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# The Effect of Thymoquinone on the Activities of Drug Metabolizing Enzymes Following Gentamicin - Induced Nephrotoxicity in Rats

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## Abstract

**Objectives:** The present study investigated the effects of thymoquinone on the renal activities of drug-metabolizing enzyme following gentamicin-induced nephrotoxicity in Wistar breed rats. Intraperitoneal administration of thymoquinone alone in rats at the dose rate of 10 mg/kg daily for ten consecutive days did not produce toxic effects in the kidney or change its drug metabolizing capacity.

**Results:** However, nephrotoxicity was produced in Rats injected intraperitoneally with gentamicin daily at the dose rate of 80 mg/kg body weight for ten consecutive days, where there was significant increase in the concentrations of serum creatinine and blood urea compared to control rats ($P < 0.0005$) and those treated with thymoquinone alone ($P < 0.0005$), or those given thymoquinone and gentamicin concomitantly (10 mg/kg and 80 mg/kg intraperitoneally daily for ten consecutive days, respectively) ($P < 0.0005$). In addition, injection of gentamicin illustrated a tendency to decrease, although not statistically significant, in the kidney concentration of reduced glutathione. Furthermore, gentamicin administration resulted in a significant decrease in the renal concentration of cytochrome P-450 ($P < 0.05$), while it could not produce significant changes in the renal activities of phase II drug metabolizing enzymes namely, UDP-glucuronyltransferase and glutathione-S-transferase compared to values obtained for control rats and those treated with thymoquinone alone or coadministered with gentamicin. These findings confirm the nephrotoxic effects of gentamicin and its ability to decrease the renal activities of phase I drug metabolizing enzymes as shown by the significant reduction in the concentration of cytochrome P-450 in the kidneys of treated rats.

**Conclusion**: It can be concluded that thymoquinone coadministration with gentamicin can induce protective effects against gentamicin nephrotoxicity accompanied with restoration of the concentration of cytochrome P-450 to normal levels in the kidneys of treated rats.

**Key words:** Drug metabolism, gentamicin; nephrotoxicity; rats; thymoquinone

## Introduction

Gentamicin is an aminoglycoside antibiotic, widely used in clinical practice for the treatment of life threatening gram-negative infections. However, its use is generally limited by its nephrotoxicity, which takes place in about 10 – 30% of treated patients *(Karahan et al., 2005)*. Nephrotoxicity induced by gentamicin is characterized by an increase in plasma creatinine and

urea levels and severe proximal renal tubular necrosis, followed by deterioration and renal failure *(Cuzzocrea et al., 2002; Al-Majed et al., 2002)*. It is well documented that gentamicin nephrotoxicity is due to enhanced generation of reactive oxygen species (*Al-Majed et al., 2002)*. Hence, several compounds known for their antioxidant properties have been investigated to combat gentamicin renal toxic effects. Among these compounds was *Nigella sativa* oil and thymoquinone *(Ali, 2004 and Sayed-Ahmed and Nagi, 2007)*. Thymoquinone is a major active constituent of *N. sativa*. It was reported to produce several pharmacological effects including antioxidant, and scavenger of free radicals and superoxide anions effects *(Mansour et al., 2001 and Badary et al., 2003)*. Other effects of thymoquinone include hepatoprotective activity and improvement of cisplatin-induced nephrotoxicity *(Badary et al., 1997 and Daba et al., 1998)*.

Nephrotoxicity produced by gentamicin may be associated with cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage *(Kehrer, 1993)*, which may be postulated to cause inhibitory effects on the activities of drug metabolizing enzymes. Changes in the activities of drug metabolizing capacity may lead to pharmacological or toxicological consequences. Therefore, in view of the protective effects of *N. sativa* and thymoquinone against gentamicin induced nephrotoxicity *(Ali, 2004 and Sayed-Ahmed and Nagi, 2007)*, it was thought of interest to investigate in this study the effects of thymoquinone on drug metabolizing enzymes activities, namely the concentration of cytochrome p-450, a major constituent of mixed function oxidase, MFO, and the activities of the phase II drug metabolizing enzymes UDP-glucuronyltransferase and glutathione-S-transferase, and whether the protective effects of thymoquinone against gentamicin toxicity may extend to the reversal of expected delirious effects produced by gentamicin on the activities of drug metabolizing enzymes in the kidneys of treated rats.

