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Ameliorative Effects of Jamun Seed (*Syzygium cumini*) and Orange Peel (*Citrus sinensis*) Extracts on Cadmium Induced Alterations in Blood Urea, Uric Acid and Creatinine of Rat

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Abstract: Wistar rats were treated as Group A: Control; Group B: Cadmium (10 mg/kg b wt.); Group C: Cadmium (10 mg/kg b wt.) and jamun seed extract (200mg/kg b wt.); Group D: Cadmium (10 mg/kg b wt.) and orange peel extract (200 mg/kg b wt.); Group E: orange peel extract (200 mg/kg b wt.) and Group F: jamun seed extract (200 mg/kg b wt.). Serum urea, uric acid and creatinine levels were analyzed on 7 and 14 day.

Rats from Group B showed slight increase after 7 day in serum creatinine level as compared to control (group A) which increased further after 14 day. There was a significant decrease in serum creatinine level in group C and group D at 7 days and 14 days treatment as compared to Group B (Cd treated). No significant changes were noticed in serum creatinine level when rats were treated with orange peel extract and jamun seed extract after 7 day and 14 day.

A progressive increase in serum urea was recorded after treatment with cadmium (group B) from 7 day to 14 days as compared to control (group A). However, the rat treated with cadmium and extract of jamun seed (group C) or orange peel (group D) showed decrease in serum urea level after 7 days and 14 days treatment as compared to Group B (treated with cadmium only). No changes were noticed in serum urea level after treatment with orange peel extract (group E) and jamun seed extract (group F) at 7 day and 14 day.

After 7 days exposure of cadmium to rats (group B) the level of serum uric acid was slightly increased however, after 14 days, there was further increase in uric acid as compared to control (group A). There was a decrease in the serum uric acid level of rats treated with cadmium and jamun seed extract (group C) or orange-peel extract (group D) on day 7 and 14 as compared to level of rat exposed to cadmium (group B). No significant difference in the uric acid level of rats was seen after treatment with orange peel extract (group E) and jamun seed extract (group F) at 7 day and 14 day.

Keywords: Heavy metal, Cadmium, Creatinine, Urea, Uric acid, Jamun seed, Orange peel, Ameliorative, Kidney

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Introduction

Cadmium (Cd) is one of the most significant hazardous heavy metals in the environment (Haouem *et al.,* 2007, Yadav *et al*., 2023). Cadmium (Cd) is a poisonous metal that is found in food, cigarette smoke, air, water, industrial and agricultural wastes (Yadav *et al*., 2023; Singh *et al*., 2023). It can enter into the human body either through inhalation, eating, or dermal contact (Wu *et al.,* 2016; Jyothi, 2021). Cadmium might also exert poisonous effects on several organ systems, however, the kidney is most affected organ (Garcia and Corredor, 2004; Genchi *et al*., 2020). Cd generates biochemical and physiological impairments in human and animal kidneys (Karami *et al.,* 2022, Yadav *et al*., 2023). Studies indicate that Cd cause adverse health effects even at lower exposure levels than previously thought, resulting primarily the kidney damage (Zhang *et al.,* 2008; Smereczański and Brzóska, 2023). Even though the mechanisms by way of which Cd affects renal dysfunction had been drastically studied by many investigators, yet specified cell mechanisms still to be established. Clinically, Cd nephropathy resembles acquired Fanconi's syndrome, i.e., polyuria, glucosuria, aminoaciduria, proteinuria, calcinuria, and phosphaturia (Garcia and Corredor, 2004; Mitra *et al*., 2022). Cadmium is a non-biodegradable heavy metal and accumulates in living system through food chain (Suhani *et al*., 2021). Metals can disrupt metabolic processes and cause renal cortical dysfunction of kidney (Siddiqui, 2010; Mitra *et al*., 2022). The accumulation of Cadmium (Cd) in the body causes grievous nephrotoxicity in humans and animals (Jacquillet *et al.,* 2007, Tahir and Ali, 2023).

