Journal of Advances and Scholarly Researches in Allied Education
Vol. XIV, Issue No. 1, October-2017, ISSN 2230-7540

Restorative Effect of Cadamba Fruit Extract on Arsenic-Induced Nephrotoxicity in Albino Mice

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Abstract – Arsenic is a metalloid that can be toxic to humans and other living organisms, occurs naturally and anthropogenic ally throughout the world at varying concentrations, including concentrations of concern in soil or groundwater. Presently, in Bihar (India) 16 districts are affected with arsenic poisoning in ground water causing lots of health hazards among the population and presently there is no solution for them. This arsenic intoxication has caused lots of problems related to kidney. The present study investigated the restorative effect Cadamba fruit extract on arsenic trioxide induced nephrotoxicity in mice. Arsenic trioxide (4 mg/kg/day b.wt) was administered to produce nephrotoxicity in rats followed by administration of Cadamba fruit extract (100 mg/kg/day p.o. 80 days) to attenuate the arsenic mediated nephro-toxicity. The kidney function tests were assayed and were found with elevated levels of urea, uric acid, and creatinine. Furthermore, their free radical assessment like lipid peroxidation levels were assayed which was found significantly high. Moreover the histopathological evaluations of kidney showed severe changes in mice treated with arsenic trioxide. But, after administration of aqueous extract of Cadamba fruit extract, it caused significant restoration in serum levels of urea, uric acid, creatinine, and lipid peroxidation levels and also in histological changes. Thus, it is evident from study that Cadamba fruit extract possesses antidote and acts effectively against arsenic induced nephrotoxicity.

Keywords: Nephrotoxicity, Creatinine, Anthropogenic Ally, Arsenic Administration, Restorative.

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INTRODUCTION

Arsenic is one of the most important global environmental toxicants and its exposure in humans comes mainly from consumption of drinking water contaminated with inorganic arsenic. In clinical trials it is considered as a first choice cancer chemotherapeutic against certain leukemia and has potential against a variety of other cancers, including solid tumors. Specifically, arsenic trioxide (As_2O_3,) is used in the treatment of acute promyelocytic leukemia and it greatly improves the clinical outcome even in refractory or multiple relapsed cases . But, toxic side effects of arsenicals are often a major concern; including the potential for fatal hepatotoxicity .The liver is a major target organ for both arsenic metabolism and toxicity. Arsenic induced hepatic injury is known to be exerted through excess production of reactive oxygen species, namely superoxide (O_2), hydroxyl OH), and peroxy (ROO) radicals and hydrogen peroxide (H_2O_2). The harmful expressions of arsenic are primarily due to an imbalance between pro-oxidant and antioxidant homeostasis in physiological system and also due to its fascination to bind sulfhydryl groups of proteins and thiols of glutathione (GSH). Thus, an agent able to reduce the toxic potential of arsenic in liver cells would clearly to be useful ccompounds for arsenical chemotherapy.

Neolamarckia cadamba primarily consist of indole alkaloids, terpenoids, sapogenins, saponins, terpenes, steroids, fats and reducing sugars. The bark also consists of tannins and an astringent principle; which is due to the presence of an acid similar to cincho-tannic acid. A new pentacyclic triterpenic acid isolated from the stem bark Neolamarckia cadamba named cadambagenic acid (18α-olean-12ene-3β-hydroxy 27, 28-dioic acid) (Fig. 1), along with this acid quinovic acid (Fig. 2) and β-sitosterol (Fig. 3) have also been isolated

The isolation and structure of 3β-dihydrocadambine and 3β-isodihydrocadambine (Fig. 8) alkaloids reported from the leaves of Neolamarckia cadamba with molecular formula ($C_{37}H_{44}N_{15}O_2$). A new saponin named saponin B ($C_{48}H_{76}O_{17}$) reported from Neolamarckia cadamba (Miq.). Neolamarckia cadamba also contain an acid called chlorogenic acid (CGA) (Fig. 9) . Recently some worker isolated two novel triterpenoidsaponins, phelasin A and phelasin B from the bark of Neolamarckia cadamba (Roxb.) Miq. Two novel monoterpenoidindole alkaloids, aminocadambine A ($C_{24}H_{27}N_30_5$) (fig. 10) and

