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Electrolyte imbalance under stress of arsenic trioxide; its amelioration by *Curcuma aromatica* leaf extract in albino rat

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Abstract

The present study was undertaken to evaluate the therapeutic efficacy of *Curcuma aromatica* leaf extract in terms of normalization of altered electrolyte concentration following arsenic trioxide induced oxidative damage in rats. Arsenic is a metalloid widely distributed in the earth's crust. Arsenic causes kidney damage at different doses by acute, subacute and chronic toxicity. Systemic electrolyte and water balance are controlled via kidneys, thus the serum electrolytes level provide vital information about the functional state of kidney. Electrolytes are ionized molecules found throughout the blood and tissues of body. Many studies have shown that various types of herbal plants have a wide range of biochemical and pharmacological effects due to their constituents. In this study, a herbal plant *Curcuma aromatica* was used which acts as a natural antioxidant.

Arsenic trioxide generates hyponatremia, hypochloremia and hyperkalemia and reduction in body weight and kidney weight in albino rat. Which were brought to normalcy after treatment with *Curcuma aromatica* leaf extract containing curcumin after acute and sub acute treatment.

Experimental results therefore reveal protective effect of *Curcuma aromatica* leaf extract under stressed condition of arsenic trioxide in albino rat.

Keywords: Arsenic trioxide, electrolytes, body weight, kidney weight, renal functions, Curcuma extract and albino rat

1. Introduction

Arsenic contamination have been reported from many parts of the world such as Australia, New Zealand, Chile, Taiwan, Mongolia, U.S.A., India, China, Bangladesh & U.K.^{1,2,3}. However, with regard to severity of the problem, Bangladesh ranks the first, followed by India and China. Groundwater arsenic contamination has assumed an alarming proportion in large part of West Bengal, India and adjoining areas of Bangladesh, so much so that it has been earmarked as "the biggest arsenic calamity in the world."⁴

Among possible target organs of heavy metals, the kidney and CNS appear to be the most sensitive ones. Any alteration in kidney or the part of kidney due to induction of arsenic trioxide, may be responsible for improper renal functioning viz. excretion of nitrogenous waste products, acid base balance and balance of electrolytes and water.⁵ The impact of arsenic trioxide on nitrogenous wastes has already been exhibited.⁶ Besides, evaluation of serum electrolytes provide vital information about kidney functions, hence have been considered as possible biomarkers of renal dysfunctioning in the present investigation.

The history of the use of herbs dates back to the time of the early man. Among herbal plants used in treatment of ailments is *Curcuma aromatica* (Salisb.). *Curcuma aromatica* (Salisb.), a member of family Zingiberaceae is an erect, perennial herb, a well listed drug in Ayurveda and other indigenous systems of medicine. Leaves are large, green, oblong-lanceolate/ oblong-elliptic, with acuminate apex, 38-60 X 10-20 cm. in size, often variegated above, pubescent beneath, base deltoid with long petiole (Fig. 1). It possesses an array of interesting pharmacological effects such as antioxidant, antimicrobial, antiinflammatory, anticarcinogenic and antidiabetic activities etc.⁷ It has a characteristic yellow colour and contain curcumin which is a natural antioxidant.⁸ Hence present study has been designed to findout the protective effect of *Curcuma aromatica* leaf extract on renal functions altered by arsenic trioxide intoxication.



Fig 1

Materials and Methods

Albino rat (*Rattus norvegicus*) weighting 100 ± 10 gm of both sex were procured from inbred colony and acclimatized at room temperature with 12 hr dark/light cycle. The animals were fed on Goldmohar brand rat feed and water was provided ad libitum. The experimental compound arsenic trioxide was obtained from Merck, India. The LD₅₀ for arsenic trioxide was determined by log dose/probit regression line method⁹ and the estimated LD₅₀ was 14.98 mg/kg body wt.

Curcuma leaves were obtained from Dept. of Forestry, Dr. B.R. Ambedkar University, Agra and crude extract of Curcuma leaves was used. A safety trial was performed to

determine the dose (50 mg/100 gm body wt.) of leaf extract. Animals were divided into 4 groups of 5 rats each. Group I (control) received only 1 ml of distilled water, Group II received leaf extract (50mg/100gm body wt.), Group III received arsenic trioxide (0.15, 0.02, 0.01 and 0.007 mg/100gm body wt.) for 1, 7, 14 and 21 days respectively, as derived from estimated LD₅₀ and Group IV received leaf extract followed by arsenic trioxide. To determine the renal functions, the blood samples were collected from the ventricle of the heart and serum was separated for the determination of –

- Serum Na⁺ by colorimetric method.¹⁰
- Serum K⁺ by colorimetric method.¹⁰
- Serum Cl⁻ by Thiocyanate method¹¹
- Estimation of body weight and kidney weight

