RENOPROTECTIVE EFFECT OF TAXIFOLIN AND/OR VITAMIN C ON DIAZINON-INDUCED RENAL INJURY IN RATS

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Insecticides have come to be used in a wrong way and uncontrollably, leading to an increase in the incidence of chronic diseases such as chronic nephropathies, diabetes, and other metabolic disorders. Objective: To evaluate the protective effect of Taxifolin and/or vitamin C against Diazinon-induced renal dysfunction. Methods: Thirty-six female rats were divided into six groups gavaged orally for 30 days. Group 1 received 20 mg/kg DZN. Group 2 received 25 mg/kg Taxifolin, 100 mg/kg vitamin C, and then 20 mg/kg DZN. Group 3 received 25 mg/kg Taxifolin and then 20 mg/kg DZN. Group 4 received 100 mg/kg vitamin C and then 20 mg/kg DZN. Group 5 received 25 mg/kg Taxifolin and then 100 mg/kg vitamin C. Finally, group 6 received distilled water. In the end, the rats were sacrificed and their blood and kidneys were collected for biochemical analysis and histopathology. Conclusion: Sub-acute administration of Taxifolin and vitamin C provides a renoprotective effect against oxidative stress induced by DZN.

INTRODUCTION

In Iraq and elsewhere in the world the uses of insecticides have come to be used in the wrong way and uncontrollably leading to the unwanted correlation between exposure to these substances and an increase incidence of chronic diseases such as chronic nephropathies, diabetes, cardiovascular disease, and other metabolic disorders. Chronic exposure to insecticides may be even more hazardous as it can lead to different types of cancers. Diazinon (DZN) is used in agriculture worldwide as an efficient insecticide is known by World Health Organization as a moderate hazard Class II chemicals1,2, and is a phosphonothioate insecticide with a pyrimidine ring attached to it3. Irreversible inhibition of cholinesterase is a unique feature of DZN, which at high doses can lead to animal death4.

There are different routes of exposure to DZN. It can be absorbed through the digestive system by consuming of pesticide-contaminated food, or absorbed via the skin and respiratory tract due to high lipid solubility to penetrate these organs5. The oxidation process which is essential for our aerobic life and metabolism involve electron transfer between two atoms. Problems may occur when DZN oxidizes inside the body by cytochrome P450 enzymes, more potent toxic metabolite may be formed in the liver such as diazoxon which may cause an unpaired electron flow, generating free radicals and reactive oxygen species6, which cause lipid peroxidation and phospholipid degeneration, and subsequently lead to cellular damage7,8. The screening of natural flavonoids for their bioactivity as antioxidants is usually carried out by determining of their ability to act as chain breaking antioxidants, though their direct free radical-scavenging activity as hydrogen- or electron-donating compounds9.

Oxidative stress is a major mechanism of DZN-induced cytotoxicity, DZN reduces the total antioxidant capacity of the cell by inhibiting vital antioxidant enzymes such as plasma glutathione peroxidase (GSH-Px),...
superoxide dismutase, and catalase. The other oxidative effects of DZN include augmenting the activity of NADPH oxidase inducible nitric oxide synthase and inhibiting the activity of glutathione reductase and glutathione transferase. From another perspective of view, we find that TNF-α could directly induce toxicity in glomerular and hepatic tissue. There is a reciprocal relationship between oxidative stress and TNF-α expression, TNF-α promotes oxidative stress. Exposure to DZN increases the expression of cyclooxygenase II and NF-κB, which is upstream of TNF-α. Therefore, increased TNF-α expression may directly affect DZN intoxication or may indirectly affects it through oxidative stress.

Citrus Flavonoids have multiple benefits, including free radical scavenging, anti-inflammatory action, and cytoprotective property. Taxifolin is a natural flavonoid found in nature. Modern pharmacological studies have shown that it can improve microcirculation and regulate immunity and has antioxidant, anti-bacterial, anti-inflammatory, and antiviral actions.

