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RESEARCH ARTICLE

Effect of cinnamon on cypermethrin-induced nephrotoxicity in albino rats

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Abstract

The present work studied the effect of cinnamon on kidney injury induced by the pyrethroid insecticides,cypermethrin in albino rats. Animals were divided into 4 groups. Group 1: control, Group 2: given cinnamon (200mg/kg b.w), Group 3: given cypermethrin at a dose level 1/10 LD_{50} of for 6 weeks, Group 4: given cypermethrin and cinnamon. Kidney cortex of cypermethrin-treated rats showed many histopathological alterations. The renal tubules lost their characteristic , the glomeruli were degenerated and the renal blood vessels were congested. The intertubular spaces were infiltrated by inflammatory leucocytic cells. Biochemical results showed that cypermethrin caused elevation in serum creatinine and urea. Moreover ,malondialdehyde (MDA) elevated and the antioxidant enzymes (SOD, CAT) decreased in kidney of cypermethrin-treated animals. Treating animals with cypermethrin and cinnamon led to an improvement in the histological structure of the kidney together with significant decrease in levels of creatinine and urea. Renal MDA was decreased and SOD and CAT were increased. The present results indicated that cinnamon has ameliorative effect against kidney damage induced by cypermethrin and this may be mediated by its antioxidant activity.

Introduction

Plants and their extracts have been investigated in the recent scientific developments throughout the world, due to their potent antioxidant activities. Many of these extracts were found to exert therapeutic effects against different diseases. Cinnamon plant (*Cinnamomum vernum*) with the generic name Cinnamon is one of the oldest medicinal plants used in traditional medicine and is used as flavoring pastries and foods. Cinnamon has anti-bacterial and anti-fungal properties (Nir et al. 2000). It is also used to treat nausea and diarrhea and in wound healing (Kamath et al. 2003). Khan et al.(2003) reported that cinnamon improves glucose and lipids of people with type 2 diabetes. It also showed anti-inflammatory (Tung et al., 2008), antioxidant (Su et al., 2007) and hypotensive effect (Preuss et al., 2006). Eidi et al. (2012) reported that cinnamon ethanolic extract had hepatoprotective, curative and antioxidant effects against CCl_4-induced liver injury in rats.

The increased uses of pesticides in agriculture have introduced serious hazards to the human beings and their livestock. Prolonged exposure to some of these chemicals causes disturbance in the physiological activities beside other pathological features (Kulkarni and Hodgson, 1980). Cypermethrin is a synthetic pyrethroid insecticide used to kill insects on cotton and lettuce, and to kill cockroaches, fleas, and termites in houses and other buildings (Cox,1996). Cypermethrin residues have been found in milk from cows wearing cypermethrin-impregnated ear tags (as a horn fly control measure) (Braun et al.1985). In countries where agriculture is labor intensive, agricultural workers are exposed to cypermethrin. Chen et al.(19991) reported that over 25 percent of the workers in Chinese cotton fields exhibited symptoms of pyrethroid (including cypermethrin) poisoning. Long-term feeding studies with laboratory animals have shown that cypermethrin causes adverse effects. In rats, it caused reduced growth rate and

increased liver weight. In mice, it caused reduced weight gain, mild anemia, and increased liver weight. In dogs, it caused loss of appetite, incoordination, and tremors (WHO,1989). Patel et al. (2006) reported that cypermethrin induces systemic genotoxicity in mice as it causes DNA damage in vital organs like brain, liver, kidney, apart from that in the haematopoietic system. The present work studied the effect of cinnamon on kidney injury induced by cypermethrin in albino rats.

Materials and Methods

Preparation of cinnamon extract

The plant materials were obtained from the local market. Shade dried cinnamon bark was milled and extracted using ethanol 80 % in Soxhlet apparatus for 8 h. Then, the extract was evaporated to dryness and the final dry extract was stored in dark at -20 °C until used for the experiments. The powder was dissolved in saline and was given to rats at a dose of 200 mg/kg b.w.

Cypermethrin

Commercial cypermethrin [a-Cyano-(3-phenoxyphenyl)methyl(±)-cis/trans-3-(2,2-dichlorovinyl)2,2dimethyl-cyclopropanecarboxylate], was used at a dose level of 1/10 LD_{50} (5.5 mg/kg b.w.) dissolved in corn oil.

Animals

Sexually mature male Wistar albino rats weighing 150 ± 10 g were used in the present study. Animals were kept in the laboratory under constant temperature (24 ± 2°C) throughout the experimental work. They were maintained on a standard rodent diet composed of 20% casein, 15% corn oil, 55% corn starch, 5 % salt mixture and 5% vitaminized starch. Water was available *ad libitum*. Maintenance of animals and experimental procedures was approved by the animal ethical committee in accordance with the guide for care and use of laboratory animals. Animals were divided into 4 groups:

Group-1. Animals of this group served as a control group.