One-way analysis of variance (ANOVA) followed by student Newman – Keul's test (SNK) was done for statistical analysis.¹²

Results

Results showed that arsenic trioxide intoxication induced significant hyponatremia, hypochloremia and hyperkalemia and reduction in body weight and kidney weight after acute (1 day) and subacute treatment. (7, 14 and 21 days)

However the changed levels of serum electrolytes and reduced body weight and kidney weight after acute (1 day) and subacute treatment. (7, 14 and 21 days) were brought to normalcy following treatment with curcuma. (Table 1)

Table 1

Biochemical parameters	Treatment days	Control	Arsenic trioxide treated	Curcuma treated	Curcuma+Arsenic treated
Na ⁺ (mEq/l)	1 day	141 ± 1.15	137 ± 0.58*	140.33 ± 0.33	138 ± 0.57*
	7 days	142 ± 1.00	135.33 ± 0.88*	140.66 ± 0.88	138.66 ± 0.33
	14 days	142 ± 1.52	134 ± 1.15*	141 ± 1.15	139 ± 0.23
	21 days	141 ± 0.58	132 ± 0.58*	142 ± 1.15	140 ± 1.15
K ⁺ (mEq/l)	1 day	4.17 ± 0.03	4.54 ± 0.04*	4.20 ± 0.01	4.44 ± 0.01*
	7 days	4.19 ± 0.02	4.82 ± 0.01*	4.21 ± 0.01	4.38 ± 0.02*
	14 days	4.18 ± 0.02	5.18 ± 0.10*	4.16 ± 0.02	4.35 ± 0.02
	21 days	4.17 ± 0.01	5.84 ± 0.07*	4.21 ± 0.01	4.30 ± 0.03
Cl ⁻ (mEq/l)	1 day	103 ± 1.15	98 ± 0.57*	102.5 ± 1.04	99.66 ± 0.33*
	7 days	102 ± 1.15	97 ± 1.00*	101.16 ± 0.68	100 ± 0.91
	14 days	102 ± 1.15	94 ± 0.57*	101.5 ± 0.76	98 ± 1.00
	21 days	103 ± 1.00	93 ± 0.57*	101 ± 1.15	99 ± 1.00

values are expressed as mean ± SEM. * P < 0.05

Discussion

The toxic effects caused by arsenic trioxide exposure are in large parts due to its ability to bind to cellular proteins containing sulfhydryl groups.¹³ This inhibits the production of energy needed to maintain tissue functions. Arsenic also induces oxidative stress by producing reactive oxygen species (ROS) both by electron gaining and electron losing.^{14,15,16} which causes subsequent depletion of antioxidant cell defences. Due to lipophilic nature, arsenic also gets attached to lipid and in turn increasing lipid peroxidation.¹⁷ Decrease in body weight may be due to starvation, lipid peroxidation and increased protein catabolism. Besides, lipid peroxidation, reduction in glomerulus size and bowman's capsule, due to arsenic

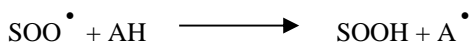
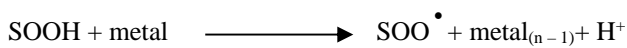
toxicity may also be a reason of reduced kidney weight.

Arsenic trioxide caused hyponatremia, hypochloremia and hyperkalemia could be possible due to attachment with proteins of renal tubular epithelium and thus producing ROS. Arsenic trioxide causes peroxidation of unsaturated fatty acids in biological membranes, leading to decrease in membrane fluidity and membrane integrity which delocalizes the Na-K ATPase from basolateral to apical membrane, resulting in electrolyte imbalance.¹⁸

Besides arsenic damages juxtaglomerular apparatus, due to which renin secretion gets decreased, and probably disturbance in renin – angiotensinogen pathway, is generally causing aldosterone reduction which perhaps results in electrolyte imbalance.^{19,20,21.}

Arsenic promotes lipid peroxidation, producing free radicals which damage the glomerular filtration membrane.²² This leads to reduced GFR. Damage in tubular epithelium causes diffusion and backleak of the filtrate across the tubular basement membrane back into interstitium and circulation. Thus both decreased GFR and backleak of filtrate leads to disturbance in the serum electrolyte balance.

Curcuma aromatica leaf extract contains curcumin as revealed by TLC in present investigation, is an antioxidant, and prevents ROS formation and reduces oxidative damage²³ *vide infra*.



where S = substance oxidized

AH = phenolic antioxidant

A[•] = Antioxidant radical

x[•] = Another radical

In conclusion, the present study demonstrates that the *Curcuma aromatica* leaf extract prevents the oxidative damage by ROS, due to its antioxidant property. Further, *Curcuma* extract ameliorates the impaired renal functions and inhibits the renal damage associated with arsenic trioxide in rats and offers itself a novel drug for future for various controlled diseases.

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