The Egyptian Journal of Hospital Medicine (Sep. 2010) Vol., 40: 350 - 364

# Low Dose Gamma Irradiation Modifies the Effect of L-Carnitine, Curcumin, Garlic Powder and Green tea Extract on Doxorubicin-Induced Nephropathy in Rats

**Rasha R. Radwan*, Esmat A. Shaban*, Hesham A. Salem and Sanaa A. Kenawy**
Department of Pharmacology and Toxicology, Faculty of Pharmacy, CairoUni.
***** Department of drug radiation research, National Center for Radiation Research and Technology, Atomic Energy Authority.

## Abstract

The possible protective potential of exposure to low dose of γ radiation in presence or absence of L-carnitine, curcumin, garlic powder or green tea extract was examined in the present study on doxorubicin (DOX)-induced experimental nephropathy in rats. Preliminary study was carried out to select the suitable dose of DOX to induce nephrotoxicity. In the current experiment 5 mg/kg, i.p. was selected as a single dose to induce nephrotoxicity during 15 days. The possible modulating effect of L-carnitine, curcumin, garlic powder or green tea extract on kidney function was examined. Animals were subdivided into three sets. Three groups of the 1st set were exposed to γ radiation at a single dose level of 0.3 Gy then received DOX, 1, 3 or 7 days postirradiation respectively. The groups of 2nd set daily received L-carnitine (40 mg/kg, i.p.), curcumin (50 mg/kg, i.p.), garlic powder (100 mg/kg, p.o.) and green tea extract (300 mg/kg, p.o.) daily for two weeks before induction of nephropathy. Groups of the 3rd set received the same doses of drugs then were injected with DOX, 1, 3 or 7 days following γ irradiation respectively. Two groups of animals, one of them received saline and served as normal and the other received DOX and served as nephropathic group were included in 1st, 2nd as well as 3rd set. Fifteen days following DOX administration, serum was collected and the animals were then sacrificed. Serum creatinine, urea and uric acid were evaluated. Data revealed that, a single DOX dose (5 mg/kg) induced marked acute nephrotoxicity manifested as significant increase in the activities of serum creatinine, urea as well as uric acid. Interestingly, pre-exposure to γ radiation at a dose level of 0.3 Gy, 1 or 3 days before DOX injection exhibited significant improvement in the above altered mentioned parameters. However, exposure to low dose radiation 7 days prior to DOX administration did not show a protective effect. Moreover, pretreatment with L-carnitine, curcumin, garlic powder or green tea extract in rats unexposed or exposed to γ radiation before DOX administration ameliorated, to a great extent, the effects induced by DOX. The present findings suggest that exposure to a single low dose of γ radiation (0.3 Gy) one day before DOX administration is a promising approach for maximizing the nephroprotective effects of L-carnitine, curcumin, garlic powder or green tea extract with minimal adverse effects of DOX.

**Key words:** doxorubicin, 0.3 Gy γ radiation, L-carnitine, curcumin, garlic powder, green tea extract, creatinine, urea and uric acid.

## Introduction

Doxorubicin (DOX) is an anthracycline antibiotic that has been used for treatment of a wide variety of cancers ***(Singal and Iliskovic, 1998)***. Cancers such as pancreatic, and endometrial carcinomas despite being less responsive to DOX, are still treated with this compound because of its benefits, ***(Singal et al., 2000)***.

The exact mechanism of DOX–induced nephrotoxicity is not yet well known. However, cellular damage induced by DOX is mediated by the formation of an iron anthracyclin free radical ***(Powis, 1989)*** which in turn causes severe damage to the plasma membrane ***(Algria et al., 1990)***.

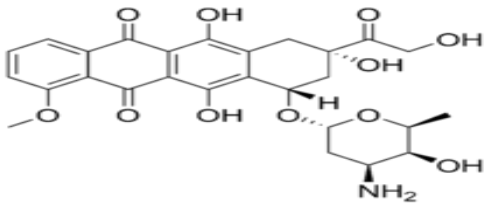

***Figure (1):*** Doxorubicin structure ***(Yilmaz et al., 2006)***.

The most possible mechanisms for the renal toxicity of DOX may be alterations of the permeability of the glomerular capillary wall or may be the consequence of oxidative stress, such as oxidation and cross-linking of cellular thiols and membrane lipid peroxidation ***(Wu et al., 1990).*** In DOX-induced nephropathy, the glomerular cells produce ROS which cause glomerular injury ***(Zima et al., 1997)***.

The clinical use of DOX is associated with nephrotic syndrome characterized by heavy proteinuria, albuminuria, hypoalbuminaemia and hyperlipidaemia**.** Several lines of evidence suggest ROS as the principal mediator in the development of nephrosis caused by DOX ***(Mimnaugh et al., 1986).*** The hypothesis was proposed, that if DOX nephrotoxicity is related to free radical formation and lipid peroxidation, then antioxidant therapy may protect DOX toxicity in kidney ***(Venkatesan et al., 2000).***

Through evolution, mammalian life forms have developed natural cancer preventative processes that are stimulated by low doses of sparsely ionizing forms of radiation (e.g., x rays, gamma rays, beta particles) ***(Liu, 2007).*** These low doses of radiations stimulate protective intercellular and intracellular signaling that leads to activated natural protection (ANP) against cancer and other genomic–instability–associated diseases ***(Sakai et al., 2006)***.

The protective processes are transient over time intervals of hours or days, rather than permanent effects of irradiation ***(Feinendegen et al., 2007).*** Stimulation of detoxification of ROS appears to reach a maximum at about 4 h after irradiation and lasts for several hours or even weeks, depending on tissue and cell type. The process involves a rise of free glutathione and increased superoxide dismutase with decreased lipid peroxidation lasting for weeks in some tissues ***(Feinendegen, 2005).***

It is known that sufficient kidney irradiation causes a radiation-induced nephropathy and often leads to renal failure ***(Robbins and Bonsib, 1995)***, but the use of low doses of radiation to slow down the progression of renal disease is poorly studied ***(Jendruczko and Drozdz, 1992; Liao and Travis, 1994)***.

The average diet contains a great number of antioxidant activities, such as polyphenols ***(Bonorden and Pariza, 1994)*** that are plant metabolites occurring widely in plant food and possess outstanding antioxidant and free radical scavenging properties ***(Scott et al., 1993)***.

L-carnitine that possesses antioxidant activity has no effect on the antitumour activity of DOX ***(Sayed-Ahmed et al., 2001)*** but produced a significant reduction in DOX-induced loss of renal function and oxidative stress ***(Chang et al., 2002)***.

It has been claimed that presence of phenolic groups in curcumin is fundamental to explain its ability to eliminate oxygen free radicals from the medium ***(Sreejayan et al., 1997)***. It has been also reported that curcumin has a nephroprotective effect that improves creatinine and urea clearance and protects the chronic renal allograft nephropathy. These beneficial effects have been explained by the induction of antioxidative enzymes ***(Osawa, 2007)***.