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aminocadambine B $C_{25}H_{29}N_3O_5$(fig. 11) obtained from the leaves of Neolamarckia cadamba, previously named Anthocephaluschinensis whereas some worker biosynthetically synthesized glucosidicindole alkaloid cadambine from its biological precursor secologanin which is the main precursor of various indole alkaloids

Three monoterpenoidgluco-indole alkaloids, 3β-isodihydrocadambine, cadambine and 3α-dihydrocadambine isolated from Nauclea cadamba (Roxb.). The flowers of Neolamarckia cadamba yield an essential oil and the main constituents of oils are linalool, geraniol, geranyl acetate, linalyl acetate, α-selinene, 2-nonanol, β-phellandrene, α-bergamottin, p-cymol, curcumene, terpinolene, camphene and myrcene. Two triterpenoid glycosides, glycosides A and B were isolated from the bark of Neolamarckia cadamba and defined as 3-o-(α-L-rhamnopyranosyl)-quinovic acid-28-o-(β-D-glucopyranosyl) ester and 3-o-(β-D- glucopyranosyl)-quinovic acid-28-o-(β-D-glucopyranosyl) ester respectively and eight different alkaloids also obtained from Neolamarckia cadamba named cadambine, CFJ 83, isomalindan, cadamine, 2 derivs. HFP34, GZM28, malindan, dihydro cadambine (Fig. 12), 2derivs. GPX71, GPX73, isomalindan, isodihydro cadambine, 2 derivs. GPX51, GPX53, malindan. The seeds of Anthocephalusindicus composed of water-soluble polysaccharides D-xylose, D-mannose and D-glucose in the molar ratio 1:3:5. Almost all parts of the plant Neolamarckia cadambais used in the treatment of various diseases. Decoction of leaves is used as gargle in aphthae or stomatitis and in the treatment of ulcers, wounds, and metorrhea. Bark of the plant is used in fever, inflammation, cough, vomiting, diarrhoea, diabetes, burning sensation, diuresis, wounds, ulcers and in the treatment of snake-bite.

Arsenic trioxide (4 mg/kg/day b.wt) was administered to produce nephrotoxicity in rats followed by administration of Cadamba fruit extract (100 mg/kg/day p.o. 80 days) to attenuate the arsenic mediated nephro-toxicity. The kidney function tests were assayed and were found with elevated levels of urea, uric acid, and creatinine. Furthermore, their free radical assessment like lipid peroxidation levels were assayed which was found significantly high. Moreover the histopathological evaluations of kidney showed severe changes in mice treated with arsenic trioxide. But, after administration of aqueous extract of Cadamba fruit extract, it caused significant restoration in serum levels of urea, uric acid, creatinine, and lipid peroxidation levels and also in histological changes. Thus, it is evident from study that Cadamba fruit extract possesses antidote and acts effectively against arsenic induced nephrotoxicity.

Cadamba fruit extract is a naturally occurring antioxidant that plays an important role by inactivating harmful free radicals produced through normal cellular activity and from various stressors thus terminating lipid peroxidation and stabilizing the molecular composition of cellular membranes, preventing the harmful effects of reactive oxygen species (ROS). Therefore cadamba fruit extract is used to ameliorate the toxic effects of arsenic.

MATERIAL AND METHOD :

Preparation of aqueous extract of cadamba fruit :

In the present study, fresh fruit of cadamba were collected from plant of Neolamarckia cadamba from premises of Mahavir Cancer Institute $Research Centre ,Patna,India. The identity of the medicinal plant was confirmed by Dr. S.K RAY . The collected fruit of cadamba were shade dried and were grinded to fine powder. The aqueous extract dose was calculated after LD50 estimation which was found to be 1500mg kg-1 body weight and the final dose was fixed to 100mg kg-1 body weight.

Animals: Thirty male swiss albino mice (28g to 32g) were obtained from animal house of Mahavir Cancer Institute & Research Centre, Patna, India . Food and water to mice were provided ad libitum (prepared mixed formulated feed by the laboratory itself). Animals were maintained in colony rooms with 12 hrs light/dark cycle at 22 ± 2^{o} C.