## Material and Methods

***Animals***

Healthy Wistar breed rats, 10-12 weeks of age and weighing 180-230 g were used. They were obtained from the Laboratory Animal House, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. Animals were housed in clean rodent cages, in a room at relative humidity not less than 30% and not exceeding 70%, at room temperature of $22^0C \pm 3^0C$, with artificial lighting with a sequence being 12 hours light and 12 hours dark. Animals were fed on a commercially prepared standard pelleted diet for rats and were supplied with drinking water *ad libitum*. Animals were randomly selected, and marked to permit individual identification, and kept in their cages for one week prior to experiment to allow for acclimatization to the laboratory conditions. The rats were maintained and all experimental procedures were executed in accordance with the NIH guidelines for the Care and Use of Laboratory Animals *(National Institutes of Health, 1985)*.

***Experimental Design***

A total of 24 male rats were used in this experiment. They were divided into four groups, each of six animals. Rats representing group A served as untreated normal controls. They were injected intraperitoneally with 1 mL of propylene glycol daily for ten consecutive days. Animals of group B were injected intraperitoneally with gentamicin (Gentam injection, SPIMACO, Qassim, Kingdom of Saudi Arabia) at the dose rate of 80 mg/kg body weight every day for ten consecutive days. Rats allocated for group C were injected

intraperitoneally daily with thymoquinone (2-isopropyl-5-methyl-1, 4-benzoquinone; Sigma-Aldrich Chemical Company, St. Louis, MO, USA) at the dose rate of 10 mg/kg (dissolved in 1ml of propylene glycol) daily for ten consecutive days. Animals of group D were injected intraperitoneally with thymoquinone at the dose rate of 10 mg/kg and one hour later they were injected intraperitoneally with gentamicin at the dose rate of 80 mg/kg daily for ten consecutive days.

Blood samples (1.5 ml) were obtained from all animals on the eleventh day, 24 hours after the last drug injections, under light ethyl ether anaesthesia, from the eyes (venous pool) by sino-ocular puncture *(Waynforth, 1980)* into heparinized tubes and centrifuged at 900 g for 10 min, to separate plasma, which was then stored at – 20$^{O}$C pending analysis for the determination of serum creatinine (mg/dL) and blood urea (mg/dL).

Rats were sacrificed by decapitation about one hour after the collection of blood samples. Carcasses of animals were opened immediately and kidneys were removed and quickly immersed in liquid nitrogen, wrapped in aluminum foil and then stored in liquid nitrogen until analysis (within two weeks).

***Tissue Preparation***

All step of tissue preparation were carried out on ice. The kidney cortex was trimmed out, homogenized in ice-cold isotonic KCl (0.15 M, pH 7.4) by 6-8 strokes in a motor-driven Teflon homogenizer to give 20% kidney homogenates. The crude homogenates were centrifuged at 4ºC at 10 000 g for 10 min in a refrigerated centrifuge. Microsomal-rich supernatants were decanted and parts were used for the estimation of the activity of UDP-glucuronyltransferase and the concentrations of protein and reduced glutathione. The left supernatants were further centrifuged at 100 000 g at 4ºC for one hour. The cytosolic fractions (the supernatants) were decanted and used for the estimation of glutathione-S-transferase activity and cytosolic protein concentration. The microsomal pellets were resuspended in ice-cold isotonic KCl (0.15 M, pH 7.4) with a homogenizer. The microsomal suspensions were employed for the determination of microsomal protein and cytochrome P-450 concentrations.

