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Research Article

Protective effects of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis)* peel extracts against cypermethrin-induced nephrotoxicity in rats

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Abstract. Phytochemicals have been reported to be present in fruits, vegetables, spices and herbs. These phytochemicals have antioxidant properties as they scavenge free radicals. The aim of the present study was to investigate histological changes in the kidney of rats induced by cypermethrin and to evaluate the protective role of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis)* peel extracts. Male Wistar rats were divided into six groups - Group A: Control; Group B: cypermethrin (CYP); Group C: cypermethrin and jamun seed extract (CYP+JSE); Group D: cypermethrin and orange peel extract (CYP+OPE); Group E: orange peel extract (OPE); Group F: jamun seed extract (JSE). The cypermethrin dose was 25 mg/ kg body wt/day whereas orange peel and jamun seed extract dose was 200 mg/kg body wt/day. For light and electron mocroscopical studies, kidney were fixed on 15 and 30 day following the treatment. In 15 day CYP (group B) treated rats kidney exhibited shrunken glomeruli, dilated tubules, hypertrophy of epithelial cells of proximal and distal tubules, obliterated tubular lumina and necrosis of kidney tubules. In CYP+JSE (group C) and CYP+OPE (group D) treated rats for 15 day, the kidney exhibit changes similar to those as noticed in CYP exposed rats. Kidney of rats treated for 15 day with OPE (group E) and JSE (Group F) have not shown any remarkable histological change. The kidney of 30 day CYP (group B) treated rats revealed shrunken glomeruli, hypertrophy of the tubular epithelium leading to congestion of tubules, increased cellularity of glomeruli, dilated tubules, separation of epithelial cells from the underlying basement membrane, degenerated kidney tubules with necrotic nuclei in the lumina, severe tubular degeneration, degenerated glomeruli containing amorphous eosin-positive material and few renal tubular cells with foamy, vacuolated and ragged appearance. In CYP+JSE (group C) and CYP+OPE (group D) treated rats for 30 day the kidney displayed increased cellularity in the glomerulus thus decreasing the urinary space. In these groups shrunken glomeruli and degeneration of glomeruli are not visible. Tubular degeneration is noticed but no degenerated nuclei in tubular lumina are seen. In OPE (Group E) and JSE (group F) treated rats for 30 day no histological changes in kidney are seen. From the present study it can be concluded that CYP caused histological alterations in the kidney of rats. These alterations can be protected by providing OPE and JSE.

Keywords: Cypermethrin; *Syzygium cumini*; *Citrus sinensis*; Kidney; Toxicity

1. Introduction

Various pesticides are designed to produce specific toxicity against certain harmful organisms. However, it is difficult to achieve total specific toxicity and therefore pesticides when entered into environment caused some risk to non-target organisms including humans [1–5]. The suitable pesticides are those which are rapidly biodegradable and less stable in the environment. Based on these criteria now-a-days pyrethroids are the most widely preferred group of pesticides due to their high effectiveness against large insect change as change, easily biodegradable and being less toxic to mammals and non-target organisms [6, 7].

Cypermethrin is a synthetic pyrethroid which is used for the control of ectoparasite infestation of animals, and agricultural and household pests [1, 5, 6, 8]. However, usage of cypermethrin caused a number of effects in humans and non-target animals by generation of reactive oxygen species [9], neurotoxic and genotoxic effects [6, 10], toxicological alterations in liver and kidney [2, 7, 11–14] , hematological [1, 13] and reproductive toxicity [11, 13, 15, 17].

Cypermethrin is termed as class II synthetic pyrethroid pesticide which acts by crossing the blood-brain barrier and provoke neurotoxicity in the central nervous system [18]. Cypermethrin opens the sodium channel system causing hyper-excitation and hypo-polarization of the neurons [18, 19].