Experimental protocol

The mice were divided into four groups of six rats each, a normal control group, a cadamba fruit extract control which received 100 mg/kg b.wt of cadmba fruit extract, one As2O3 (4 mg/kg b.wt) administered group and a combination group treated with 4 mg/kg b.wt of As2O3 and 100 mg/kg b.wt of cadamba fruit extract. 0.2% DMSO solution was used as vehicle for cadamba fruit extract administration. Experimental groups received this via oral intubation daily for a period of 80 days. At the end of the experimental period animals were decapitated, blood was collected and centrifuged at 3 000 rpm for 20 minutes; the clear serum obtained was used for the determination of marker enzymes. kidney was removed immediately, washed in ice cold 0.15M NaCl and blotted on a filter paper. Then the tissue was weighed and homogenized by using Teflon glass homogenizer (1/10th weight/volume) in ice cold tris-HCl buffer (0.2M, pH 7.4). The homogenate was centrifuged at 10 000g for 20 min at 4 C and the supernatant was used for the estimation of lipid peroxidation and various enzymatic and non enzymatic assays.

Plasma specimens were obtained and used for determination of creatinine , urea and uric acid using an automatic analyser (Reflotron plus system , roche , Germany). Kidney homogenates were obtained using a tissue homogenizer . the homogenates (1:10 w/v) were prepared using a 100 mM KCL buffer (7:00 pH) containing EDTA 0.3 mM

. all homogenates were centrifuged at 1500 rpm for 30 min at 4 degree celcius and the supernatants were used for the biochemical assays of glutathione (GSH) and superoxide dismutases (SOD) levels using GSH and SOD assays kits (sigma-Aldrich com.) according to the manufacture's instruction with some modification . also , kidneys were quickly removed , immersed in 10% formalin , dehydrated and embedded in paraffin , sectioned at 4 µm, stained with hematoxylin and cosin (H&E) and evaluated by light microscopey. Images representative of typical histological profile in control and all treated groups were captured with the aid of motic imaging software.

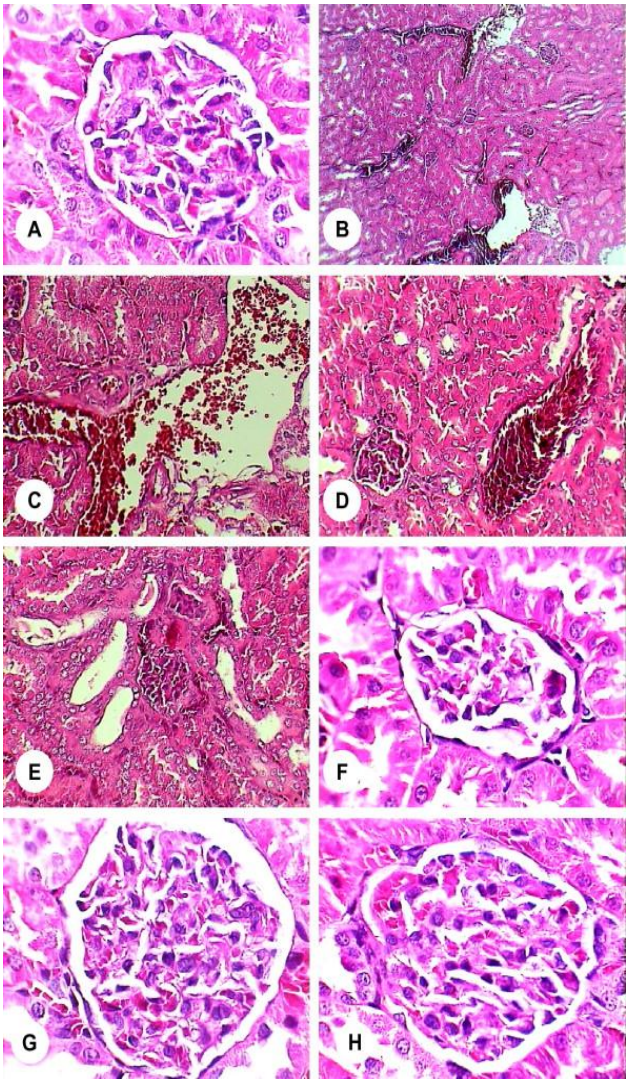
Statistical analysis

The calculations and statistical analysis were carried out using the statistical package for social sciences (SPSS) for windows version 12.0 software. All data were represented as mean ±standard deviation (SD). Data e=were subjected to one-way analysis of variance (ANOVA) followed by student's t-test .statistical probability of $p < 0.05$ was considered to be significant.