Group-2. Animals of this group were orally administrated cinnamon extract at a dose level of 200 mg/kg b. w. 5 days / week for 6 weeks.

Group-3. Animals of this group were orally given cypermethrin at a dose level of 1/10 LD_{50} (5.5 mg/kg b.w.) 5 days / week for 6 weeks.

Group-4: Rats were given 1/10 LD_{50} of cypermethrin and cinnamon extract 5 days/ week for 6 weeks.

Histological Study

Animals were dissected and their kidneys were removed. For histological preparations, the kidney was fixed in 10% neutral formalin, dehydrated, cleared and embedded in paraffin wax. Paraffin sections of 5 microns thickness were prepared and stained with Ehrlich's haematoxylin and eosin.

Biochemical assays

For biochemical study sera were obtained by centrifugation of the blood samples and stored at 2O°C until assayed for the biochemical parameters. Creatinine and urea were estimated using the methods of Henry (1974) and Patton and Crouch (1977), respectively. In kidney tissue samples, the extent of lipid peroxidation was estimated as the concentration of thiobarbituric acid reactive product (malondialdhyde) according to (Ohkawa et al., 1979). Superoxide dismutase activity was measured using the methods of Rest and Spitznagel (1977). The principal of this method depends on the ability of SOD to inhibit the power of phenazine methosulphate mediated to reduce the nitroblue tetrazolium. Catalase activity was determined from the rate of decomposition of H_2O_2 (Aebi et al., 1974)**.**

Statistical analysis

Data were expressed as mean values ± SD and statistical analysis was performed using one way ANOVA to assess significant differences among treatment groups. The criterion for statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS statistical version 16 software package (SPSS® 4 Inc., USA).

Results

1. Histological results

Histological examination of the kidney cortex of control rat revealed normal structure of renal corpusles, convoluted tubules (proximal and distal) and collecting ducts. The renal corpuscle consists of a tuft of capillaries, the glomerulus , surrounded by a double walled epithelial capsule, Bowman's capsule. The proximal convoluted tubule is lined by simple cuboidal or columnar epithelium. Its cells have an acidophilic cytoplasm. The distal convoluted tubule is lined by simple cuboidal epithelium (Fig.1a). No histopathological alterations were observed in cinnamon -treated animals. Examination of kidneys of rats treatment with cypermrthrin for 4 weeks showed significant changes. The cortex showed dilated and congested blood vessels (Fig. 1b). Blood hemorrhage appeared in the intertubular spaces (Fig.1c). The intertubular spaces were infiltrated by inflammatory leucocytic cells (Fig. 1d). After 6 weeks, most of the renal tubules rendered so highly damage that they have almost lost their characteristic appearance and their lumen filled with amorphous cellular derbis (Fig.2a).The walls of Bowman's capsule were eroded and the glomeruli were fragmented and atrophied (Fig.2b). Treating animals with cypermethrin and cinnamon revealed an improvement in the histological appearance of the cortex and most of the renal tubules appeared normal (Fig.2c).

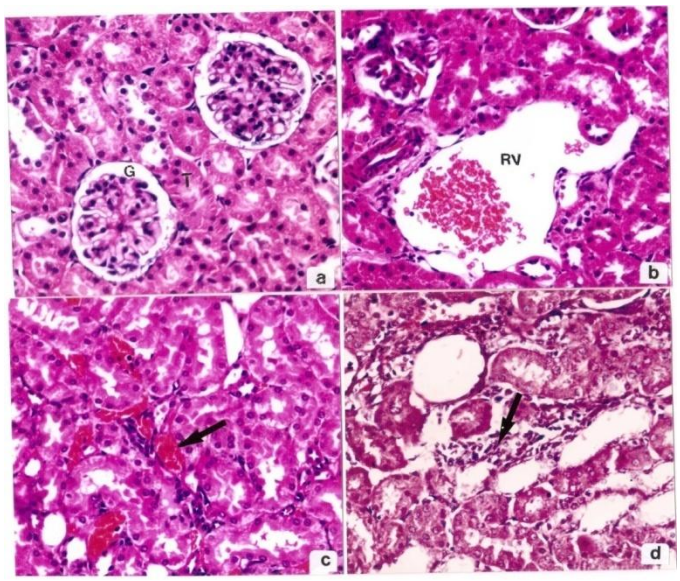

Fig.1. a. Section in kidney cortex of a control rat showing glomeruli (G) and renal tubules (T),
b. Section in kidney of a rat treated with cypermethrin for 4 weeks showing enlarged and congested renal vessel (RV),
c. Kidney section of a treated rat showing intertubular blood haemorrhage (arrow),
d. Kidney section of a treated rat showing leucocytic infiltrations (arrow), (H&E, X400).