Fruits, vegetables, Spices and herbs have been reported to possess phytonutrients/phytochemicals which have antioxidant activities as they scavenge free radicals [7, 12, 20–22]. Jamun (*Syzygium cumini*) contains antioxidant compounds namely flavonoids, phenolic acids and anthocyanins [7, 15, 23]. This fruit has antidiabetic, antimalarial, antibacterial, free radical scavenging, anti-ulcerogenic and antifertility properties [7, 18, 24, 25]. Jagetia [26] has reported that jamun reduce free radicals and stimulates the activation of different enzymes like catalase glutathione peroxidase, glutathione-s-transferase and increased synthesis of glutathione and depletes lipid peroxidation. *Citrus sinensis* is used because they are rich source of vitamin C, flavonoids, acridone alkaloids, carotenoids, limonoids etc. [7, 15, 21, 27]. *Citrus* peels contain hespiridin [22]. The peels possess antioxidant, anti-inflammatory, anti-cancer and anti-lipedemic activities [22]. Ahmed et al. [21] have reported that *Citrus* peels contain naringin and naringenin which have antimicrobial, antidiabetic and toxicity protecting activities. In rats hesperidin has been reported to increase superoxide dismutase (SOD), glutathione–*S*–transferase (GST) and total glutathione (GSH) after chemical induction of oxidative stress [28]. Jeon et al. [29] has reported that naringin, present in citrus peel, increased levels of superoxide dismutase, catalase (CAT) and vitamin E in high cholesterol fed New Zealand White rabbits. Therefore, the present study aimed to investigate the changes in renal structure induced by cypermethrin exposure to rats and to highlight the possible protecting role of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis)* peel extracts.

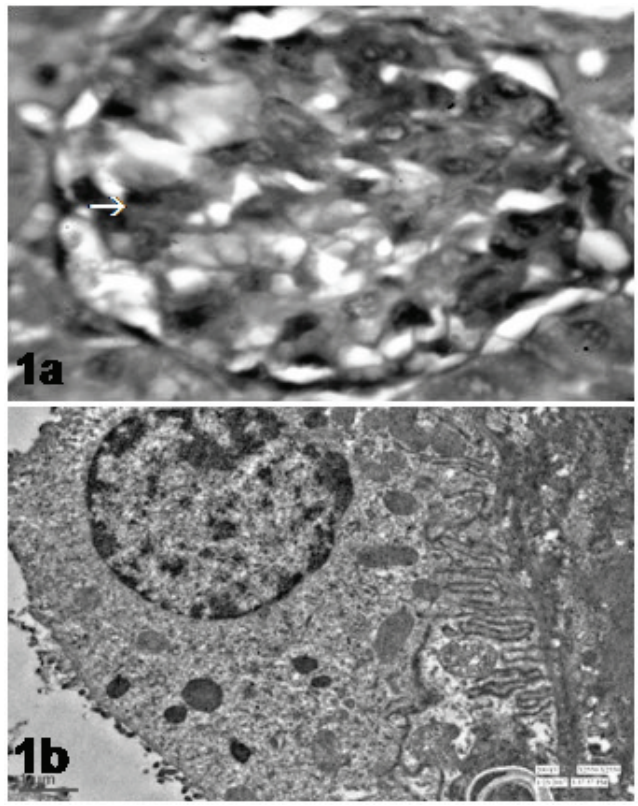

Figure 1: Kidney of control rat (a) showing glomerulus (arrow) HE x 500., (b) electron micrograph of tubule.

2. Materials and Methods

Male Wistar rats (115-130 g) were accommodated in labeled polypropylene cages having steel grid tops under natural photoperiod. Rats were acclimatized for two weeks prior to the start of the experiment. Rats were maintained on the standard laboratory feed and water *ad libitum* throughout the acclimation and experimental periods. The study was permitted by Ethics Committee of the DDU Gorakhpur University, India (F.Sc. 9008/DIS/3-4-2014).