Orange (family Rutaceae) peel is one of the profitable biomass squanders. Within the world, oranges occupy 75% of the entire *citrus* natural products. Orange (*Citrus sinensis)* peel is mostly made up of cellulose, flavanone glycosides hesperidin, neohesperidin, naringin, rutin, hemi-cellulose, pectin substances, chlorophyll pigments, and other small molecules like limonene (Xiaomin *et al.,* 2008, Alfarajat *et al*., 2023). The orange peel extract shows potential benefits for the kidney. It protects renal impairment from toxic heavy metals as well as drugs (Srivastava *et al.,* 2021b). It works as specific renal antioxidant and protect against renal disease or renal failure and also improves kidney function (Asif, 2012; Ahmed *et al*., 2018).

Syzigium cumini (family Myrtaceae) commonly known as black plum or Jamun or Jambul/Jamul. Different phytochemical constituents are present in the bark and seed of *Syzigium cumini*. The significant biochemical compounds present in the edible part (pulp) and seed are oxalic acid, myricetin, gallic acid, diglucoside, hotrienol, phytosterols, flavonoids, carotenoids and polyphenols, citronellol, cyanidin as well as micronutrients, which accounts for various health benefits (Chhikara *et al.,* 2018; Srivastava *et al.,* 2021a,b). The ripen fruits of Jamun are used to make several products like juices, squashes and medicines and pulp extract which act as an effective antioxidant against renal function (Abbas *et al.,* 2016). Human urine has major organic compounds such as urea, uric acid, and creatinine (Chhikara *et al.,* 2018). Increased levels of creatinine, urea and uric acid caused Azotemia, uramea, hyperuracemia and kidney failure.

There exists no report regarding the protective effects of orange peel extract and jamun seed extract on the kidney function test in mammals after exposure to cadmium. Therefore, the present study was aimed to investigate the changes in serum creatinine, urea and uric acid levels induced by cadmium exposure to rats and evaluated the probable ameliorative role of extracts of orange (*Citrus sinensis*) peel and jamun (*Syzygium cumini*) seed.

Materials and Methods

One hundred twenty Wistar rat (50-60 g; 2 months age) were procured from Asia Scientific Emporium, Varanasi, India. Animals were kept under standard laboratory conditions in polypropylene cages at room temperature of 27-30°C with a 12 h dark/light cycle for 2 weeks.

They were provided with water and feed *ad libitum*. The doses used in this study for cadmium, orange peel extract and jamun seed extracts are based on the reports of previous investigators---cadmium (5 and 10 mg/kg b wt. –Tripathi and Srivastav, 2011a, b; 15-30 mg/kg b wt. --Andjelkovic *et al.,* 2019; 5 mg/kg b wt. --Ijaz *et al*., 2023; 4, 5, 6.66, 10 and 20 mg/kg b wt. --Vandjiguiba *et al*., 2016); orange peel extract (200 mg/kg b wt.— Srivastava *et al*., 2021a,b; 750 and 1250 mg/kg b wt. -- Amber *et al*., 2020; 250 and 500 mg/kg b wt. -- Ekhatar *et al*., 2022) and jamun seed extract (200 mg/kg b wt. -- Srivastava *et al*., 2021a,b; 250 mg/kg b wt. -- Sharma *et al*., 2013; 5 to 160 mg/kg b wt.—Jagetia *et al.*, 2005).

Purified Cadmium Chloride ($CdCl_2.H_2O$) was purchased from Central Drug House (P) Ltd, Mumbai, India. 1 g Cadmium was dissolved in 200 ml of distilled water (stock solution) and further dilutions were made for use in experiment.

The seeds of jamun, *Syzygium cumini* were purchased from commercial supplier (M/S SVM Naturals, Tamil Nādu, India). The fruits of orange, *Citrus sinensis* were purchased locally from Gorakhpur and peels were separated. The jamun seeds and orange peels were washed thoroughly with fresh water and dried at 40℃. After drying, these were crushed to small pieces and powdered. Powdered jamun seeds and orange peels were mixed separately with 90% ethanol in 1:20 ratio (w/v) and were kept on an orbital shaker for 48 h. Then the samples were filtered with Whatman No.1 filter paper. The filtrates were dried in rotary evaporator at 40℃. The dried residue was weighed and kept at -20℃ for further use in this study, Soxhlet extraction was not used in this extraction process to prevent denaturation of heat-labile several compounds present in orange peels and jamun seeds. For use in this experiment, the dried residues of orange peels and jamun seeds were reconstituted in ethanol to provide desired dose to be given to rats (Srivastava *et al*., 2021a,b). Experimental design was approved by the Research Degree Committee, D.D.U. Gorakhpur University.