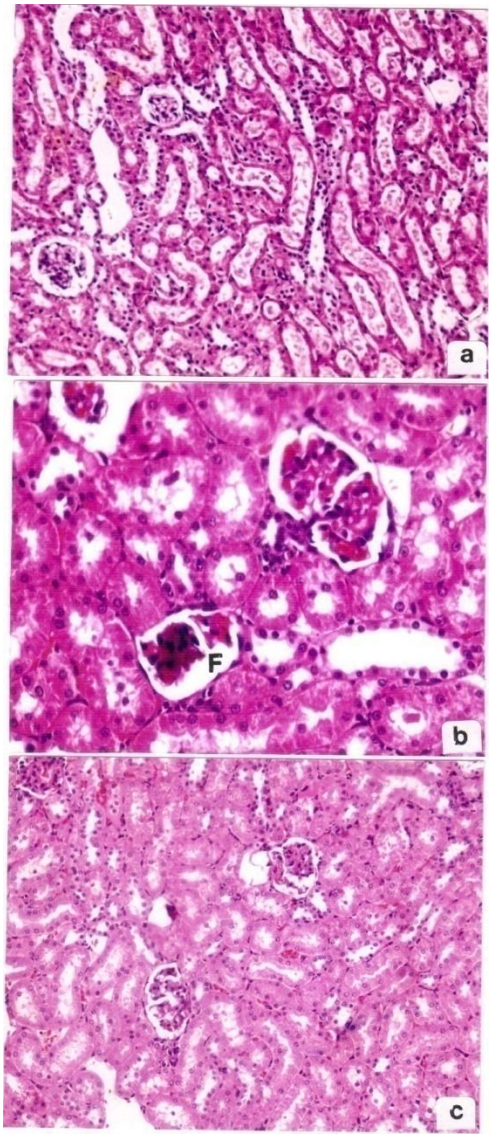

Fig.2. a. Section in kidney of a rat treated with cypermethrin for 6 weeks showing renal lumens filled with amorphous cellular derbis,

b. Kidney section of a treated rat showing fragmented glomerulus (G),

c. Kidney section of a rat treated with cypermethrin and cinnamon showing an improvement in renal tubules and glomeruli, (H&E, X400).

2. Biochemical results

a. creatinine and urea

Data in table 1 showed that there is no significant difference in values of creatinine and urea between control and cinnamon groups, after 6 weeks of the treatments. Treating animals with cypermethrin caused significant elevation ($p<0.05$) in creatinine and urea. On the other hand, significant decrease was recorded after treatment with cypermethrin and cinnamon.

b.The oxidative stress markers

The activity of MDA in the cypermethrin -treated group was significantly ($P<0.05$) increased when compared to the control animals. Treatment with cinnamon decreased the level of MDA compared to the cypermethrin treated rats (Fig.3) Renal SOD activity was decreased significantly ($p<0.05$) in the cypermethrin treated-animals compared to control group. Treatment with cinnamon elevated the SOD levels as compared to the cypermethrin -treated animals (Fig.4). The CAT level was reduced significantly in the cypermethrin treated group as compared to the control group ($p<0.05$). However on treatment with cinnamon the CAT level was found to be enhanced significantly ($p<0.05$) (Fig.5).

Table (1). Change in creatinine and urea nitrogen in sera of rats treated with cypermethrin alone or in combination with cinnamon

Animal group	creatinine (mg / dl)	urea nitrogen (mg / dl)
Control	0.53 ± 0.01	35.50 ± 1.8
Cinnamon	0.51±0.02	34.16 ± 2.2
Cypermethrin	0.86 ± 0.01*	59.33 ± 2.4*
Cypermethrin+cinnamon	0.55±0.02**	38.50±3.2**

-Values are expressed as (Mean ±SD).

