal articles, reports and book chapters, because of limited information regarding the topic of interest. Moreover, the research question could be answered by any type of study. All titles and abstracts were screened first, followed by a full-text review of relevant review articles and their references, including meta-analyses, and published studies based on original data. Then all the suitable references were added to the list of articles.

Results and Discussion

Various preclinical cell culture and animal studies suggest curcumin as an antiproliferative, anti-invasive, and antiangiogenic agent. It is also shown to be a mediator of chemoresistance and radioresistance; a chemopreventive agent; and therapeutic agent in wound healing, diabetes, Alzheimer disease, Parkinson disease, cardiovascular disease, pulmonary disease, and arthritis.[8]Pilot phase I clinical trials have shown curcumin to be safe even when consumed at a daily dose of 12 g for 3 months.[8] Other clinical trials suggest a potential therapeutic role for curcumin in diseases such as familial adenomatous polyposis, inflammatory bowel disease, ulcerative colitis, colon cancer, pancreatic cancer, hypercholesteremia, atherosclerosis, pancreatitis, psoriasis, chronic anterior uveitis and arthritis.[8]Antioxidant effect of Curcumin has also been reported by others.[9-10] The tolerance of curcumin in high single oral dose appears to be excellent. Seven of twenty-four subjects (30%) experienced only minimal toxicity that did not appear to be dose-related. No curcumin was detected in the serum of subjects administered 500,1000, 2000, 4000, 6000 or 8000 mg. Low levels of curcumin were detected

in two subjects administered 10,000 or 12,000 mg. No side effects of Curcumin was observed with a dose of 8000 mg/day, with histological improvement in two cases of Bowens disease.[11-12]

There is enough evidence to suggest that curcumin could be of help in the treatment of several neurodegenerative diseases and other age-associated diseases to significantly improve health span. This could be due to its well-known anti-oxidant and anti-inflammatory properties, but could be also the result of a modulation of protein aggregation through the regulation of protein homeostasis or a dietary restriction-like mechanism. Studies demonstrated that a process, long associated with age-related neurodegenerative disease is also a general feature of aging, suggesting that the loss of protein homeostasis could be a common mechanism of aging and disease.[13]

In a study by Girish et al, the phytochemicals picroliv, curcumin, and ellagic acid showed hepatoprotective activities comparable to silymarin in CCl_4-induced hepatotoxicity in mice. The protective action was improved further by doubling the dose of the phytochemicals. Apart from the anti-lipid peroxidative and antioxidant actions, these active phytochemicals might have played a role in restoring the cytochrome P450 enzyme system or promoted the liver regenerative activity.[14]

Oxidative stress to DNA is considered as an important mechanism in arsenic induced toxicity including carcinogenesis. The exposure to arsenite (as trioxide) or arsenate has been shown to result in generation of reactive oxygen species (ROS) in laboratory animals and human cells.[15-16] A phytochemical, curcumin, from turmeric appears to be potent antioxidant and antimutagenic agent. DNA damage prevention with curcumin could be an effective strategy to combat arsenic toxicity.[17]

A field trial in Chakdah block of West Bengal evaluated the role of curcumin against the genotoxic effects of arsenic. In this study three months curcumin intervention reduced the DNA damage, retarded ROS generation and lipid peroxidation and raised the level of antioxidant activity. Thus curcumin may have some protective role against the DNA damage caused by arsenic.[17]

Limited information is available in the literature regarding the long-term effect of chronic arsenic toxicity after stoppage of consumption of arsenic-contaminated water. Changes of severity of skin lesions were reported amongst affected cohort of arsenicosis patients in Southern Thailand where interventions to reduce arsenic contaminated water had been implemented. Over 10 year period, both regression and progression of lesions occurred, though the majority of the subjects followed up remained the same.[18]Another cohort follow-up study was carried out on 1074 people (arsenic exposed people 623, control population 451) in 2000, five years after the original clinical examination done on the same population at South 24 Parganas, West Bengal. Out of 199 people with skin lesion among the arsenic exposed population who were consuming safe water during the previous 5 years, the skin lesions cleared or decreased in 49.7% of people. Out of 306 people who did not have such lesions previously, new skin lesions appeared in 32 (10.5%).[19] In a study conducted in Nadia, West Bengal the skin score was found to improve significantly at the end of each year after supply of arsenic free water, and it wasfound to be reduced significantly from 2.17 ± 1.09 to 1.23 ± 1.17; $P < 0.001$ at the end of 3 years intervention study indicating beneficial effect of safe water on skin lesions.[20] Similar findings were also found in several studies in Inner Mongolia China.[21]