Garlic is a condiment, that has been used for its medicinal purposes. ***(Effraim et***

***al., 2000)*.** Garlic was able to decrease significantly the DOX–induced changes in the oxido–reductive status of the red blood cells. Moreover, oil soluble organosulfur compounds from garlic have been found to protect the cells against the free radical generation provoked by DOX ***(Dwivedi et al., 1998)*.**

Green tea is an excellent source of polyphenol antioxidants, particularly of a group known as green tea catechins ***(Hrelia et al., 2002)***. The antioxidant properties of tea extracts have been attributed to their content of polyphenols, which have been reported to inhibit oxidative processes in biological systems ***(Auger et al., 2004; Osman et al., 2009)***.

The aim of the present study is to examine the possible protective potential of rat whole body exposure to low dose of γ radiation in presence or absence of L-carnitine, curcumin, garlic powder or green tea extract in doxorubicin (DOX)-induced experimental nephropathy.

## Material and methods

### Animals

Adult male Wistar rats, purchased from the National Research Centre (Giza Egypt) weighing 150-200 g were used in this study. They were housed in wire - mesh cages and kept under appropriate conditions of, temperature, humidity and light (temperature 25±2 °C, relative humidity 60-70 % and 12h cycle light ). The animals were allowed free access to food consisting of standard pellets obtained from El-Nasr Chemical Company, (Cairo Egypt) and water *ad libitum*. The rats were acclimatized in the animal facilities of the National Centre for Radiation Research and Technology for at least one week before starting the experiments. The study was carried out according to the international guidelines and approved by the Ethical Committee for Animal Experimentation at Faculty of Pharmacy, Cairo University.

### Drugs

1. **L-Carnitine:** it was i.p daily administered for two weeks in a dose of 40 mg/kg. (Freshly dissolved in distilled water)
2. **Curcumin:** it was i.p daily administered for two weeks in a dose of 50 mg/kg. (freshly dissolved in distilled water)
3. **Garlic powder:** it was orally daily administered for two weeks in a dose of 100 mg/kg. (freshly dissolved in distilled water)
4. **Green tea extract:** it was orally daily administered for two weeks in a dose of 300 mg/kg. (freshly dissolved in distilled water)
5. **Doxorubicin:** it was used in the form of an injectable commercial product (Adriblastina vials), each vial contains doxorubicin hydrochloride as a freeze-dried powder. The contents of each vial were freshly dissolved in a sterile saline solution just before use. It was used as an i.p. single dose of 5 mg/kg. (The dose is selected after a preliminary experiment).

### Experimental design

Preliminary study was carried out to select the suitable dose of DOX to induce nephrotoxicity. Four groups of animals were used in this study. The 1st gp. included normal animals, while the other three groups received a single i.p injection of DOX in doses of 5, 10 or 15 mg/kg respectively and were examined 3, 10 or 15 days following DOX administration. In the current experiment 5 mg/kg, i.p. was selected as a single dose to induce nephrotoxicity during 15 days.

Animals were subdivided into three sets. Three groups of the 1st set were exposed to γ radiation at a single dose level of 0.3 Gy then received DOX, 1, 3 or 7 days postirradiation respectively. The groups of 2nd set daily received L-carnitine (40 mg/kg, i.p.), curcumin (50 mg/kg, i.p.), garlic (100 mg/kg, p.o.) and green tea extract (300 mg/kg, p.o.) for two weeks before induction of nephropathy. Groups of the 3rd set received the same doses of drugs then injected with DOX, 1, 3 or 7 days following γ irradiation respectively. Two groups of animals, one of them received

saline and served as normal and the other received DOX and served as nephropathic group were included in 1st, 2nd as well as 3rd set. At the 15th day of DOX–treatment, the animals were anesthetized with urethane (1.2 g/kg, i.p), blood was collected by heart puncture then the animals were sacrificed by decapitation,

**Measured parameters**

1. Creatinine was determined in serum. The creatinine colorimetric assay was performed using a test reagent kit according to the method of ***Jeffe (1886)***.
2. Urea was determined in serum. The urea colorimetric assay was performed using a test reagent kit according to the method of ***Patton and Crouch (1977)***.
3. Uric acid was determined in serum. The uric acid colorimetric assay was performed using a test reagent kit according to the method of ***Barham and Trinder (1972)*** and ***Fossati et al. (1980)***.

**Irradiation of animals**

Rats were exposed to whole body gamma radiation at a single dose level of 0.3 Gy delivered at a dose rate of 0.46 Gy/min. The radiation source was $^{137}$ Cs using a Canadian gamma cell-40 biological irradiator, belonging to the National Center for Radiation Research and Technology, Cairo, Egypt.

**Statistical Analysis**

All the values were expressed as means ± S.E. Comparisons between means were carried out using one-way ANOVA followed by Tukey-Kramer multiple comparisons test using Instat software, version 2 (Graphpad Software, Inc., San Diego, USA).

% protection = Treated gp – DOX treated gp / Normal gp – DOX treated gp * 100

## Results

**Effect of administration of different doses of doxorubicin (DOX) on serum levels of creatinine, urea and uric acid in rats 3, 10 or 15 days following its administration.**

The results are shown in table ( 1 ).

Administration of DOX in a single dose (15 mg/kg) induced a significant increase in serum creatinine level at 3 days post DOX treatment relative to normal value. However, neither 5 nor 10 mg/kg of DOX showed any change in serum creatinine level 3 days following DOX treatment.

Injection of DOX at three different dose levels 5, 10 or 15 mg/kg resulted in a dose-dependent increase in serum creatinine levels at 10 and 15 days post

DOX treatment relative to normal value.

Administration of DOX at different dose levels namely 5, 10 or 15 mg/kg to rats resulted in a dose-dependent increase in serum urea levels at 3, 10 and 15 days post DOX treatment as compared to the corresponding normal value.

Administration of DOX in a single dose (15 mg/kg) induced a significant elevation in serum uric acid concentration at 3 days post DOX treatment. On the other hand, administration of DOX in doses, 5 or 10 mg/kg did not produce any significant effect in serum uric acid levels relative to normal value 3 days following DOX treatment.

Serum uric acid levels were increased at 10 days following DOX administration in doses, 10 and 15 mg/kg, while, 5 mg/kg did not significantly alter serum uric acid level at 10 days following DOX administration.

Fifteen days following DOX administration, serum uric acid concentrations were significantly elevated by the three dose levels of DOX as compared to the corresponding normal value.

To this end, data revealed that, treatment of rats with DOX in a dose of 5 mg/kg, produced the charachteristic signs of a nephritic syndrome including increase in serum creatinine, urea and uric acid at 15 days following DOX administration.

**Effect of administration of DOX (5 mg/kg) on serum levels of creatinine, urea and uric acid in rats 1, 3 or 7 days following exposure to radiation at a dose level of 0.3 Gy.**

Administration of DOX in a single dose (5 mg/kg) induced a marked elevation in serum creatinine, urea and uric acid levels relative to normal value (Tables 2-10).