Taxifolin is a promising future component of dietary supplements as it is rich-antioxidant functional groups, it is also known as dihydroquercetin and is commonly found in Pseudotsuga Taxifolia, Dahurian larch, syn Larix dahirica Turoz, onions, citrus fruits, milk thistle, and pine bark. Ascorbic acid (vitamin C) is a broad-spectrum antioxidant effective against a wide variety of ROS. Citrus fruits, red and green peppers, berries, tomatoes, spinach, and broccoli are rich in vitamin C. Humans, unlike most mammals, cannot synthesize vitamin C and hence derive it from their diet. At physiological concentrations, vitamin C is a potent free radical scavenger that protect the cells against oxidative damage caused by ROS. The vitamin C antioxidant effect reduces the formation of potentially damaging ROS; instead, resonance-stabilized and relatively stable ascorbate free radical serves as a one-electron donor. Recent studies have shown that vitamin C protects against memory deficits associated with several medical condition, such as Alzheimer’s disease.

Aim of the study
Nephrotoxicity may occur in various clinical situations, following a total or regional injury to the kidney. This study was conducted to determine the protective effects of different antioxidants, such as Taxifolin, vitamin C, and their combination, against DZN-induced experimental renal injury.

MATERIALS AND METHODS

Materials
Biazinon 10 EC (Endimaj for specialized chemical & pharmaceutical industries Co/Jordan), as a 10% active ingredient formulation and diluted in corn oil to get an emulsion of the final concentration. Taxifolin 10 mg tablet (Super Smart Co./UK), Vitamin C (ALPHA CHEMIKA/India) both are dissolved in distilled water for final use.

Animals
Thirty-six adult Sprague-Dawley female rats with (weights of 180-270 gm) were involved in this experiment. The rats were purchased from College of Science /Kufa University and acclimated for a week before starting experiment. Plastic cages with standard bedding and each cage had three animals. All the experiments in this study were completed in adherence to the National Institute of Health Guidelines for using Laboratory Animals (86/609/EEC) and the ethical approval was obtained from the Pharmacy College /University of Basrah / Ethics Committee 3/5/115 in September/2020.

The animals were hosted and fed in groups under appropriate conditions at room temperature of 25± 3 °C and humidity, with regular day-night rhythm 12 hrs. light /12 hrs. dark and fed a pellet diet and always supplied drinking water.

Experimental work
Thirty six rats were divided randomly into 6 groups of 6 rats in each group. The rats’ weights were measured at the start of the experiment then measured every week until they were euthanized. The tail of each rat was marked with it is weight to distinguish it from the other rats. They were given an accurate dose via oral gavage for 30 days. The animals in Group 1 represented the DZN induced toxicity on the kidney that received DZN (20 mg/kg). Group 2 received co- administered Taxifolin (25 mg/kg), and vitamin C (100
mg/kg) before being given DZN (20 mg/kg). Group 3 received Taxifolin (25 mg/kg) before DZN (20 mg/kg) administration. Group 4 received vitamin C (100 mg/kg) before DZN (20 mg/kg) administration. Group 5 was positive Control 1, and it received co-administered Taxifolin (25 mg/kg) and vitamin C (100 mg/kg) to exclude the effects of protective compounds. The last group, Group 6 was negative Control 2, and it received only corn oil and distilled water at volumes equal to those used for the dilution of substances in all the other groups. Dose selection was in accordance with previous articles 13,17, and 18.

Water and food intake were measured daily for 30 days, and the vital signs of the rats were daily reported. At day 31, the rats were euthanized after an entire night of fasting under chloroform anesthesia. Blood was withdrawn from posterior vena cava, and serum was collected for biochemical analysis. Both kidneys were removed surgically and weighted for biochemical and histopathological investigations to assess the derangement in the functioning of kidney. The relative kidney weight (RKW) was calculated according to the following equation:

\[ \text{RKW} = \left( \frac{\text{kidney weight}}{\text{rat weight}} \right) \times 100. \]

**Biochemical assays**

Serum concentrations of urea and creatinine were analyzed via the spectrophotometric technique using a COBAS INTEGRA® 400 plus. The basic principles of measurement depend on conversion of urea to form ammonium and carbonate by urease enzyme and the established determination of hydrogen peroxide after conversion of creatinine with the aid of creatininase enzyme. For glutathione peroxidase measurements, one kidney was homogenized using specialized homogenizer with 9 ml buffer phosphate (pH 7.4) appropriate for 1 g tissue pieces (according to instruction from rat glutathione peroxidase [Gpx1] kit, Catalogue No. RDEER0274) using the ELIZA technique.