***Biochemical Analysis***

Plasma creatinine concentration was estimated according to the method of *Larsen (1972)*. Blood urea was determined using the method of *Hallet and Cook (1971)*. All assays were done using samples in triplicate for each animal. The kidney reduced glutathione concentration was determined by the method of *Sedlak and Lindsay (1968)*. Protein concentration in microsomal-rich supernatants of kidney homogenates, in the cytosolic fractions and in the microsomal suspensions was determined according to the method of *Lowry et al. (1951)*, as modified by *Miller (1959)*, using bovine albumin as a standard. The obtained protein concentrations were used for the adjustment of protein concentrations in enzymatic reactions mixtures and for the calculation of cytochrome P-450 concentration and drug metabolizing enzymatic activities. The concentration of cytochrome P-450 was determined according to the method of *Omura and Sato (1964)*, as described by *Mazel (1971)*. The activity of UDP-glucuronyltransferase was estimated according to the method described by *Dutton and Storey (1962)* by estimating o-aminophenyl-glucuronide concentration using o-aminophenol as a substrate. The cytosolic fraction activity of glutathione-S-transferase was determined by the spectrophotometric method of *Habig et al. (1974)* by determining the concentration of 2,4-dinitrophenylglutathione. Before embarking on the estimation of drug metabolizing enzyme activities, preliminary experiments were carried out to adjust for the optimum conditions of the reactions; particularly, substrate concentration, pH of buffer used, amount of homogenate and incubation period. All enzymatic reactions were conducted at 37ºC under air at conditions of initial velocity with appropriate blanks. Linearity with protein concentration and with time was ensured.

***Statistical Analysis***

The data is presented as arithmetic means ± SD. Data was analyzed using one-way analysis of variance (ANOVA) to compare means, Bonferroni test was used to find significant

differences among means and to adjust for multiple comparisons using SPSS version 12 statistical analysis software for Windows (SPSS Inc., Chicago, IL, USA). P values of less than 0.05 were considered significant.

## Results

During the period of the experiment no clinical abnormalities were observed in all rats. No animal died. Postmortem examinations of internal organs of rats didn't show evidence of pathological changes. Table I shows that the administration of thymoquinone either alone or combination with gentamicin produced no change in the concentrations of creatinine and blood urea compared to control rats. While the injection of gentamicin induced significant increase in the concentrations of serum creatinine and blood urea compared to control rats.

There was no change in the concentration of reduced glutathione in the kidneys of animals treated either with gentamicin or thymoquinone alone or when gentamicin was injected together with thymoquinone as compared to untreated control rats (Table I). As illustrated in Table II, significant reduction was observed in the concentration of renal microsomal cytochrome P-450 in rats treated with gentamicin when compared to untreated control rats and those treated with thymoquinone alone ($P < 0.05$ and $P < 0.0025$, respectively). However, treatment with thymoquinone was shown to produce no change in the concentration of cytochrome P-450 in the kidneys of rats in comparison to control animals. Administration of thymoquinone or gentamicin either alone or together in rats caused no significant change in the renal activities of UDP-glucuronyltransferase or glutathione S-transferase enzymes in comparison to untreated control animals.

## Discussion

The present study has confirmed the toxicity of gentamicin in the kidneys of rats. The evidence for this nephrotoxicity is depicted by the rise in the concentrations of serum creatinine and blood urea. In the present study, although the kidney concentration of reduced glutathione was not significantly reduced in gentamicin treated rats, however, it showed a tendency for decrease, which demonstrates a further indication to the nephrotoxicity of gentamicin in the treated rats. These findings are agreement with the previous observations that gentamicin nephrotoxicity leads to significant elevations in the concentrations of plasma creatinine, blood urea and kidney reduced glutathione *(Ali, 2002 and Ajami, et al., 2010)*. However, concomitant injection of thymoquinone with gentamicin was able to produce complete restoration of the normal levels of plasma creatinine and blood urea and reversal of kidney glutathione to the values observed in untreated control and thymoquinone treated rat. Therefore, our results confirm the ability of thymoquinone which the active constituent of *N. sativa* to protect the kidneys of rats from the toxic effects of gentamicin as reported by *Sayed-Ahmed and Nagi (2007)* for thymoquinone, and *Ali (2004)* and *Yaman et al. (2010)* for *N. sativa*.