Exposure to γ radiation at a dose level of 0.3 Gy, 1 or 3 days before administration of DOX exhibited significant protective effect against DOX–induced elevation in serum creatinine, urea and uric acid levels. On the other hand, exposure to γ radiation (0.3 Gy), 7 days before administration of DOX did not produce any significant protective effect (Table 2).

***Table (1):*** **Effect of administration of different doses of doxorubicin (DOX) on serum levels of creatinine, urea and uric acid in rats 3, 10 or 15 days following its administration.**

| Groups | Time After Treatment | Serum | | |
|---|---|---|---|---|
| | | **Creatinine** (mg/dl) | **Urea** (mg/dl) | **Uric acid** (mg/dl) |
| **Normal (saline)** | **3 Days** | 0.64 ± 0.02 | 24.52 ± 0.96 | 1.72 ± 0.23 |
| **Dox 5 mg/kg** | | 0.78 ± 0.03 | 35.02* ± 1.21 | 1.92 ± 0.36 |
| **Dox 10 mg/kg** | | 0.86 ± 0.08 | 39.28* ± 0.93 | 2.27 ± 0.47 |
| **Dox 15 mg/kg** | | 0.95* ± 0.06 | 43.64* ± 1.54 | 3.52* ± 0.57 |
| **Normal (saline)** | **10 Days** | 0.72 ± 0.02 | 17.48 ± 0.58 | 1.92 ± 0.46 |
| **Dox 5 mg/kg** | | 1.23* ± 0.10 | 22.67* ± 1.23 | 3.72 ± 0.74 |
| **Dox 10 mg/kg** | | 1.45* ± 0.15 | 24.98* ± 1.08 | 4.52* ± 0.29 |
| **Dox 15 mg/kg** | | 1.65* ± 0.12 | 29.86* ± 1.04 | 4.90* ± 0.39 |
| **Normal (saline)** | **15 Days** | 0.61 ± 0.03 | 21.34 ± 1.05 | 1.97 ± 0.20 |
| **Dox 5 mg/kg** | | 1.24* ± 0.07 | 30.48* ± 0.94 | 4.07* ± 0.33 |
| **Dox 10 mg/kg** | | 1.48* ± 0.14 | 33.52* ± 1.29 | 4.30* ± 0.53 |
| **Dox 15 mg/kg** | | 1.70* ± 0.25 | 57.73* ± 1.69 | 4.87* ± 0.47 |

* Significantly different from normal group at $p \leq 0.05$.

**Effect of L-carnitine, curcumin, garlic powder or green tea extract administration on DOX-induced changes in serum creatinine, urea and uric acid levels in rats.**

Administration of L-carnitine (40 mg/kg, i.p.), curcumin (50 mg/kg, i.p.), garlic powder (100 mg/kg, p.o.) or green tea extract (300 mg/kg, p.o.) daily for two weeks to normal animals did not produce any significant change in serum levels of creatinine, urea as well as uric acid (Tables 3–6).

Pretreatment with L-carnitine (40 mg/kg, i.p.), curcumin (50 mg/kg, i.p.), garlic powder (100 mg/kg, p.o.) or green tea extract (300 mg/kg, p.o.) daily two weeks prior to DOX administration, ameliorated DOX–induced elevation of serum creatinine, urea and uric acid levels. It was found that, L-carnitine showed the best protective effect against DOX–induced increase in serum creatinine and urea by 83 and 75.4 %, respectively, while, curcumin showed the best protective effect against DOX–induced increase in serum uric acid by 80.7 % (Tables 3–6).

**Effect of combined L-carnitine, curcumin, garlic powder or green tea extract administration and radiation exposure on DOX–induced changes in serum levels of creatinine, urea and uric acid in rats.**

Combined therapy of daily L-carnitine (40 mg/kg, i.p.), curcumin (50 mg/kg, i.p.), garlic powder (100 mg/kg, p.o.) or green tea extract (300 mg/kg, p.o.)

for 14 successive days and exposure to single low dose of γ radiation (0.3 Gy) 1, 3 or 7 days prior to DOX injection resulted in reduction of serum creatinine, urea and uric acid levels as compared with DOX–treated group (Tables 7–10). It was observed that, L-carnitine followed by γ irradiation (0.3 Gy) 1 day before DOX injection showed the best protective effect against DOX–induced elevation in serum creatinine and urea by 95.1 and 88.2 %, respectively, while, curcumin followed by γ irradiation (0.3 Gy) 1 day before DOX injection showed the best protective effect against DOX–induced increase in serum uric acid by 88.7 % (Tables 7–10).

***Table (2):*** **Effect of administration of DOX (5 mg/kg) on serum levels of creatinine, urea and uric acid in rats 1, 3 or 7 days following exposure to radiation at a dose level of 0.3 Gy.**

** Significantly different from normal group at $p \leq 0.05$.*
*@ Significantly different from DOX-treated group at $p \leq 0.05$.*

| Parameters / Groups | Serum | | | | | |
|---|---|---|---|---|---|---|
| | Creatinine | | Urea | | Uric acid | |
| | (mg/dl) | % protection | (mg/dl) | % protection | (mg/dl) | % protection |
| **Normal** | 0.66 ± 0.13 | | 18.55 ± 1.41 | | 1.69 ± 0.20 | |
| **DOX** (5 mg/kg) | 1.29 * ± 0.16 | | 33.63 * ± 1.75 | | 3.85 * ±0.49 | |
| **Irrad** (1Day)+**DOX** (5 mg/kg) | 0.78 @ ± 0.08 | 80.9 % | 22.06 @ ± 2.00 | 76.7 % | 1.88 @ ± 0.32 | 91.2 % |
| **Irrad** (3Days)+**DOX** (5 mg/kg) | 0.83 @ ± 0.05 | 73 % | 25.86 *@ ± 2.29 | 51.5 % | 2.17 @ ± 0.34 | 77.7 % |
| **Irrad** (7Days)+**DOX** (5 mg/kg) | 1.12 * ± 0.09 | 26.9 % | 29.75 * ± 0.84 | 25.7 % | 3.43 * ± 0.55 | 19.4 % |

***Table (3):*** **Effect of L-carnitine administration on DOX-induced changes in serum creatinine, urea and uric acid levels in rats.**

| Parameters / Groups | Serum | | | | | |
|---|---|---|---|---|---|---|
| | Creatinine | | Urea | | Uric acid | |
| | (mg/dl) | % protection | (mg/dl) | % protection | (mg/dl) | % protection |
| **Normal** | 0.63 ± 0.06 | | 18.03 ± 0.78 | | 1.29 ± 0.14 | |
| **DOX** (5 mg/kg) | 1.28* ± 0.11 | | 33.13* ± 2.77 | | 3.57* ± 0.31 | |
| **L-Carnitine** (40 mg/kg/day) | 0.59@ ± 0.04 | | 16.08@ ± 1.23 | | 1.52@ ± 0.13 | |
| **L-Carnitine** (40 mg/kg/day) + **DOX** (5 mg/kg) | 0.74@ ± 0.06 | 83 % | 21.73@ ± 1.62 | 75.4 % | 1.92@ ± 0.16 | 72.3 % |