**Histopathological assessments**

One other kidney was prepared for pathological evaluation. The rats’ kidneys were fixed in 10% formalin, sectioned, and embedded in paraffin. They were then sectioned to 4-5 μm pieces and stained using hematoxylin and eosin (H&E) stain to evaluate renal dysfunction via microscopic investigation.

**Statistical analysis**

Results are expressed as Mean ± SEM. To compare treated groups with control groups, a one-way analysis of variance with Tukey post hoc was used. Values are considered significantly different at p < 0.05. The analysis was carried out using GraphPad Prism software (Version 7).

**RESULTS AND DISCUSSION**

**Results**

Abnormal signs and behaviors were reported in rats within each study group. Different symptoms of cholinergic toxicity were observed in the intoxicated Group 1, e.g., fatty diarrhea associated with abnormal-colored stool, frequent urination, reduction in general movement and reduction in food intake—especially in the last days of the study period. There were significant increase in body weights in all treated and control groups except the DZN Group 1 as seen in figure (1).

![Fig. 1: Rats weight in DZN, treated and control groups. All values are presented as mean ± SEM in each group. columns(a) represent rat weight in the starting point while columns (b) represent rat weight after 30 days of experiment, P < 0.05 representing significant difference in the same group with different periods.](image)

A significant increase in RKW was observed in Group 1 compared with remaining groups (Figure 2); this was associated with
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Glomerulus degeneration and bowman capsule dilation. Sloughing in lining of cortical renal tubules and hemorrhage may be found, contrary to the control group, as seen in the histogram in (figure 3). A significant reduction in the RKW was observed after oral administration of Taxifolin and/or vitamin C to rats; the reason may be that the protection and typical renal glomeruli architecture were significant compared with those of Control 1. Administration of Taxifolin alone showed protection associated with normal structure of glomeruli and renal tubules compared with other studied groups. Even though separate administration of vitamin C showed some protection, the bowman capsule was thicker compared with those in the control groups; this showed normal renal glomeruli and cortical tubules.

**Fig. 2:** RKW in DZN treated and control groups. All values are presented as mean ± SEM in each group.* Representing significant difference between groups $P<0.05$.

**Fig. 3:** Light micrograph of kidney with H&E x40. **Group 1:** show atrophy and degeneration of glomeruli (black arrow), dilated of bowman capsule (red arrow), sloughing and bleeding in renal tubules (blue arrow). **Group 2:** showing predominantly normal renal tubule (black arrow) was noted, as well as normal renal glomeruli (red arrow) **Group 3:** shows health and normal structure that consists of glomeruli (black arrow) and renal tubules (red arrow). **Group 4:** show the normal of glomeruli (black arrow), thickness of bowman capsule (blue arrow), and majority of renal tubules appeared normal respectively (red arrow). **Group 5:** showing normal renal glomeruli (black arrow), thickness of bowman capsule (blue arrow), and majority of renal tubules appeared normal respectively (red arrow). **Group 6:** normal control group section of kidney has showing normal glomeruli (black arrow) and renal tubules (red arrow).
The serum concentrations of some biomarkers (creatinine and urea) were assessed to evaluate renal injury induced by DZN and the possible renoprotective role of some available antioxidants (taxifolin and vitamin C). Following DZN administration in Group 1, the serum creatinine level significantly increased (figure 4), revealing the existence of renal problems and renal atrophy (figure 3). Combined treatment with Taxifolin and Vitamin C reduced serum creatinine levels significantly to concentrations comparable to that in the control groups. When vitamin C was separately administered in Group 4, the serum creatinine level did not significantly differ from that in Group 1. By contrast, a significant difference was observed compared with that of control 1, and exhibited some protection against DZN-induced renal damage. On the other hand, Taxifolin administration alone showed significant reduction in serum creatinine level with significant improvement in renal architecture as seen in histogram Figure (4).

DZN led to a significant increase in serum urea compared with those of the remaining groups. Pretreatment with Taxifolin and Vitamin C as combined or separate treatments showed a significant reduction in serum urea as seen in Figure (5).