After acclimatization the rats were divided into six groups (A—F, each group contained 20 animals). Following treatments were given daily to these groups at 08:00 each day throughout the experiment:

Group A: Control

Group B: CYP-treated: Rats received daily cypermethrin (25 mg/ kg body wt)

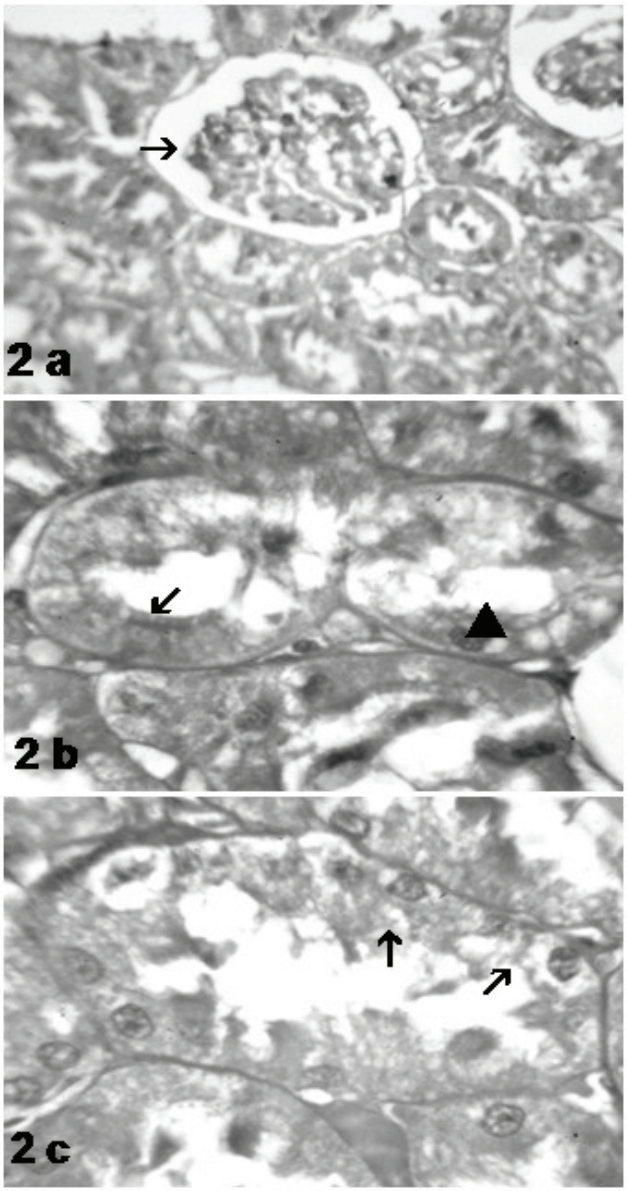

Figure 2: Kidney of 15 day cypermethrin exposed rat showing (a) Shrunken glomerulus (arrow) HE x 200, (b) hypertrophy of tubular epithelium (arrow) and obliterated lumen (arrow head) HE x 500, (c) **T**ubular degeneration (arrows) HE x 500.