Experimental design:

The acclimated rats were randomly divided into six groups- A, B, C, D, E, and F, each consisting of 20 animals. Following treatments were orally given with help of gavages, daily to the groups at 8:00 a.m. each day throughout the experiment:

Group A: Control: No treatment was given

Group B: Cadmium – these rats received daily cadmium (10 mg/kg b wt.)

Group C: Cadmium + Jamun seed extract (Cd + JSE): These rats were given daily cadmium (10 mg/kg b wt.) and Jamun seed extract (JSE) (200 mg/kg b wt.) simultaneously

Group D: Cadmium (10 mg/kg b wt.) + orange peel extract (Cd + OPE): These rats received daily cadmium (10 mg/kg b wt.) and orange peel extract (OPE) (200 mg/kg b wt.) simultaneously

Group E: Orange peel extract (OPE): rats received daily orange peel extract (200 mg/kg b wt.)

Group F: Jamun seed extract (JSE): rats received daily Jamun seed extract (200 mg/kg b wt.)

Rats (10 from each group) from all the groups were sacrificed 24 h after last dose on the 7^{th} and 14^{th} day after initiation of the experiment under light ether anaesthesia. Animals were fasted overnight before sacrifice.

On the last day of experimentation, final body weight of each animal was recorded. Blood samples were collected through cardiac puncture and centrifuged at 3000 rpm for 5 min and serum was separated and stored at -20℃ until analyzed for urea, creatinine and uric acid levels (Kit method, Beacon Diagnostics Private Ltd, India). Duplicates analysis were performed for each sample.

Statistical analysis:

Data are presented as mean ± S.E. of six specimens. For multiple group comparisons, One-way Analysis of Variance (ANOVA) was used. Differences between groups were determined by Student's t test and Bonferroni post hoc test.