Nephrotoxicity effect is one of the most clinically important and common side effects of aminoglycoside antimicrobial drugs, mainly gentamicin *(Karahan, et al. 2005)*. Following parenteral administration of gentamicin, it is largely excreted through the kidney. It tends to accumulate in the renal cortex leading to cellular necrosis *(Cuzzocrea et al., 2002 and Nagai and Takano, 2004)*. It is believed that nephrotoxic effects induced by gentamicin may be mediated through the liberation of oxygen free radicals, particularly superoxide anion and hydrogen peroxide *(Yanagida, et al. 2004 and Karahan, et al. 2005)*. These oxygen free radicals lead to vasoconstriction and decrease glumerular filtration rates. In addition, they cause cellular injury and necrosis through lipid peroxidation and protein modification. Accordingly, several antioxidant agents have shown protective effects against gentamicin-induced nephrotoxicity, these antioxidant plants and plant products include *N. sativa* oil *(Ali, 2004 and Yaman et al., 2010)*, thymoquinone *(Sayed-Ahmed and Nagi, 2007)*, *Crocus sativus (Ajami, et al., 2010)* and *Rhazya stricta Decne (Ali, 2002)*.

The present study indicates that the treatment of rats with thymoquinone has no effect on the

renal concentration of cytochrome P-450 and the phase II drug metabolizing enzymes UDP-glucuronyltransferase and glutathione-S-transferase. However, injection of gentamicin was able to decrease the concentration of cytochrome P-450 in the kidneys of rats. This reduction may be related to the interference of gentamicin toxicity with the integrity of renal endoplasmic reticulum in gentamicin treated rats. It is well documented that gentamicin nephrotoxicity is related to oxidative damage. The drug induces reactive oxidative species which is associated with depletion of intracellular concentration of reduced glutathione, which may lead to increased cellular sensitivity to oxidative and chemical injury, and consequently might result in decreased concentration of cytochrome P-450, and inhibition in the activities of dependent phase I drug metabolizing enzymes *(Conklin, 2000)*. Whereas, thymoquinone when was administered concomitantly with gentamicin resulted in the restoration of cytochrome P-450 concentration to the renal levels determined in normal untreated and thymoquinone treated rats. This observation is accord with the cellular protective and antioxidant properties of thymoquinone in the kidneys of treated rats, as confirmed by the present study and previously published research reports *(Ali, 2004; Sayed-Ahmed and Nagi, 2007 and Yaman et al., 2010)*, who stated that coadministration of thymoquinone with gentamicin was able to reverse deleterious effects induced by the latter drug in the renal tissues of rats. It was observed that UDP-glucuronyltransferase and glutathione-S-transferase were relatively insensitive to the nephrotoxic effects produced by gentamicin, which is in agreement to the previous finding that phase II drug metabolizing enzymes are more resistant to chemical and drug-induced cellular injury *(Gregus et al., 1982)*, because they are located in the inner layers of the endoplasmic reticulum.

In conclusion, the present findings demonstrated that gentamicin may produce deleterious effects on renal phase I drug metabolizing enzymes as illustrated by the decrease concentration of cytochrome P-450, which could be reversed by concomitant administration of thymoquinone. In the same time phase II drug metabolizing enzymes are resistant to gentamicin induced renal cellular oxidative damage. Therefore, in view of these facts, effects of gentamicin on renal activities of drug metabolizing enzymes may lead pharmacological and toxicological consequences. Therefore, caution should be taken for drugs used for therapeutic purposes as gentamicin.