RESULT

Histopathology of kidney tissue

Histopathological examination of the kidney specimens showed severe alterations in mice exposed to heavy metals . Renal tubular dilatations with congestion of blood vessels with hemorrhage and degeneration of renal corpuscles were notedcompared to the normal structure of control group .Administration of cadamba flower extract protected the kidney exposed to arsenic trioxide as evidenced by appearance of normal structures of kidney, specially renal corpuscles .Additionally, the histopathological evaluation of only cadamba flower extract treated mice showed normal renal corpuscle (A–H) Histological changes of kidney in each group. (A) Normal structure of renal corpuscle in control mice (1000×). (B) Renal cortex and medulla structure of arsenic trioxide related mice (100×). (C–E) Renal cortex structures of arsenic trioxide treated mice (400×). (F) Renal corpuscle structure of arsenic trioxide treated mice (1000×). (G) Renal corpuscle structure of arsenic trioxide pluscadamba flower extract treated mice (1000×). (H) Renal corpuscle structure of cadamba flower extract treated mice (1000×).



Parameters	Control	Arsenic trioxide	Cadamba	Arsenic Trioxide + Cadamba
Plasma creatinine (mg/dL)	0.36 ± 0.04	0.92 ± 0.05 (+151.4%)	0.37 ± 0.02 (0.0%)	0.45 ± 0.06 (+24.3%)
Plasma urea (mg/dL)	13.96 ± 1.37	25.46 ± 3.02 (+82.4%)	14.71 ± 1.42 (+5.4%)	14.87 ± 2.47 (6.7%)
Plasma Uric acid (mg/dL)	1.89 ± 0.12	3.08 ± 0.32 (+64.4%)	1.75 ± 0.26 (−7.5%)	1.82 ± 0.24 (−2.7%)
Kidney GSH (µmol /g tissue)	3.43 ± 0.49	2.46 ± 0.48 (−27.8%)	3.26 ± 0.23 (−4.4%)	3.31 ± 0.43 (−3.5%)
Kidney SOD	4.59 ± 0.37	2.75 ± 0.66 (−41.0%)	4.79 ± 0.51 (+4.8%)	4.40 ± 0.51 (−3.8%)

P < 0.05: Student's t-test (significance levels shown for difference between control and treated groups).

P < 0.05: Student's t-test (significance levels shown for difference between mice exposed to Arseic trioxide and arsenic trioxide plus cadamb).

P < 0.05: Student's t-test (significance levels shown for difference between mice exposed to arsenic trioxide and cadamba).

P < 0.05: Student's t-test (significance levels shown for difference between mice exposed to arsenic trioxide plus cadamb and cadamb).

Plasma creatinine level was found to be 0.36 +/- 0.04 mg/dL in control. When control was treated with arsenic trioxide for 80 days, the plasma creatinine level was found to be increased upto 155.56% i.e. 0.92 +/- 0.05 mg/dL from 0.36 +/- 0.04 mg/dL. When this arsenic treated mice was further treated with cadamba extract, a significant decrease of 59.78% in plasma cretinine level was observed. When arsenic trioxide and cadamba extract were given to control simultaneously for 80 days, the plasma creatinine level was found to increase by 5% which is very less as compare to 155.56% increase when mice was treated with arsenic trioxide alone.

Hence, it was observed that administration of cadamba extract reduces the toxic effect of arsenic trioxide on the kidney of mice.

Plasma urea level was found to be 13.96 +/- 1.37 mg/dL in control. When control was treated with arsenic trioxide for 80 days, the plasma urea level was found to be increased upto 82.38% i.e. 25.46 +/- 3.02 mg/dL from 13.96 +/- 1.37 mg/dL. When this arsenic treated mice was further treated with cadamba extract, a significant decrease of 42.22 % in plasma urea level was observed. When arsenic trioxide and cadamba extract were given to control simultaneously for 80 days, the plasma urea level was found to increase by 6.52 % which is very less as compare to 82.38 % increase when mice was treated with arsenic trioxide alone.