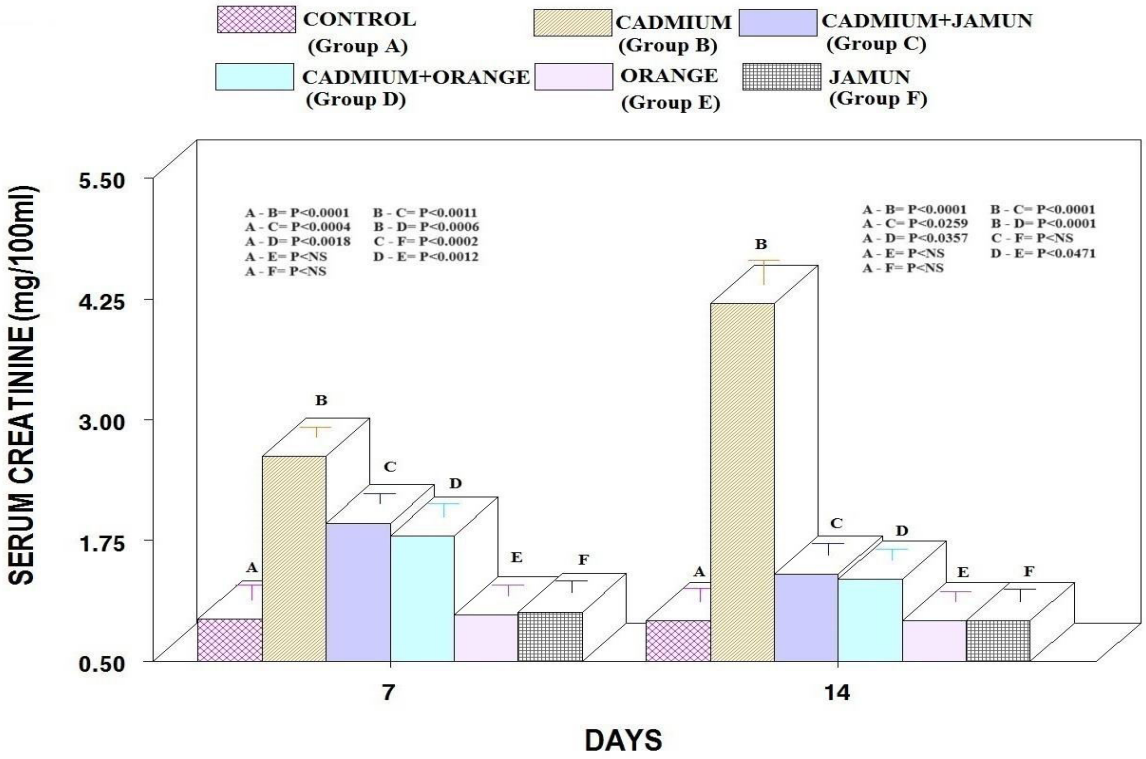

Fig. 1: Serum creatinine levels (mg/100 ml) of Wistar rat treated either with cadmium, cadmium+jamun seed extract, cadmium+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

Results

In this study, rats from Group B (Cd: 10 mg /kg b wt.) showed slight increase after 7 day in serum creatinine level as compared to control (group A). A further increase in Creatinine level was recorded after 14 day Cd treatment (Fig. 1). There was a significant decrease in serum creatinine level in group C (Cd + Jamun seed extract) and group D (Cd + orange peel extract) at 7 days and 14 days treatment as compared to Group B (Cd treated). No significant changes were noticed in serum creatinine level when rats were treated with orange peel extract (group E: 200 mg /kg b wt.) and jamun seed extract (group F: 200 mg/kg b wt.) after 7 day and 14 day (Fig. 1). Analysis of variance (ANOVA) indicates that the treatments are significant (7 day-- F=30.358, P< 0.0001; 14 days-- F=69.853, P< 0.0001).

In the present study a progressive increase in serum urea was recorded after treatment with cadmium (group B) from 7 day to 14 days as compared to control (group A) (Fig. 2). However, the rat treated with cadmium and extract of jamun seed (group C) or orange peel (group D) showed decrease in serum urea level after 7 days and 14 days treatment as compared to Group B (treated with cadmium only). This shows that OPE and JSE are effective in reversing the toxic effects of cadmium on urea level (Fig. 2). No changes were noticed in serum urea level after treatment with orange peel extract (group E) and jamun seed extract (group F) at 7 day and 14 day. Analysis of variance (ANOVA) indicates that the treatments are significant (7 day-- F=28.312, P< 0.0001; 14 days-- F= 52.598, P< 0.0001).

After 7 days exposure of cadmium to rats (group B) the level of serum uric acid was slightly increased however, after 14 days, there was further increase in uric acid as compared to control (group A) (Fig. 3). There was a decrease in the serum uric acid level of rats treated with