- (*) Significant increase at $P < 0.05$ compared with control group
- (**) Significant decrease at $P < 0.05$ compared with cypermethrin group

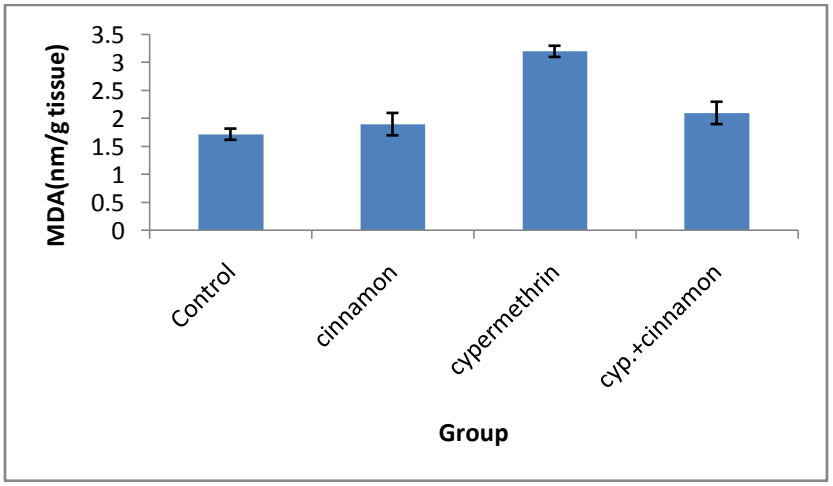

Fig.3. Effect of different treatments on MDA in kidney of rats.

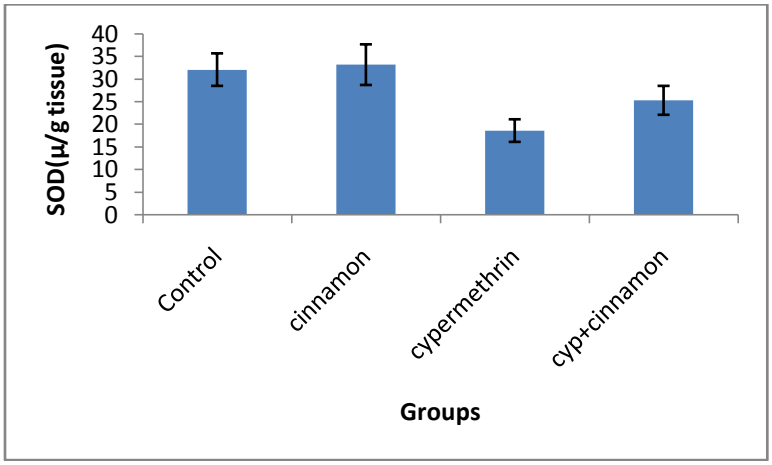

Fig.4. Effect of different treatments on SOD in kidney of rats.

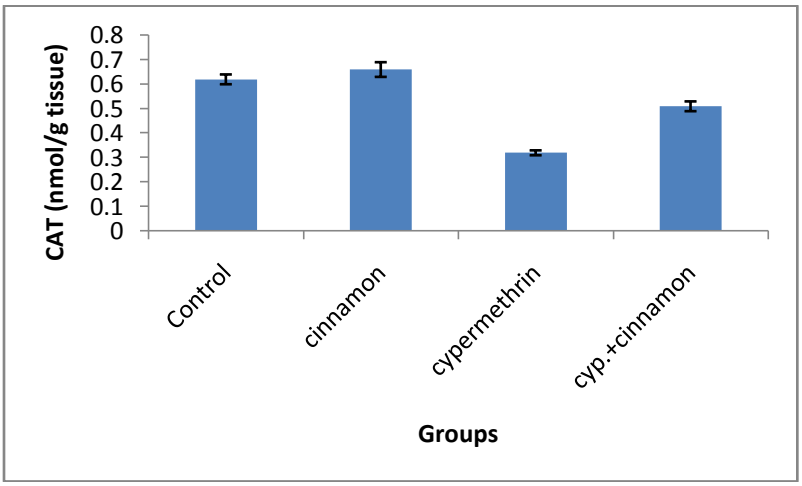

Fig.5. Effect of different treatments on CAT in kidney of rats.

Discussion

The present results showed that cyperimethrin induced many histopathological alterations in the kidney of rats. The renal tubules lost their characteristic appearance and their lumens were filled with amorphous cellular derbis. The glomeruli were degenerated and the renal blood vessels were congested. Morover, creatinine and urea were elevated in sera of cypermethrin-exposed rats. Similarly, Abdo et al. (2012) reported that cypermethrin caused histological and degenerative effects in kidney of rats. Also, the levels of urea and creatinine were significantly increased. Cypermethrin administration was found to cause elevation of blood biochemical markers in liver (ALT, AST) and kidney (creatinine, urea) (Sankar et al.2012). Inayat et al. (2007) reported that dermal exposure of cypermethrin to rats caused congestion of vessels, diffuse and focal lymphocytic infiltration, odema and necrosis of proximal tubules of the kidney. Lakkawar et al.(2004) reported that cypermithrin-treated rabbits showed histopathological alterations including coagulative necrosis, perivascular/periductal fibrocellular reaction along with