Hence, it was observed that administration of cadamba extract reduces the toxic effect of arsenic trioxide on the kidney of mice.

Plasma uric acid level was found to be 1.89 +/- 0.12 mg/dL in control. When control was treated with arsenic trioxide for 80 days, the plasma uric acid level was found to be increased upto 62.96 % i.e. 3.08 +/- 0.32 mg/dL from 1.89 +/- 0.12 mg/dL. When this arsenic treated mice was further treated with cadamba extract, a significant decrease of 43.18 % in plasma uric acid level was observed. When arsenic trioxide and cadamba extract were given to control simultaneously for 80 days, the plasma uric acid level was found to increase by 1.59 % which is very less as compare to 62.96 % increase when mice was treated with arsenic trioxide alone.

Hence, it was observed that administration of cadamba extract reduces the toxic effect of arsenic trioxide on the kidney of mice.

Kidney GSH value of control mice was measured to 3.43 +/- 0.49. When control was treated with arsenic trioxide for 80 days, the kidney GSH value was found to be decreased upto 28.28 % i.e. 2.46 +/- 0.48 mg/dL from 3.43 +/- 0.49 mg/dL. When this arsenic treated mice was further treated with cadamba extract, a significant increase of 32.52 % in kidney GSH level was observed. When arsenic trioxide and cadamba extract were given to control simultaneously for 80 days, the kidney GSH value was found to decrease by 3.50 % which is very less as compare to 28.28 % decrease when mice was treated with arsenic trioxide alone.

Hence, it was observed that administration of cadamba extract reduces the toxic effect of arsenic trioxide on the kidney of mice.

Kidney SOD value of control mice was measured to 4.59 +/- 0.37. When control was treated with arsenic trioxide for 80 days, the kidney SOD value was found to be decreased upto 40.09 % i.e. 2.75 +/- 0.66 mg/dL from 4.59 +/- 0.37 mg/dL. When this arsenic treated mice was further treated with cadamba extract, a significant increase of 74.18 % in kidney SOD value was observed. When arsenic trioxide and cadamba extract were given to control simultaneously for 80 days, the kidney SOD value was found to decrease by 4.14 % which is very less as compare to 40.09 % decrease when mice was treated with arsenic trioxide alone.

Hence, it was observed that administration of cadamba extract reduces the toxic effect of arsenic trioxide on the kidney of mice.

DISCUSSION:

The present study showed that cadamba flower extract has protective effect on heavy metals-induced renal and testicular oxidative stress and injuries. our study therefore suggests that cadamba flower extract may be a useful preventive agent against the effect of the studied heavy metals at least partly due to its antioxidant properties.

There are three parts of the study. First part is to know the effect of arsenic trioxide on the kidney of the swiss albino mice. In second phase of our study, these arsenic treated mice were treated with cadamb fruit extract to find out the remedial action of cadamba fruit on the arsenic affected organs of the mice. This part of the study confirmed that cadamb fruit can be used in treatment of arsenic induced toxicity. The final part of the study comprises the determination of combine effect of arsenic trioxide and cadamb extract on the organs of Albino mice. The study concludes that when the people who are bound to intake arsenic trioxide due to its presence in water given cadamb fruit, can get relief from the toxic effects of arsenic.

In most of the areas of Bihar, Uttar Pradesh and Madhya Pradesh, arsenic trioxide is present in significant amount in groundwater. People living in these areas are bound to drink this water. Although

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there are a number of techniques to purify the drinking water, but these are too costly to be availed by the economically weaker section of the population living in these areas. Cadamba fruit is available in these areas in abundant and is in reach of every person. Therefore, the study was oriented in the direction of finding the most economical remedy for the most common and severe health problems of Bihar, Uttar Pradesh and Madhya Pradesh etc. Now we discuss about the major cause of sufferings for the people of these states i.e. arsenic and the diseases caused by this.

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