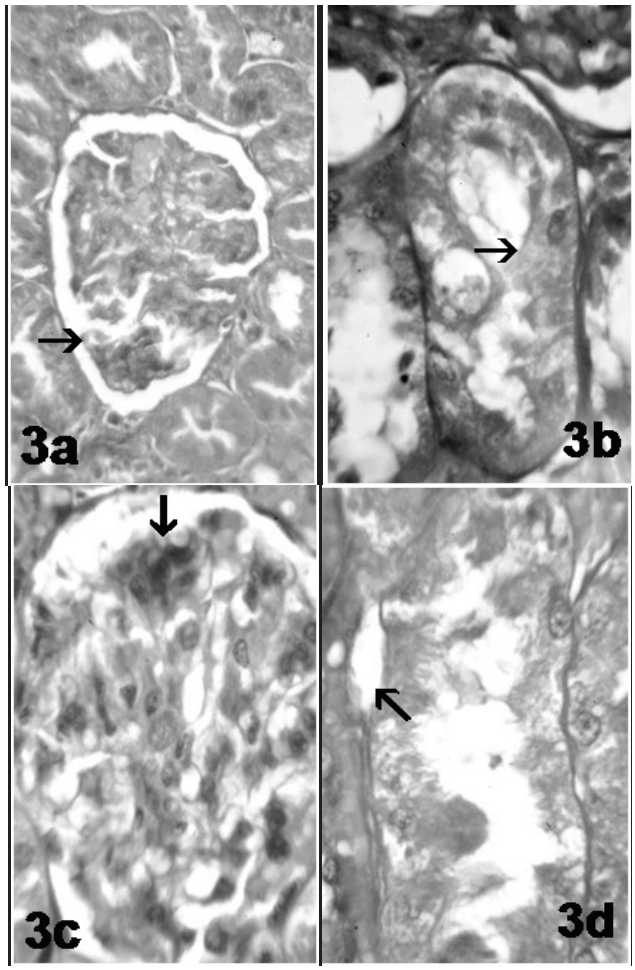

Figure 3: Kidney of 30 day cypermethrin exposed rat showing (a) Shrunken glomerulus (arrow) HE x 500, (b) Kidney tubule showing hypertrophy of epithelium (arrow) HE x 500, (c) Glomerulus (arrow) exhibiting hypercellularity and reduced space between the glomerulus and Bowman's capsule HE x 500, (d) Separation of tubular epithelium from basement membrane (arrow) HE x 500.

Group C: CYP+JSE: These rats were given daily cypermethrin (25 mg/ kg body wt) and jamun seed extract (200 mg/kg body wt) simultaneously

Group D: CYP+OPE:These rats were given daily cypermethrin (25 mg/ kg body wt) and orange peel extract (200 mg/kg body wt) simultaneously

Group E: OPE: Rats received daily orange peel extract (200 mg/kg body wt)

Group F: JSE: Rats received daily jamun seed extract (200 mg/kg body wt)

Dose of CYP used in this study has been selected considering the doses used earlier by other investigators—(i) 40-120 mg/kg b wt [8], (ii) 30 mg/ kg b wt [14] and (iii) 21.5-85 mg/kg b wt [30]. The dose of jamun seed extract used in this study has been selected on the basis of doses used by earlier workers – (i) 250 mg/kg b wt [31], (ii) 200-800 mg/kg b wt [32] and (iii) 200 and 400 mg/kg b wt [33]. Dose of orange peel extract used in this study has been selected considering the doses used earlier by other investigators—(i) 125, 250 and 500 mg/kg b wt [34], (ii) 100, 200 and 400 mg/kg b wt [35] and 200 mg/kg b wt [22].

Rats (10 from each group) from all the groups were sacrificed 24 h after last dose on 15^{th} and 30^{th} day after initiation of the experiment under light ether anesthesia Animals were fasted overnight before sacrifice. Details regarding the preparation of jamun seed and orange peel extracts have been given by Srivastava et al. [7].