Figure 6 summarized kidney glutathione peroxidase levels in study groups. Administration of DZN significantly decreased glutathione peroxidase (as an antioxidants biomarker) in Group 1. Treatment with Taxifolin and Vitamin C combination increased glutathione peroxidase value to an extent comparable to that observed in control groups. Administration of Taxifolin and Vitamin C separately in Group 3 and Group 4 showing significant improvement in antioxidant levels, especially with Vitamin C administration, the highest level of glutathione peroxidase with significant antioxidant capacity observed in Group 2 and Control 1 rat Groups.

Fig. 4: Effect of Taxifolin and/or vitamin C on serum creatinine levels after DZN induced toxicity in rats. All values are presented as mean ± SEM in each group.

Fig. 5: Effect of Taxifolin and/or vitamin C on serum urea levels after Diazinon induced toxicity in rats. All values are presented as mean ± SEM in each group. * Representing significant difference between groups P<0.05.

Fig. 6: Effect of Taxifolin and/or vitamin C on renal glutathione peroxidase levels after DZN induced toxicity in rats. All values are presented as mean ± SEM in each group. *, ** and *** representing significant differences between groups p<0.05.
Discussion

Human and animal exposure to DZN is rising progressively in terms of environmental levels. The present study was designed to evaluate the putative implication of subacute exposure to DZN on the kidney of rats and explore the possible protective role of Taxifolin and vitamin C.

The kidney is particularly vulnerable to the harmful effects of xenobiotics because of its metabolic and excretory processes; thus, excessive DZN exposure can result in acute or chronic nephrotoxicity. It is well known that DZN-induce cytotoxicity and oxidative stress plays a crucial role in this toxicity. This investigation and earlier in vivo and in vitro studies have shown that DZN causes lipid peroxidation, malfunctioning enzymes, and genotoxicity by increasing the formation of free radicals that interact with renal cellular macromolecules in a dose-dependent manner. This reflect the formation of ROS in rat kidneys.

In this study, DZN induced a significant (p <0.05) reduction of body weight gain in Group1 as compared other treated and control groups, the prominent symptoms in Group 1 were overall weakness and decrease in food intake, and the food consumption of this group was less than that of the control group, such alterations are typical of acetylcholinesterase inhibition, including acetylcholine buildup and subsequent activation of nicotinic and muscarinic cholinergic receptors. Our finding comes in accordance with those of other studies.

The current study found that subacute (30 days) DZN administration resulted in a considerable rise in RKW as compared to existing procedures. The evaluation of kidney weight data is a variable parameter, with some toxicologists using variations in kidney weight to detect renal toxicity. Increased kidney weight refers to edema caused by kidney dysfunction, lipid infiltration and possibly enzyme induction. These results align with Deng Y et al.’s findings in which an increase in RKW was detected after oral subacute organophosphorous administration. Contrary to our result, Majid Z et al. found that DZN decreases RKW significantly compared to RKW in control group. Histopathological findings might confirm that Taxifolin and vitamin C are responsible for maintaining nephron structural and architectural integrity in subacute DZN toxicity with many pathways, such as antioxidant properties.

Taxifolin can also protect kidney by regulating glucose, inhibiting excessive activation of the renin angiotensin aldosterone system (RAAS), improving water and sodium retention, reducing inflammatory reaction and improving disorders of glucose metabolism and water-salt metabolism in kidney through the PI3K/AKT signaling pathway. The deterioration of kidney function expressed by elevated level of creatinin and urea, which are critical measures of kidney function, was considerably higher in the DZN-induced group than in the control group. Such elevations have been attributed to oxidizing strain, pro-inflammatory activities, impacts on DNA and metabolism as a result of increasing ROS production, and decreased endogenous antioxidant enzyme activities. Co-administration of the antioxidant Taxifolin and vitamin C dramatically reduced serum creatinine and urea in the treated groups.

Creatinine and urea are primarily eliminated in urine as metabolic waste products. As a result, elevated levels of these markers after DZN exposure may indicate renal impairment. Increased serum creatinine implies a lower glomerular filtration rate, but elevated urea levels indicate abnormal renal tubular reabsorption. In earlier studies, both glomerular and renal tubular impairments were observed in response to exposure to organophosphorus.