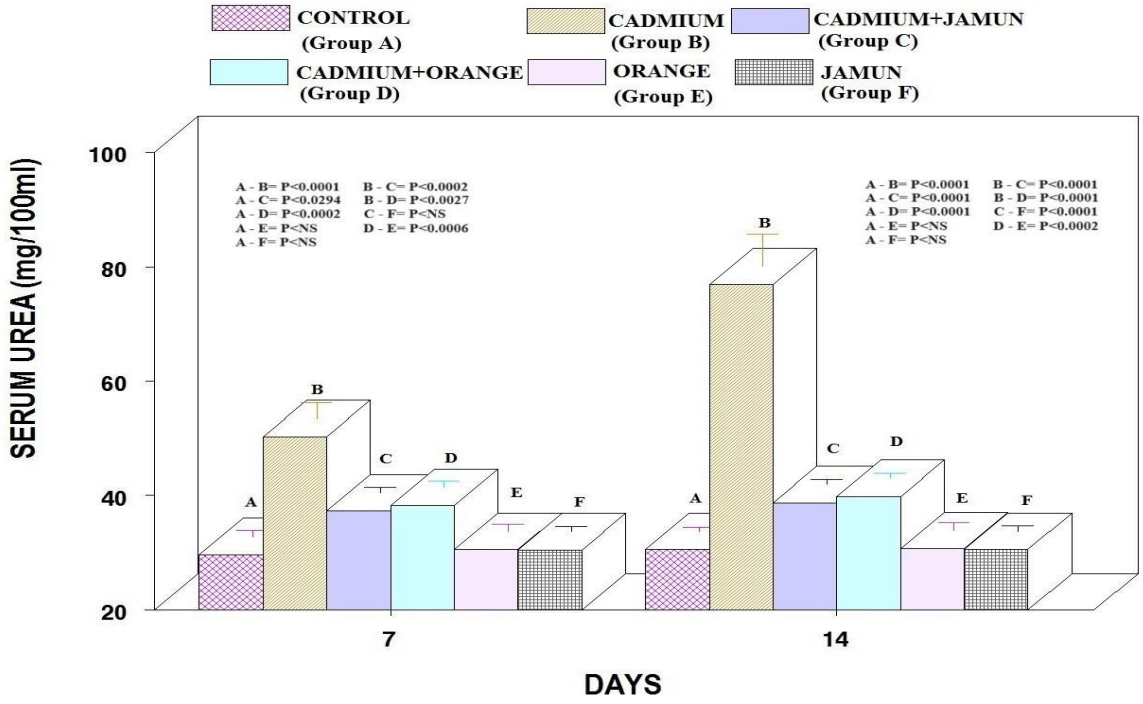

Fig. 2: Serum urea levels (mg/100 ml) of Wistar rat treated either with cadmium, cadmium+jamun seed extract, cadmium+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

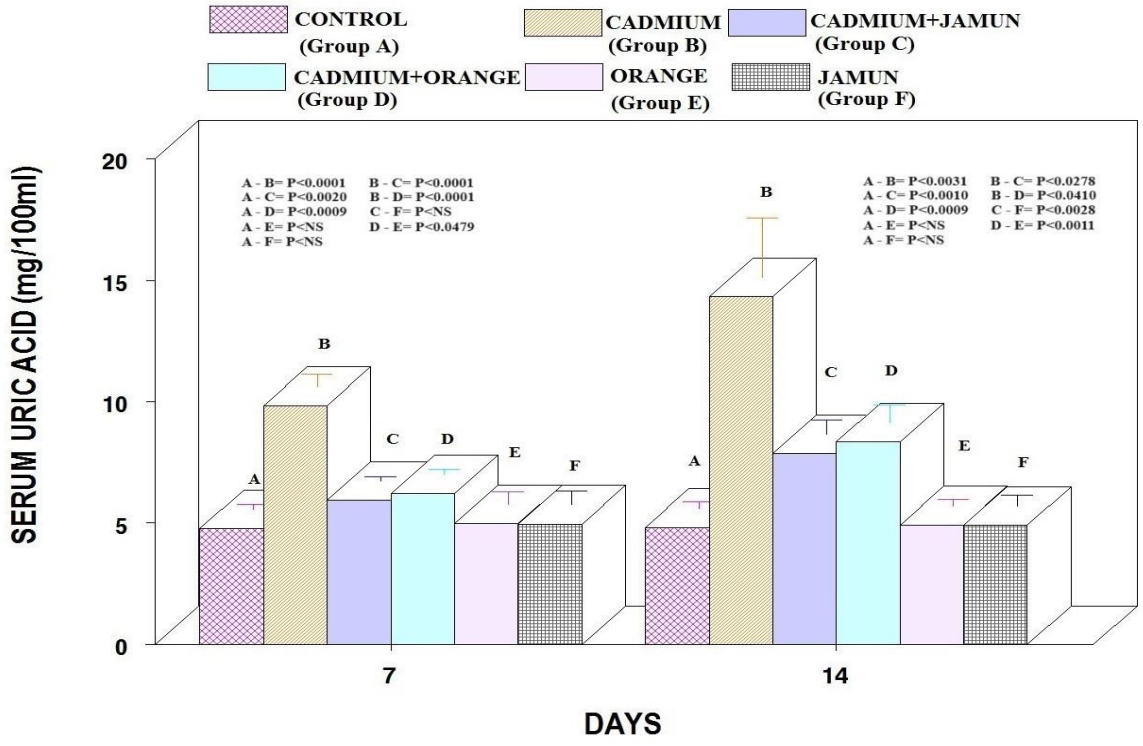

Fig. 3: Serum uric acid levels (mg/100 ml) of Wistar rat treated either with cadmium, cadmium+jamun seed extract, cadmium+orange peel extract, orange peel extract or jamun seed extract. All values indicate mean ± SE of six specimens.

cadmium and jamun seed extract (group C) or orange-peel extract (group D) on day 7 and 14 as compared to level of rat exposed to cadmium (group B) (Fig. 3). This clearly evident that OPE and JSE prevents the effects of cadmium on uric acid. No significant difference in the uric acid level of rats was seen after treatment with orange peel extract (group E) and jamun seed extract (group F) at 7 day and 14 day (Fig. 3). Analysis of variance (ANOVA) indicates that the treatments are significant (7 day-- $F=22.770$, $P< 0.0001$; 14 days-- $F= 11.32$, $P< 0.0001$).