** Significantly different from normal group at $p \leq 0.05$.*
*@ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (4):*** **Effect of curcumin administration on DOX-induced changes in serum creatinine, urea and uric acid levels in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.63 ± 0.06 | | 18.03 ± 0.78 | | 1.29 ± 0.14 | |
| **DOX** (5 mg/kg) | 1.28* ± 0.11 | | 33.13* ± 2.77 | | 3.57* ± 0.31 | |
| **Curcumin** (50 mg/kg/day) | 0.61$^{@}$ ± 0.05 | | 17.20$^{@}$ ± 1.72 | | 1.21$^{@}$ ± 0.12 | |
| **Curcumin** (50 mg/kg/day) **+ DOX** (5 mg/kg) | 0.78$^{@}$ ± 0.07 | 76.9 % | 22.25$^{@}$ ± 2.34 | 72 % | 1.73$^{@}$ ± 0.16 | 80.7 % |

** Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (5):*** **Effect of DOX, garlic and their combination on serum creatinine, urea and uric acid levels in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.63 ± 0.06 | | 18.03 ± 0.78 | | 1.29 ± 0.14 | |
| **DOX** (5 mg/kg) | 1.28* ± 0.11 | | 33.13* ± 2.77 | | 3.57* ± 0.31 | |
| **Garlic** (100 mg/kg/day) | 0.69$^{@}$ ± 0.04 | | 20.31$^{@}$ ± 1.01 | | 1.73$^{@}$ ± 0.15 | |
| **Garlic** (100 mg/kg/day) **+ DOX** (5 mg/kg) | 0.78$^{@}$ ± 0.04 | 76.9 % | 23.96$^{@}$ ± 1.16 | 60.7 % | 2.30*$^{@}$ ± 0.16 | 55.7 % |

** Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (6):*** **Effect of green tea extract on DOX-induced elevated serum levels of creatinine, urea and uric acid in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.63 ± 0.06 | | 18.03 ± 0.78 | | 1.29 ± 0.14 | |
| **DOX** (5 mg/kg) | 1.28* ± 0.11 | | 33.13* ± 2.77 | | 3.57* ± 0.31 | |
| **Green tea** (300 mg/kg/day) | 0.67$^{@}$ ± 0.06 | | 19.59$^{@}$ ± 1.23 | | 1.63$^{@}$ ± 0.16 | |
| **Green tea** (300 mg/kg/day) **+DOX** (5 mg/kg) | 0.81$^{@}$ ± 0.06 | 72.3 % | 24.52$^{@}$ ± 1.83 | 57 % | 1.96$^{@}$ ± 0.16 | 70.6 % |

**Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (7):*** **Effect of combined L-carnitine administration and radiation exposure on DOX–induced changes in serum levels of creatinine, urea and uric acid in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.59 ± 0.03 | | 20.30 ± 0.94 | | 1.82 ± 0.07 | |
| **DOX** (5 mg/kg) | 1.21* ± 0.09 | | 37.50* ± 1.20 | | 4.42* ± 0.25 | |
| **L-Carnitine** (40 mg/kg/day) **+Irrad** (1 day) **+ DOX** (5 mg/kg) | 0.62$^{@}$ ± 0.05 | 95.1 % | 22.32$^{@}$ ± 1.80 | 88.2 % | 2.07$^{@}$ ± 0.15 | 90.3 % |
| **L-Carnitine** (40 mg/kg/day) **+Irrad** (3days) **+ DOX** (5 mg/kg) | 0.66$^{@}$ ± 0.06 | 88.7 % | 23.80$^{@}$ ± 1.36 | 79.6 % | 2.25$^{@}$ ± 0.16 | 83.4 % |
| **L-Carnitine** (40 mg/kg/day) **+Irrad** (7 days) **+ DOX** (5 mg/kg) | 0.70$^{@}$ ± 0.06 | 82.2 % | 24.33$^{@}$ ± 1.38 | 76.5 % | 2.45$^{@}$ ± 0.19 | 75.7 % |

** Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (8):*** **Effect of combined curcumin administration and radiation exposure on DOX-induced changes in serum creatinine, urea and uric acid levels in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.59 ± 0.03 | | 20.30 ± 0.94 | | 1.82 ± 0.07 | |
| **DOX** (5 mg/kg) | 1.21***** ± 0.09 | | 37.50* ± 1.20 | | 4.42* ± 0.25 | |
| **Curcumin** (50 mg/kg/day) **+Irrad** (1day) **+ DOX** (5 mg/kg) | 0.66$^{@}$ ± 0.04 | 88.7 % | 23.10$^{@}$ ± 1.46 | 83.7 % | 1.90$^{@}$ ± 0.11 | 96.9 % |
| **Curcumin** (50 mg/kg/day) **+Irrad** (3days) **+ DOX** (5 mg/kg) | 0.70$^{@}$ ± 0.05 | 82.2 % | 24.20$^{@}$ ± 1.48 | 77.3 % | 2.15$^{@}$ ± 0.09 | 87.3 % |
| **Curcumin** (50 mg/kg/day) **+Irrad** (7days) **+ DOX** (5 mg/kg) | 0.72$^{@}$ ± 0.05 | 79 % | 24.81$^{@}$ ± 1.59 | 73.7 % | 2.35$^{@}$ ± 0.22 | 79.6 % |

**Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (9):*** **Effect of combined garlic administration and radiation exposure on DOX-induced changes in serum creatinine, urea and uric acid levels in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.59 ± 0.03 | | 20.30 ± 0.94 | | 1.82 ± 0.07 | |
| **DOX** (5 mg/kg) | 1.21* ± 0.09 | | 37.50* ± 1.20 | | 4.42* ± 0.25 | |
| **Garlic** (100 mg/kg/day) **+Irrad** (1day) + **DOX** (5 mg/kg) | 0.67$^{@}$ ± 0.05 | 87 % | 23.49$^{@}$ ± 1.52 | 81.4 % | 2.11$^{@}$ ± 0.15 | 88.8 % |
| **Garlic** (100 mg/kg/day) **+Irrad** (3days) + **DOX** (5 mg/kg) | 0.71$^{@}$ ± 0.06 | 80.6 % | 26.20*$^{@}$ ± 1.29 | 65.6 % | 2.35$^{@}$ ± 0.21 | 79.6 % |
| **Garlic** (100 mg/kg/day) **+Irrad** (7days) + **DOX** (5 mg/kg) | 0.74$^{@}$ ± 0.05 | 75.8 % | 27.22*$^{@}$ ± 1.56 | 59.7 % | 2.90*$^{@}$ ± 0.23 | 58.4 % |

**Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

***Table (10):*** **Effect of combined green tea administration and radiation exposure on DOX-induced changes in serum creatinine, urea and uric acid levels in rats.**

| Parameters / Groups | *Serum* | | | | | |
|---|---|---|---|---|---|---|
| | ***Creatinine*** | | ***Urea*** | | ***Uric acid*** | |
| | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** | ***(mg/dl)*** | ***% protection*** |
| **Normal** | 0.59 ± 0.03 | | 20.30 ± 0.94 | | 1.82 ± 0.07 | |
| **DOX** (5 mg/kg) | 1.21* ± 0.09 | | 37.50* ± 1.20 | | 4.42* ± 0.25 | |
| **Green tea** (300 mg/kg/day) **+Irrad** (1day) + **DOX** (5 mg/kg) | 0.70$^{@}$ ± 0.05 | 82.2 % | 23.71$^{@}$ ± 1.19 | 80.1 % | 2.02$^{@}$ ± 0.11 | 92.3 % |
| **Green tea** (300 mg/kg/day) **+Irrad** (3 days) + **DOX** (5 mg/kg) | 0.74$^{@}$ ± 0.06 | 75.8 % | 26.93*$^{@}$ ± 1.14 | 61.4 % | 2.30$^{@}$ ± 0.17 | 81.5 % |
| **Green tea** (300 mg/kg/day) **+Irrad** (7 days) + **DOX** (5 mg/kg) | 0.75$^{@}$ ± 0.04 | 74.1 % | 27.42*$^{@}$ ± 2.11 | 58.6 % | 2.51$^{@}$ ± 0.17 | 73.4 % |

**Significantly different from normal group at $p \leq 0.05$.*
*$^{@}$ Significantly different from DOX-treated group at $p \leq 0.05$.*

## Discussion:

Results of the present study revealed that, a single dose of DOX (5 mg/kg) induced marked acute nephrotoxicity 15 days after DOX injection which was manifested as significant increase in serum levels of creatinine, urea as well as uric acid.

The results of ***Wapstra et al. (1999)*** demonstrated that 3 mg/kg of DOX induced renal damage after 6 weeks, whereas, it was shown that nephrotoxicity was induced by 25 mg/kg dosage of DOX after 2 days ***(Saad et al., 2001)***.

The study of ***Mansour et al. (1999)*** showed that, a single dose of DOX (15 mg/kg) induced nephrotoxicity manifested biochemically by a significant increase in serum urea after 4, 24 and 48 h. Similar results by ***Yagmurca et al. (2004)*** demonstrated that 20 mg/kg single injection of DOX to rats caused renal injury including glomerular and tubular lesions 10 days after the DOX injection.

In contrast, DOX treatment in a dose of 5 mg/kg did not induce any change in plasma creatinine or urea levels ***(He et al., 2008)***. Furthermore, rats did not show significant change in serum creatinine 6 weeks following injection of DOX in a dose of 7.5 mg/kg ***(Kavukcu et al., 2003)***.

Although the exact mechanism of DOX–induced nephrotoxicity remains unknown, it has been believed to be mediated through free radical formation, iron–dependent oxidative damage of biological macromolecules, and membrane lipid peroxidation ***(Pritsos and Ma, 2000; Saad et al., 2001)***.

Two different pathways of free radical formation by DOX have been described. The first implicates the formation of a semiquinone free radical by the action of several NADPH-dependent reductases that produce a one-electron reduction of DOX to the corresponding DOX semiquinone. In the presence of oxygen, redox cycling of DOX–derived quinine–semiquinone yields superoxide radicals ($O^{2\bullet-}$).

In the second pathway, DOX free radicals are produced by a non-enzymatic mechanism that involves reactions with iron. Iron–DOX complex can reduce oxygen to $H_2O_2$ and reactive oxygen species (ROS), which cause oxidative damage of a variety of tissues including the kidneys ***(Singal et al., 2000; De Beer et al., 2001)***.

It has been suggested that oxidative stress promotes the formation of a variety of vasoconstrictors that can affect renal function directly or by decreasing the glomerular capillary ultrafiltration coefficient, and thus reduce glomerular filtration rate ***(Mohamadin et al., 2005)***. The study by ***Yagmurca et al. (2004)*** supported the idea that nephrotoxicity induced by DOX is mainly related to oxidant injury.

The present study revealed that, pre-exposure to γ radiation at a dose level of 0.3 Gy, 1 or 3 days before DOX injection exhibited significant improvement in the elevated serum levels of creatinine, urea and uric acid. However, exposure to low dose of radiation 7 days prior to DOX administration did not show any protective effect. These results were in accordance with that of ***Aunapuu et al. (2004)***.

The study of ***Kataoka et al. (2007)*** examined the inhibitory effects of prior low–dose X-irradiation on ischemia/reperfusion injury in mouse paw and their findings suggested that the ischemia/reperfusion injury was inhibited by the enhancement of antioxidation function by 0.5 Gy irradiation. ***Nomura et al. (2002)*** suggested that low dose irradiation might be effective for prevention or treatment of ROS related diseases.

Interestingly, it has been reported that the protective responses to single exposures tended to be maximally expressed after about 0.1 Gy and there were very little protective response after more than about 0.5 Gy radiation ***(Shadley and Wiencke, 1989; Feinendegen et al., 1996)***.

In this study, DOX caused renal injury as evidenced by increased levels of creatinine urea and uric acid. L-carnitine can reverse these effects. These results were consistent

with the observation of ***Boonsanit et al. (2006)*** who mentioned that a 7.5 mg/kg single injection of DOX in rats caused renal injury by reducing glomerular filtration rate with glomerular and tubular lesions at 16 days of treatment. Administration of L-carnitine markedly improved glomerular filtration rate, reduced plasma lipids, renal histopathological lesions and possibly reduced renal oxidative stress. In addition, L-carnitine was also effective in preventing renal injury in many renal injury models such as gentamicin ***(Kopple et al., 2002)*** and cisplatin ***(Chang et al., 2002).***

Curcumin treatment significantly attenuated the DOX–mediated increase in serum creatinine, urea as well as uric acid. This effect may be related to the antioxidant properties of curcumin since it has been found that ROS may be involved in the impairment of glomerular filtration rate ***(Hughes et al., 1996)***.

Earlier studies have also shown that curcumin pretreatment decreases ischemia/reperfusion–induced rise in serum creatinine levels in rats ***(Shoskes, 1998)***.

Curcumin possesses antiinflammatory and antioxidant effects as well as anticancer properties ***(Kumar and Singh, 2008)***; therefore, there is considerable interest in the various health–promoting benefits of this drug ***(Sun et al., 2008)***. In addition, it is a powerful scavenger of the superoxide anion, hydroxyl radicals and nitrogen dioxide and protects DNA against singlet oxygen–induced strand breaks ***((Sreejayan and Rao, 1997)***. It is also protective in DOX–induced renal injury and ferric nitrilotriacetate–induced oxidative renal damage ***(Okada et al., 2001)***.

In the current experiment, administration of garlic before DOX injection ameliorated the damaging effects of DOX on serum levels of creatinine, urea as well as uric acid in rats. This was in agreement with the results of ***Thabrew et al. (2000)*** and ***Sener et al. (2002)***.