mononuclear cellular infiltration in the liver, mucosal eruptions with inflammatory reaction in the gastrointestinal tract and hyalinization of the tubular epithelium of the kidneys. Yavasogluet al.(2006) applied cypermethrin dermally to rats for 28 days in two doses, 50 mg/kg and 250-mg/kg-body weight. Changes in the kidney were observed after administration of 250mg/kg. These included degenerative changes in the epithelial cells of the proximal tubules such as thickening of the basal lamina, widening of endoplasmic reticulum and swelling of mitochondria. Administration of cypermethrin to mice caused infiltrations of mononuclear cells between the proximal tubules, increase in the number and size of autophagous vacuoles and accumulation of electron dense bodies. In addition, a clear widening of the Golgi structures was noted (Luty et al.2000).

The current results showed that cypermethrin treatment caused elevation in MDA and decrease of CAT and SOD. In accordance with this results, oral administration of cypermethrin was found to produce significant oxidative stress in cerebral and hepatic tissues of rats, as was evident by the elevation of the level of thiobarbituric acid reactive substances (TBARS) in both tissues (Giray et al.2001). Atesshin et al. (2005) reported that MDA,the indicator of lipid peroxidation increased in brain, liver and kidney of cypermethrin-treated rats. They added that cypermethrin caused an increase in GSH-Px activity in liver and erythrocytes while it caused a decrease in CAT activity in all tissues,except erythrocytes. Sharma et al.(2014) reported that Cypermethrin treated rats showed elevation in lipid peroxidation and inhibition in glutathione superoxide dismutase, catalase, glutathione-S-transferase, glutathione reductase , glutathione peroxidase , total protein and acetylcholinesterase activity in rat brain. From the obtained results, it is postulated that accumulation of cypermethrin increased oxidative stress with increase in ROS.

Regarding the effect of cinnamon, animals treated with both cypermethrin and cinnamon revealed an improvement in histopathological and biochemical alterations when compared with animals given cypermethrin alone. In agreement with these results, Tanomand and Najafian (2013) reported that cinnamon bark extract was able to protect against the nephrotoxicity induced by gentamicin in rats as indicated by decrease of creatinine, uric acid and urea. The nephroprotective effects of cinnamon were recorded by El-Yamani (2011) who observed decreased serum urea and creatinine levels in diabetic rats treated with cinnamon. Mishra et al. (2010) studied the effect of cinnamon oil against diabetic nephropathy. Histological studies of the kidney proved the protective effect of cinnamon oil by reducing the glomerular expansion, eradicating hyaline casts, and decreasing the tubular dilatations. Ullah *et al*. et al.(2013) observed that cinnamon significantly attenuated aminoglycosides-kidney toxicity by improving the urea, creatinine, uric acid, urinary protein levels and histopathological alterations of the kidneys.

Oxidative stress is presently accepted as a causative factor in the development of many diseases. On the other hand, antioxidant dietary intakes could be a possible method to reduce the incidence of these diseases. The present results showed that cinnamon decreased the MDA, the lipid peroxidation marker, and increased the enzymes, SOD and CAT. Cinnamon and its extracts were found to have antioxidant activity. Cinnamon, a natural product with a long history of safety, is rich in polyphenolic components that have been shown to possess in vitro antioxidant activity (Shobana and Naidu,2000). Roussel et al. (2009) reported that cinnamon extracts, at 500 mg/d for twelve weeks, decreased oxidative stress and improved impaired fasting glucose. Cinnamon extracts exhibit a protective capacity against irradiation induced lipid peroxidation in liposomes, and quench hydroxyl radicals and hydrogen peroxide (Murcia et al., 2004). Moselhy and Ali (2009) reported that ethanolic extract of cinnamon has potent hepatoprotective action against CCl_4 by lowering the MDA level and elevating antioxidants enzymes activities (SOD and CAT).

It was reported that cinnamon bark contains flavonoids, glycosides, coumarins, alkaloids, anthraquinone, steroids, tannins and terpenoids (Shihabudeen et al., 2011). Numerous studies have suggested that flavonoids commonly function as antioxidants (Gould and Lister, 2006) and this antioxidant capacity is attributed to the high reactivity of the hydroxyl substituent, with the number of hydroxyl groups on the B-ring being correlated with ROS scavenging capability (Heim et al., 2002). In conclusion, the present results indicated the nephroprotective of cinnamon which attributed to its antioxidant effects.

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