Much research has found evidence that natural antioxidants have a beneficial effect on kidney function and protect the kidney against organophosphorus-induced injury. For example, chrysin has been demonstrated to protect against DZN-induced renal toxicity, and administration of oleuropein decreases organophosphorus nephrotoxicity.

Furthermore, DZN treatment alone lowers glutathione peroxidase levels, resulting in ROS and tissue damage, whereas Taxifolin combined with vitamin C raises the levels significantly, as free radical scavenger gives protection against DZN-induced kidney injury. The findings of this study align with results obtained by Muhammad D. et al and Mohamed A. et al, who found a clear depletion of...
glutathione peroxidase level after oral administration of DZN\textsuperscript{5,11}.

Natural antioxidant therapy is one of the most acceptable therapeutic options to prevent and slow the advancement of chronic kidney diseases and their complications, including diabetic nephropathy, inflammatory kidney damage, pyelonephritis and other renal disorders\textsuperscript{27}. It has been demonstrated that medicinal plant antioxidants prevent oxidative stress-induced kidney damage; these plants have antioxidant activities due to phytochemicals, including phenolic and carotenoid compounds.

Vitamin C provides protection to the endothelium due to its potent antioxidant effects, which neutralizes the harmful effects superoxide an ions and prevents microvascular dysfunction\textsuperscript{28}. Vitamin C inhibits ROS via quick aqueous-phase electron transfer, which reduces both neutrophil production of oxygen free radicals and subsequent lipid peroxidation. In ischemic kidneys, it also improves renal hemodynamics and lowers oxidative stress, inflammation, and fibrosis\textsuperscript{29}. Many articles provide the evidence that natural antioxidants protect the kidneys against different toxic compounds, such as Tocotrienol which has been shown to protect against renal injury induced by potassium dichromate\textsuperscript{30}; vitamin E supplementation, which has been shown to ameliorate glomerular dysfunction\textsuperscript{31} and melatonin which has a renoprotective effect as antioxidant\textsuperscript{32}. The antioxidants system of the body is complex, and antioxidants usually act as parts of complicated networks. Taxifolin and Vitamin C are both present in citrus fruit, and in this study they were used in combination to achieve the maximum antioxidant effect and hence the most effective kidney protection. In Conclusion, sub-acute oral administration of pharmacological doses of Taxifolin and vitamin C exerts renoprotective and antioxidant effects against diazinon-induced renal injury in rats.

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تقييم التأثر في التأثير المضاد للأكسدة للعلاج المركب تاكسيفولين وفيتامين ج ضد الاختلال الكولي الناجم عن الديازينون

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أن زيادة استخدام المبيدات الحشرية بطريقة خاطئة لا يمكن السيطرة عليها أدى بذلك إلى زيادة الإصابات بالأمراض المزمنة مثل اعتلال الكلية المزمن والسكري واضطرابات التمثيل الغذائي الأخرى.

الهدف من هذه الدراسة: تقييم التأثير في التأثير المضاد للأكسدة للعلاج المركب تاكسيفولين وفيتامين ج ضد الاختلال الكولي الناجم عن الديازينون. طريقة: تم تقسيم ستة وثلاثين أنثى من جرذانسبراكالي ست مجموعات (ن = 6 لكل مجموعة) وتتم تطعيمها شفويًا لمدة ٣٠ يومًا. تلقت المجموعة الأولى ٢٠ مجم/كجم من الديازينون. تلقت المجموعة الثانية ٥ مجم/كجم من تاكسيفولين. تلقت المجموعة الثالثة ٢٥ مجم/كجم من تاكسيفولين. تلقت المجموعة الرابعة ٢٠٠ مجم/كجم من تاكسيفولين. تلقت المجموعة الخامسة ٢٥٠ مجم/كجم من تاكسيفولين. وأخيرًا، تلقت المجموعة السادسة الماء المقدر. وفي نهاية التجربة، تم التضحية بالجرذان وتم جمع الدم والكليتين للتحليل الكيميائي الحيوي (الجلوتاتيونوكسيداسي) والتشريح المرضي. الخلاصة: لا إعطاء تاكسيفولين وفيتامين ج شبه الحاد له تأثير وقائي للكلي ضد الإجهاد التأكسدي الناجم عن الديازينون.