The antioxidant ability of garlic is well known ***(Banerjee et al., 2003; Rahman and Lowe, 2006)*** and has been associated with its protective effect in several experimental models ***(Gedik et al., 2005; Pal et al., 2006)***.

The effect of oral garlic supplementation on the activities of some antioxidant enzymes and lipid peroxidation in red blood cells of mice with oxidative stress produced by chronic administration of the antitumour drug DOX has also been investigated ***(Thabrew et al., 2000)***. At doses of 20 or 100 mg/kg, garlic was able to decrease DOX–induced changes in the oxido–reductive status of the red blood cells. Moreover, oil soluble organosulfur compounds from garlic have been found to protect the cells against the free radical generation provoked by DOX ***(Dwivedi et al., 1998)***.

Tea is a rich source of polyphenolics, particularly flavonoids. *In vitro* and *In vivo* studies continue to provide strong evidence that tea polyphenols may possess the capacity to affect the pathogenesis of several chronic diseases, especially cardiovascular disease and cancer ***(McKay and Blumberg, 2002; Osman et al., 2009)***.

The current work showed that, administration of green tea extract alone had no effect on serum creatinine, urea or uric acid levels as compared to the control group. These results were consistent with the findings of ***Mohamadin et al. (2005)*** and ***Yapar et al. (2009)***.

Moreover, the findings of this study revealed that, pretreatment with green tea extract in rats before DOX administration ameliorated the elevated levels of serum creatinine, urea as well as uric acid induced by DOX. These results are consistent with previous studies reported by other investigators ***(Takako et al., 2005; Renno et al., 2008; Yapar et al., 2009)***.

Green tea can act as a protector agent against cisplatin–induced kidney damages which was manifested by modulating the elevation in serum creatinine and blood urea nitrogen levels ***(Yapar et al., 2009)***.

The effects of green tea tannin on nephrectomized rats were examined by ***Yokozawa et al. (1996)***. There were increases in blood urea nitrogen, serum creatinine, and urinary protein, and a decrease in creatinine clearance in the nephrectomized control rats, whereas better results for these parameters were obtained in rats given green tea tannin after

nephrectomy, demonstrating a suppressed progression of the renal failure.

As a very rich source of polyphenol compounds, the strong antioxidant and oxygen radicals scavenging effects of tea have been documented ***(Samman et al., 2001; Yang et al., 2002)***. Moreover, the investigation by ***Arteel et al. (2002)*** reported that simple dietary antioxidants, such as those found in green tea prevent early alcohol–induced liver injury, most likely by preventing oxidative stress.

In conclusion, based on the experimental findings, the role of oxidative stress in the renal damage induced by DOX has been supported by the fact that some antioxidants such as L-carnitine, curcumin, garlic powder or green tea extract are able to ameliorate DOX–induced nephrotoxicity and oxidative damage.

## References

***Algria A, Rodriguez M, and Hermandez J (1990).*** Semiquinones derived from anthraquinone –containing antitumor drugs can partition into phosphatidylcholine bilayers. Biochem. Biophys. Acta, 1035 (1): 51–55.

***Arteel G, Uesugi T, Bevan L, Gabele E, Wheeler M, and McKim S (2002).*** Green tea extract protects against early alcohol–induced liver injury in rats. Biol. Chem., 383 (3-4): 663–670.

***Auger C, Al-Awwadi N, and Bornet A (2004).*** Catechins and procyanidins in Mediterranean diets. Food Res. Int., 37: 233.

***Aunapuu M, Pechter U, Gerskevits E, Marjamfigi M, Suuroja S, Arend A, Kolts I, Kiilmel W, and Ots M (2004).*** Low-dose radiation modifies the progression of chronic renal failure. Ann. Anat., 186: 277-282.

***Banerjee S, Mukherjee P, and Maulik S (2003).*** Garlic as an antioxidant: the good, the bad and the ugly. Phytother. Res., 17: 97–106.

***Barham D, and Trinder P (1972).*** Enzymatic colorimetric method for determination of uric acid in serum plasma and urine. Analyst., 97:142–145.

***Bonorden W, and Pariza M (1994).*** Antioxidant nutrients and protection from free radicals. In: Kotsonis F. N., Mackey M., Hjelle J., eds. Nutritional Toxicology. New York: Raven Press: 19–48.

***Boonsanit D, Kanchanapangka S, and Buranakarl C (2006).*** L-carnitine ameliorates doxorubicin–induced nephritic syndrome in rats. Nephrology, 11: 313–320.

***Chang B, Nishikawa M, Sato E, Utsumi K, and Inouc M (2002).*** L-carnitine inhibits cisplatin-induced injury of the kidney and small intestine. Arch. Biochem. Biophys., 405: 55–64.

***De Beer E, Bottone A, and Voest E (2001).*** Doxorubicin and mechanical performance of cardiac trabeculae after acute and chronic treatment: a review. Eur. J. Pharmacol., 415: 1–11.

***Dwivedi C, John L, Schmidt D, and Engineer F (1998).*** Effects of oil-soluble organosulfur compounds from garlic on doxorubicin-induced lipid peroxidation. Anticancer Drugs, 9: 291-/294.

***Effraim K, Modu S, and Hamzah H (2000).*** Effect of crude garlic extract on nicotine induced hyperglycaemia and hyperlipidemia in rats. Afr. J. Biomed. Res., 3: 125–127.

***Feinendegen L (2005).*** Evidence for beneficial low level radiation effects and radiation hormesis. The British J. Rad., 78: 3–7.

***Feinendegen L, Bond V, Sondhaus C, and Muehlensiepen H (1996).*** Radiation effects induced by low doses in complex tissue and their relation to cellular adaptive responses. Mutat. Res., 358: 199-205.

***Feinendegen L, Pollycove M, and Neumann R (2007).*** Whole-body responses to low-level radiation exposure: New concepts in mammalian radiobiology. Whole-body responses to low-level radiation exposure: New concepts in mammalian radiobiology. Experimental Hematology, 35 (1): 37–46.

***Fossati L, and Berti G (1980).*** Use of 3,5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urine. Clin. Chem., 26 (2): 227–231.

***Gedik N, Kabasakal L, Sehirli O, Ercan F, Sirvanci S, Keyer-Uysal M, and Sener G (2005).*** Long-term administration of aqueous garlic extract (AGE) alleviates liver fibrosis and oxidative damage induced by biliary obstruction in rats. Life Sci., 76: 2593–2606.

***He L, Rong X, Jiang J, Liu P, and Li Y (2008).*** Amelioration of anti-cancer agent adriamycin–induced nephrotic syndrome in rats by Wulingsan (Gorei-San), a blended traditional Chinese herbal medicine. Food Chem. Toxicol., 46: 1452–1460.

***Hrelia S, Bordoni A, Angeloni C, Leoncini E, GallinaToschi T, Lercker G, and Biagi P (2002).*** Green tea extracts can counteract the modification of fatty acid composition induced by doxorubicin in cultured cardiomyocytes.