Discussion

Cadmium has been reported to cause toxic effects in mammals such as teratogenicity, genotoxicity, osteoporosis, hepatotoxicity, neurotoxicity and nephrotoxicity (Srivastava *et al*., 2021b; Cirmi *et al*., 2021). In the present study significant preventive effects of jamun seed extract or orange peel extract on cadmium induced nephrotoxicity in rats have been noticed which is evident by the restoration of urea, uric acid and creatinine levels to near control value. Present study depicted that administration of cadmium chloride significantly increased creatinine, urea and uric acid levels in rats. Similar results were also observed by other investigators in rats after exposure to toxicants---Mercery (Desai *et al*., 2021), Arsenic (Cardenas-Gonzalez *et al*., 2016), Nicotine (Goniewicz *et al*., 2017), Chromium (Abbas *et al*., 2016, Cardenas-Gonzalez *et al*., 2016), Indoxacarb (Ali *et al*., 2018), Diazines (Al-Attar and Abu Zeid, 2013) and Aflatoxin and Cypermethrin (Hussain *et al*., 2009). Several toxicants also alter the serum creatinine levels in - (i) fishes---Dimethoate (Narra, 2017), Malathion (Bharti and Rasool, 2021), Bisphenol A (Akram *et al*., 2021), Imidacloprid (Priya *et al*., 2012); and (ii) Amphibian---Atrazine (Sena *et al*., 2021) and Oxyfluorfen (Ghada *et al*., 2019).

In the present study, the creatinine levels in group C (Cd+ JSE) and group D (Cd+ OPE) decreased on 7 days and 14 days in comparison to Group B (Cadmium exposed). It may indicate that both the jamun seed extract and orange peel extract recovered the serum creatinine levels which was increased after the treatment with Cadmium. It clearly indicates nephroprotective role of JSE and OPE with regards to nephrotoxicity provoked by cadmium exposure. No change was noticed in creatinine levels after jamun seed extract and orange peel extract treatment.There exists no report regarding the effects of jamun seed extract and orange peel extract treatment on creatinine levels of rat. .

In this study there was significant increase in serum urea level of rats after treatment with cadmium after 7 day and 14 days. Other researchers have also noticed increased serum urea level in rats after exposure to toxicants---Arsenic - Yousuf *et al*. (2023); Ammonia – Peyghan and Takamy (2002); and Arsenic and Nicotine – Jain *et al*. (2015). When JSE or OPE were given in combination with cadmium the serum urea level significantly decreased as compared to Group B (only cadmium exposed rats). Abbas *et al*. (2016) have also noticed increased urea level in mice after treatment with chromium; the urea levels were restored to near control levels after exposure to Jamun pulp extract. No significant changes were noticed in serum urea level in group E (OPE) and group F (JSE) which was treated with the jamun seed extract and orange peel extract.

Serum uric acid level was increased in cadmium treated rats (group B) as compared to control (group A). The results of present study derive support from the study of Abbas *et al*. (2016), Abungabl *et al.* (2020) and Yousuf *et al*. (2023) who have also reported increased uric acid level after exposure to heavy metals. In current study the rats treated with cadmium in combination with Jamun seed extract (Group C) or orange peel extract (Group D) showed significantly reduced level of uric acid which clearly depicts the nephroprotective effects against heavy metal toxicity. No alternation was noticed in Group E (orange peel extract) and Group F (Jamun seed extract).

Conclusion

It is concluded that exposure to cadmium

adversely affected the serum urea, uric acid and creatinine levels of the rats. The disturbances in these vital parameters could be protected by supplementation of extracts of jamun seed and orange peel. It is advisable that the organisms exposed to cadmium should be given dietary supplement of these botanical extracts which would ease the toxic symptoms.

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