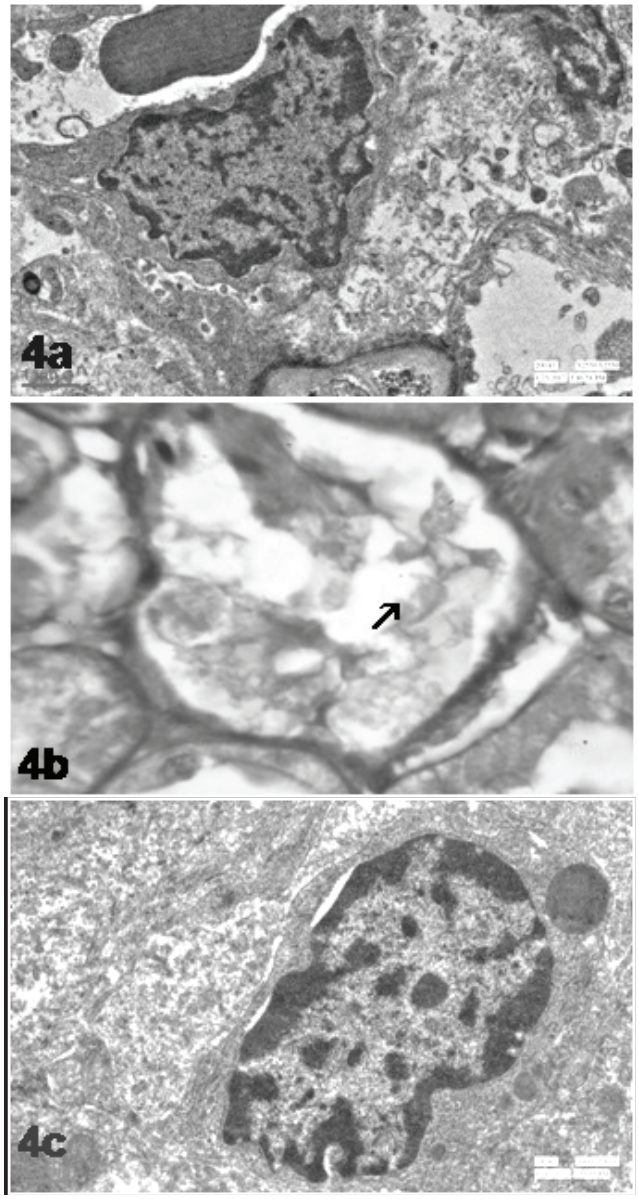

Figure 4: Kidney of 30 day cypermethrin (a and b) and cypermethrin and jamun seed extract (c) exposed rat showing (a) Electron micrograph displaying degeneration of tubular nucleus, (b) degeneration of glomerulus (arrow) HE x 500, (c) Electron micrograph exhibiting degeneration of tubular nucleus.

Kidneys were fixed in Bouin's fluid and processed with routine histological method and sections (6 µm) were stained with hematoxylin and eosin (HE). For Electron Microscopic studies, small pieces of kidney were fixed in paraformaldehyde and glutaraldehyde mixture for 4 h at 4 ºC, washed with phosphate buffer and stored at 4 ºC. These tissues were processed with EM (Model TECNAI-G20, S-Twin, HR-TEM, FEI Company, The Netherlands) at Sophisticated Analytical Instrument Facility, All India Institute of Medical Sciences, New Delhi, India.

3. Results

In control rats kidney, when stained with HE, revealed that it is made up of numerous nephrons. Each nephron is divisible into a dilated portion, the renal corpuscle; the proximal tubule; loops of Henle and the distal tubules. In the renal corpuscles there is present a tuft of capillaries, the glomerulus which is surrounded by the Bowman's capsule (Fig. 1a). There is space known as urinary space between the glomerulus and Bowman's capsule (Fig. 1a) The proximal tubule is lined by simple cuboidal (Fig. 1b) or columnar epithelium and the distal tubule is lined by simple cuboidal epithelium.

In 15 day CYP (group B) treated rats the glomeruli at few places are seen shrunken thus the urinary space between Bowman's capsule and glomerulus is increased (Fig. 2a). Few tubules are dilated. Hypertrophy of epithelial cells has been noticed in proximal and distal tubules (Fig. 2b). Lumina of few tubules are obliterated (Fig. 2b). In CYP treated rats epithelium of the kidney tubules show necrosis (Fig. 2c). In CYP+JSE (group C) and CYP+OPE (group D) treated rats for 15 day, the kidney exhibit changes similar to those as noticed in cypermethrin exposed rats—shrunken glomeruli, increased urinary space, dilatated tubular lumina, hypertrophy of kidney tubules, obliterated lumina and necrosis. Kidney of rats treated for 15 day with OPE (group E) and JSE (Group F) have not shown any remarkable histological change.