Prostaglandins, Leukotrienes and Essential FattyAcids, 66 (5–6): 519–524.

***Hughes A, Stricklett K, Padilla E, and Kohan D (1996).*** Effect of reactive oxygen species on endothelin-1 production by human mesangial cells. Kid. Int., 49: 181–189.

***Jeffe M (1886).*** Uber den Niederschlag welchen Pikrinsaure in normalem Ham erzeugt und uber eine neue Reaktion des Kreatinins. Z. Phys. Chem., 10: 391-400.

***Jendruczko A, and Drozdz M (1992).*** Effect of low dose ionizing irradiation on rat metabolism. Pol. J. Occup. Med. Environ. Health, 5: 251–256.

***Kataoka T, Mizuguchi Y, Yoshimoto M, Taguchi T, and Yamaoka K (2007).*** Inhibitory Effects of Prior Low-dose X-irradiation on Ischemia–reperfusion Injury in Mouse Paw. J. Rad. Res., 48 (6): 505-513.

***Kavukcu S, Soylu A, Turkmen M, Kuralay F, Yilmaz O, and Sarioglu S (2003).*** Unilateral ureteroperitoneostomy in the management of hypoproteinemia in nephrotic rats with normal renal function. Tohoku J. Exp. Med., 201: 67–73.

***Kopple J, Ding H, and Letoha A (2002).*** L-carnitine ameliorates gentamicin-induced renal injury in rats. Nephrol. Dial. Transplant., 17: 2122–2131.

***Kumar A, and Singh A (2008).*** Possible nitric oxide modulation in protective effect of *(Curcuma longa, Zingiberaceae)* against sleep deprivation–induced behavioral alterations and oxidative damage in mice. Phytomedicine, 15: 577–586.

***Liao Z, and Travis E (1994).*** Unilateral nephrectomy 24 hours after bilateral kidney irradiation reduces damage to the function and structure of the remaining kidney. Radiat. Res., 139: 190-199.

***Liu S (2007).*** Cancer control related to stimulation of immunity by low-dose radiation. Dose-Response, 5 (1): 39-47.

***Mansour M, El-Kashef H, and Al-Shabanah O (1999)***. Effect of captopril on doxorubicin-induced nephrotoxicity in normal rats. Pharmacol. Res.,39: 233–237.

***McKay D, and Blumberg J (2002).*** The role of tea in human health: An update. J. Am. Nutr., 21(1): 1.

***Mimnaugh E, Trush M, and Gram T (1986).*** A possible role for membrane lipid peroxidation in anthracycline nephrotoxicity. Biochem. Pharmacol., 35: 4327–4335.

***Mohamadin A, El-Beshbishy H, and El-Mahdy M (2005).*** Green tea extract attenuates cyclosporine A–induced oxidative stress in rats. Pharmacol. Res., 51: 51–57.

***Nomura T, Yamaoka K, and Sakai K (2002).*** Elevation of antioxidants in the kidneys of mice by low-dose irradiation and its effect on $Fe^{3+}$-NTA–induced kidney damage. International Congress Series, 1236: 481–485.

***Okada K, Wangpoentrakul C, Tanaka T, Toyokuni S, Uchida K, and Osawa T (2001).*** Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress–induced renal injury in mice. J. Nut., 131: 2090–2095.

***Osawa T (2007).*** Nephroprotective and hepatoprotective effects of curcuminoids. Adv. Exp. Med. Biol., 595: 407–423.

***Osman N, Hussien E, and Farag M (2009).*** Black tea *(Camellia sinensis)* role in modulating antioxidant enzymes and biochemichal changes in γ-irradiated rats. Egypt. J. Rad. Sci. Applic., 22 (1): 287–304.

***Pal R, Vaiphei K, Sikander A, Singh K, and Rana S (2006).*** Effect of garlic on isoniazid and rifampicin–induced hepatic injury in rats. World J. Gastroenterol., 12: 636–639.

***Patton C, and Crouch S (1977).*** Spectrophotometric and kinetics investigation of the Berthelot reaction for the determination of ammonia. Anal.Chem., 49: 464–469.

***Powis G (1989).*** Free radical formation by antitumor quinones. Free Radical Biol. Med., 6 (1): 63–101.

***Pritsos C, and Ma J (2000).*** Basal and drug-induced antioxidant enzyme activities correlate with age–dependent doxorubicin oxidative toxicity. Chem. Biol. Interact., 127: 1–11.

***Rahman K, and Lowe G (2006).*** Garlic and cardiovascular disease: a critical review. J. Nutr., 136: 736S –740S.

***Renno W, Abdeen S, Alkhalaf M, and Asfar S (2008).*** Effect of green tea on kidney tubules of diabetic rats. Br. J. Nutr., 100 (3): 652–659.

***Robbins M, and Bonsib S (1995).*** Radiation nephropathy: a review. Scanning Microsc., 9 : 535–560.

***Saad S, Najjar T, and Al-Rikabi A (2001).*** The preventive role of deferoxamine against acute doxorubicin–induced cardiac, renal and hepatic toxicity in rats. Pharmacol. Res., 43 (3): 211–218.

***Sakai K, Nomura T, and Ina Y (2006).*** Enhancement of bio protective functions by low dose/dose-rate radiation. Dose-Response, 4 (4): 327–332.

***Samman S, Sandstrom B, Toft M, Bukhave K, Jensen M, and Sorensen S (2001).*** Green tea or rosemary extract added to foods reduces nonheme-iron absorption. Am. J. Clin. Nutr., 73 (3): 607–612.

***Sayed-Ahmed M, Salmanc T, Gaballahb H, Abou El-Nagab S, Nicolaid R, and Calvanid M***

***(2001).*** Propionyl-l-carnitine as protector against adriamycin–induced cardiomyopathy. Pharmacol. Res., 43(6): 513–520.

***Scott B, Butler J, Halliwell B, and Aruoma O (1993).*** Evaluation of the antioxidant action of ferulic acid and catechin. Free Rad. Res. Commun., 19: 241–253.

***Sener G, Sehirli A, Altunbas H, Ersoy Y, Askaloglu K, Arbak S, and Ayanoglu-Dulger G (2002).*** Melatonin protects against gentamicin–induced nephrotoxicty in rats. J. Pineal Res., 32: 231–236.

***Shadley J, and Wiencke J (1989).*** Induction of the adaptive response by X rays is dependent on radiation intensity. Int. J. Radiat. Biol., 56: 107–118.

***Shoskes D (1998)***. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. Transplant., 90: 2593–2597.

***Singal P, and Iliskovic N (1998).*** Adriamycin cardiomyopathy. N. Engl. J. Med., 339: 900–905.

***Singal P, Li T, Kumar D, Danelisen I, and Iliskovic N (2000).*** Adriamycin–induced heart failure: mechanism and modulation. Mol. Cell. Biochem., 207: 77–86.