Chelation therapy for chronic arsenic toxicity is thought to be the specific therapy for relief of clinical manifestations and reduction of arsenic stores in the body. Efficacy of a specific chelation therapy with DMSA (Dimercaptosuccinic Acid), a chelating agent related to BAL, for patients suffering from chronic arsenic toxicity has not yielded better efficacy than control subjects treated with placebo studied in a placebo controlled trial in West Bengal.[22] Efficacy of treatment of DMPS(Dimercapto propane sulphonate), another chelating agent, has also been studied by GuhaMazumder et al.[4] in a single-blind placebo-controlled trial in patients suffering from chronic arsenic toxicity in WestBengal, India. The results of this study indicate that DMPS is more effective than a placebo in improving clinical features of chronic arsenic toxicity including skin score of pigmentation. However, the drug was found to be costly, not available in many of the developing countries. Further, the drug requires regular hematological monitoring on different trace elements during its use and hence could not be used for large number of arsenic affected poor village population in most affected regions of the world. Ahmad et al. in 1998 evaluated the effectiveness of management of chronic arsenicosis in Bangladesh by administering antioxidants like vitamin A, E or C regimen.[23]

Thiaprasit[5] and Piamphongsant [6] reported case-series with improvement of cutaneous arsenicosis (Keratosis) who were treated with oral etretinate, a synthetic aromatic retinoid for prolonged period. However, because retinoids and high-dose retinol may have adverse effects, including teratogenesis and hepatic toxicity, such trials will require careful attention to patient selection and surveillance.

Prevention of arsenic-induced oxidative stress and induction of repair enzymes by curcumin, may be an effective strategy to combat the adverse effects of arsenic. A number of oxidative stress-related genes, such as heme oxgenase-1 and metallothionein, have often increased following acute high-dose arsenic exposure.[24,25]There is direct evidence for the involvement of curcumin in reducing As III induced oxidative stress in Swiss albino mice by virtue of its antioxidant potential and trapping of free radicals.[26]Natural phytochemicals like curcumin may have the efficacy in reducing arsenic induced genotoxicity, in scavenging ROS and in enhancing the process of DNA repair in V79 cells.[27]In a study conducted among chronically arsenic-exposed asymptomatic volunteers in West Bengal it was found that arsenic-inhibited DNA repair was induced by curcumin, both at protein and genetic levels. Thus, curcumin intervention may be a useful modality for the prevention of arsenic-induced carcinogenesis.[28, 29]

Environmental exposure to arsenic is unavoidable and medicinal use of arsenicals in the treatment of certain cancers is increasing.[30] Though chronic arsenic toxicity due to drinking of arsenic contaminated water has been reported from many countries, reports of large number of affected people in West Bengal, India and Bangladesh are unprecedented. The source of the contamination is geological; arsenic in ground water has been found above 50 μg/l (the current drinking water standard in the country) in eight of the 16 districts of West Bengal. More than 40 million people live in this arsenic affected region of the State. It is suspected that about 5 million people drink arsenic contaminated water in West Bengal.[31]Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this disease; patients once affected may not recover. Only cessation of exposure to drinking water or items of elevated concentration of arsenic was believed to provide effective remedy. Inorganic arsenic (As) is considered as a human carcinogen because it is associated with cancers of skin, lung, liver and

bladder in exposed population[20] and curcumin intervention may be a useful modality for the prevention of arsenic-induced carcinogenesis. Primary prevention by rising levels of awareness among primary care providers of the local region about signs and symptoms of arsenicosis and available intervention will definitely help to mitigate this important public health problem.[20]

Conclusion:

Curcumin intervention may be a useful modality for the prevention of arsenic-induced carcinogenesis. In future, the derivatives of these phytochemicals or their combinations may show efficacy in various experimental toxic models. They may be developed as future drugs for use in human diseases with antioxidant, antifibrotic, immunomodulatory, antiviral, and regenerative properties. Thus, curcumin, a spice once relegated to the kitchen shelf, has moved into the clinic and may prove to be "Curecumin".

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