The kidney of 30 day CYP (group B) treated rats reveal shrunken glomeruli at few places (Fig. 3a). Hypertrophy of the tubular epithelium cause congestion of tubules (Fig. 3b). At few places the cellularity of glomeruli is increased thus there exist no space between the Bowman's capsule and glomerulus (Fig. 3c). The tubules are dilated and exhibit separation of epithelial cells from the underlying basement membrane (Fig. 3d). Degenerated kidney tubules with necrotic nuclei in the lumina are also visible. Severe tubular degeneration is also noticed at some places (Fig. 4a). Degenerated glomeruli containing amorphous eosin-positive material are also encountered (Fig. 4b). Few renal tubular cells appeared foamy, vacuolated and displayed ragged appearance. In CYP+JSE (group C) and CYP+OPE (group D) treated rats for 30 day the kidney displayed increased cellularity in the glomerulus thus decreasing the urinary space. In these groups shrunken glomeruli and degeneration of glomeruli are not visible. Tubular degeneration is noticed (Fig. 4c) but no degenerated nuclei in tubular lumina are seen. In OPE (Group E) and JSE (group F) treated rats for 30 day no histological changes in kidney are seen.

4. Discussion

Histological alterations in the kidney have been noticed in CYP challenged rats which are – shrinkage of glomeruli,

tubular dilation, hypercellularity in glomeruli, tubular epithelium hypertrophy, degeneration of glomerulus and renal tubules and deposition of eosin-positive substances in the glomerulus and renal tubules. Shrinkage of glomerulus as observed in cypermethrin exposed rats is in conformity with the findings of other investigators who have also recorded glomerular shrinkage in rats after exposure to various toxicants –paraquat [36] cadmium [37] and chlorpyrifos [38].

Renal tubules of CYP treated rats exhibit dilation. Similar findings have been noticed in other vertebrates after exposure to various toxicants – lead [39, 40], cadmium [37, 41], fenthion [42], fenitrothion [43], endosulfan [44], chlorpyrifos [38, 45], fluoride [46], landfill leachates containing toxic metals [47] and microcystin LR [48–50].

In the foregoing study, tubular degeneration has been noticed in CYP challenged rats. This derives support from the observations of earlier workers who have also reported tubular degeneration in animals exposed to toxicants – microcystin LR [48, 49, 51-56], chlorpyrifos [38, 45], lead [40, 57, 58], cadmium [37, 41, 59-65], cypermethrin [66, 67], fluoride [46], metal mixture [68], paraquat [36, 69,70], fenthion [42] and carbon tetrachloride [71]. In contrast to these reports no histological alterations have been noticed in bifenthrin exposed fish kidney [72].

In CYP exposed rats degenerated cells have been encountered in tubular lumina. Similar findings have also been reported earlier by few investigators –Brzoska et al. [62] (rats exposed to cadmium), Shashi et al. [46] (rabbits exposed to fluoride), Hooser et al. [48](rats exposed to microcystin), Suput [49] (rats exposed to microcystin), Almansour et al. [40] (quail exposed to fluoride), Tripathi and Srivastav [38] (rats exposed to chlorpyrifos). Tripathi and Srivastav [37] (rats exposed to cadmium) and Xiping et al. [50] (mice exposed to microcystin).

Cypermethrin treated rats revealed glomerular hypertrophy and hypercellularity. This is in concordant with the reports of other workers who have also encountered glomerular hypertrophy in toxicant treated quail (lead – [40]), rat (cadmium – [37, 44, 60, 62, 63] and rabbit (fluoride – [46]). Degenerated glomeruli and deposition of eosin-positive substances have been noticed in cypermethrin treated rats. This is in similarity with the findings reported from toxicant exposed fish [45, 59, 73, 74] and rat [37, 38, 49, 53, 70, 75]. Amorphous substances in glomeruli and tubules suggest the incapability of kidney to counter the accumulated residues resulting from cypermethrin induced metabolic and structural alterations.

Phytonutrients present in OPE and JSE may be beneficial for the organisms who are under severe oxidative stress as these phytonutrients have been reported to increase superoxide dismutase (SOD), glutathione–*S*–transferase (GST), total glutathione (GSH), catalase (CAT) and vitamin E. These supplementations should be provided over time and not as a single administration.

From the present study it can be concluded that CYP caused histological alterations in the kidney of rats. These alterations can be protected by providing OPE and JSE.

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Competing Interests

The authors declare no competing interests.

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