***Sreejayan N, and Rao M (1997).*** Nitric oxide scavenging by curcuminoids. J. Pharm. Pharmacol., 49: 105–107.

***Sreejayan N, Rao M, Priyadarsini K, and Devasagayam T (1997).*** Inhibition of radiation–induced lipid peroxidation by curcumin. Int. J. Pharm., 151: 127–130.

***Sun D, Nizamutdinova I, Kim Y, Cai X, Lee J, Kang S, Kim Y, Kang K, Chai G, Chang K, and Kim H (2008).*** Bisacurone inhibits adhesion of inflammatory monocytes or cancer cells to endothelial cells through down-regulation of VCAM-1 expression. Int. Immunopharmacol., 8: 1272–1281.

***Takako Y, Takako N, Takeshi O, Tsutomu O, and Juneja L (2005).*** Green tea polyphenols and dietary fibre protect against kidney damage in rats with diabetic nephropathy. J. Pharm. Pharmacol., 57(6): 773–780.

***Thabrew M, Samarawickrema N, Chandrasena L, and Jayasekera S (2000).*** Protection by garlic against adriamycin induced alterations in the oxidoreductive status of mouse red blood cells. Phytother. Res., 14: 215–217.

***Venkatesan N, Punithavathi D, and Arumugam V (2000).*** Curcumin prevents adriamycin nephrotoxicity in rats. British J. Pharmacol., 129: 231–234.

***Wapstra F, Van Goor H, De Jong P, Navis G, and De Zeeuw D (1999).*** Dose of doxorubicin determines severity of renal damage and responsiveness to ACE–inhibition in experimental nephrosis. J. Pharmacol. Toxicol., 41: 69–73.

***Wu S, Yang Y, and Wang Z (1990).*** Role of oxygen radicals in adriamycin–induced nephrosis. Clin. Med. J. Engl., 103: 283–289.

***Yagmurca M, Erdoganb H, Irazc M, Songurd A, Ucare M, and Fadilliogluf E (2004)***. Caffeic acid phenethyl ester as a protective agent against doxorubicin nephrotoxicity in rats. Clinica Chimica Acta, 348: 27–34.

***Yang C, Maliakal P, and Meng X (2002).*** Inhibition of carcinogenesis by tea. Annu. Rev. Pharmacol. Toxicol., 42: 25–54.

***Yapar K, Cavuşoğlu K, Oruç E, and Yalçin E (2009).*** Protective effect of royal jelly and green tea extracts effect against cisplatin–induced nephrotoxicity in mice: a comparative study. J. Med. Food, 12 (5): 1136–1142.

***Yilmaz S, Atessahin A, Sahna E, Karahan I, and Ozer S (2006).*** Protective effect of lycopene on adriamycin–induced cardiotoxicity and nephrotoxicity. Toxicology, 218: 164–171.

***Yokozawa T, Chung H, He L, and Oura H (1996).*** Effectiveness of green tea tannin on rats with chronic renal failure. Biosci. Biotechnol. Biochem., 60: 1000–1005.

***Zima T, Tesar V, and Stipek S (1997).*** The influence cyclosporin on lipid peroxidation and superoxide dismutate adriamycin nephropathy in rats. Nephron, 75: 464–468.

# *التعرض لجرعة صغيرة من أشعة جاما تعدل تأثير ال كارنتين و كوركومين ومسحوق الثوم و خلاصة الشاى الأخضر فى الاعتلال الكلوى المحدث بدوكسروبسين فى الجرذان*

**سناء عبد الباقى قناوى رشا رضوان رضوان* ,عصمت عبد السلام شعبان* , *هشام على سالم* و**
قسم الأدوية و السموم – كلية الصيدلة – جامعة القاهرة
* قسم البحوث الدوائية الإشعاعية – المركز القومى لبحوث و تكنولوجيا الإشعاع – هيئة الطاقة الذرية

تم دراسة التأثير الوقائى المحتمل للتعرض لجرعة صغيرة من أشعة جاما فى وجود أو غياب ال كارنتين , كوركومين , مسحوق الثوم أو مستخلص الشاى الأخضر فى الاعتلال الكلوى المحدث بدوكسروبسين فى الجرذان.

تم اجراء تجربة مبدئية و ذلك لأختيار الجرعة المناسبة لدواء دوكسروبسين لاحداث اعتلال كلوى. و فى هذه التجربة وقع الأختيار على جرعة 5 مجم/كجم كجرعة واحدة لاحداث اعتلال كلوى فى خلال 15 يوم. و تمت دراسة التعديلات المحتملة فى وظائف الكلى.

و تضمنت هذه الدراسة ثلاثة مجاميع رئيسية من الجرذان, حيث صممت المجموعة الأولى لدراسة تأثير التعرض لجرعة صغيرة من الإشعاع فى الوقاية من الاعتلال الكلوى المحدث بدوكسروبسين و كذلك صممت المجموعة الرئيسية الثانية لتعيين الدور الوقائى لكوركومين و ال كارنتين و مسحوق الثوم و مستخلص الشاى الأخضر ضد الاعتلال الكلوى المحدث بدوكسروبسين بينما صممت المجموعة الرئيسية الثالثة لتقييم الأستخدام المؤازر لجرعة صغيرة من الإشعاع مع ال كارنتين أو كوركومين أو مسحوق الثوم أو مستخلص الشاى الأخضر فى الاعتلال الكلوى المحدث بدوكسروبسين فى كلى الجرذان.

اوضحت النتائج ان جرعة واحدة (5 مجم/كجم) من دوكسروبسين أدت إلى إحداث اعتلال كلوى فى خلال 15 يوم من تناول الدواء بدلالة الزيادة الملحوظة فى مستوى كرياتينين و يوريا و حمض اليوريك فى الدم.

قبل حقنها بدوكسروبسين بيوم أو ) 0.3 Gyجدير بالذكر أن تعرض الجرذان لجرعة صغيرة من الإشعاع ( ثلاثة أيام أدى إلى تحسن ملحوظ فى مستوى كرياتينين و يوريا و حمض اليوريك فى الدم على الرغم من أن تعرض الجرذان لنفس الجرعة من الإشعاع قبل حقنها بدوكسروبسين بسبعة أيام لم يكن له أى تأثير واقى فى حماية الكلى من الأضرار المحدثة بواسطة دوكسروبسين.

أظهر العلاج الوقائى بإستخدام ال كارنتين , كوركومين , مسحوق الثوم أو مستخلص الشاى الأخضر فى الجرذان المعرضة أو غير المعرضة لجرعة صغيرة من أشعة جاما قبل حقنها بدوكسروبسين وقاية من المتغيرات المفترض حدوثها بواسطة دوكسروبسين.

قبل حقنها ) 0.3 Gyو قد خلصت الدراسة إلى أن تعرض الجرذان لجرعة واحدة صغيرة من أشعة جاما ( بدوكسروبسين بيوم يزيد التأثير الواقى لكوركومين و ال كارنتين و مسحوق الثوم و مستخلص الشاى الأخضر ضد الاعتلال الكلوى المحدث بواسطة دواء دوكسروبسين فى الجرذان.