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**Table I.** Concentrations of Serum Creatinine, Blood Urea and Kidney's Reduced Glutathione in Rats Following Treatment with Gentamicin Alone or with Thymoquinone

| | Control | Treated | | |
|---|---|---|---|---|
| | Group A (n=6) | Group B (n=6) | Group C (n=6) | Group D (n=6) |
| Serum creatinine (mg/dL) | 0.35 ± 0.12 [a,] | 1.86 ± 0.52 [a,b,c] | 0.31 ± 0.12 [b] | 0.56 ± 0.15 [c] |
| Blood urea (mg/dL) | 55.0 ± 9.4 [a] | 149.3 ± 25.1 [a,b,c] | 53.8 ± 13.0 [b] | 66.7 ± 15.1 [c] |
| Glutathione (umol/g) | 2.77 ± 0.88 | 1.80 ± 0.52 | 2.97 ± 0.89 | 2.85 ± 0.78 |

Values in the table are means ± SD.
Rats of group A were untreated controls, animals of group B were injected with gentamicin alone; animals of group C were administered with thymoquinone; rats of group D were treated with gentamicin and thymoquinone.
Values with similar superscript letters are significantly different: [a,b, c] at the level of $P < 0.0005$

**Table II.** Activities of Some Drug Metabolizing Enzymes in the Kidneys of Rats Treated with Gentamicin Alone or with Thymoquinone

| | Control | Treated | | |
|---|---|---|---|---|
| | Group A (n = 6) | Group B (n = 6) | Group C (n = 6) | Group D (n = 6) |
| Cytochrome P- 450* | 0.079 ± 0.016 [a] | 0.053 ± 0.012 [a,b] | 0.082 ± 0.016 [b] | 0.063 ± 0.011 |
| UDP-glucuronyltransferase** | 0.33 ± 0.05 | 0.30 ± 0.05 | 0.36 ± 0.07 | 0.33 ± 0.05 |
| Glutathione-S-transferase*** | 51.7 ± 9.5 | 42.8 ± 5.9 | 48.8 ± 8.2 | 47.8 ± 11.9 |

Values in the table are means ± SD.
Rats of group A were untreated controls, animals of group B were administered with gentamicin alone; animals of group C were injected with thymoquinone; rats of group D were treated with gentamicin and thymoquinone.
* Cytochrome P-450 Concentration (nmol/mg microsomal protein)
** UDP-glucuronyltransferase activity (nmol of o-aminophenylglucuronide formed/mg microsomal protein/min)
*** Glutathione-S-transferase activity (nmol of 2,4- dinitrophenylglutathione formed/mg cytosolic protein/min)
Values with similar superscript letters are significantly different: [a] At the level $P < 0.05$; [b] at the level $P < 0.025$

# تأثير الثايموكوينون على نشاط إنزيمات أيض الدواء بعد أحداث السمية في كلى الفئران بدواء الجنتمايسين

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**الهدف:** أجريت هذه الدراسة لتقصي الآثار التي يمكن أن يحدثها حقن مركب الثايموكوينون (المادة الفعالة في الحبة السوداء) في فئران الوستار على نشاط إنزيمات أيض الدواء في الكلى بعد إحداث السمية في الكلى بواسطة دواء الجنتمايسين.

**النتائج:** لم يحدث حقن مركب الثايموكوينون في داخل الصفاق في الفئران بجرعة 10 ملج لكل كيلوجرام يومياً لمدة عشرة أيام متتالية أي آثار سمية أو تغييرات في نشاط إنزيمات أيض الدواء في كلي الفئران التي تمت معالجتها بالمركب. لكن نتج عن حقن دواء الجنتمايسين، داخل الصفاق في الفئران المعالجة بجرعة 80 ملج لكل كيلوجرام يومياً لمدة عشرة أيام متتالية، سمية في الكلى، حيث وجد أن هنالك ارتفاعاً معتبراً في تركيز الكرياتينين في المصل واليوريا في الدم، عند مقارنتها بفئران مجموعة السيطرة و تلك التي تم حقنها بمركب الثايموكوينون منفرداً، أو مجموعة الفئران التي تم حقنها في نفس الوقت بالثايموكوينون و الجنتمايسين (معدل الجرعة 10 ملج لكل كيلوجرام و 80 ملج لكل كيلوجرام، على التوالي). بالإضافة إلى ذلك فقد لوحظ أن لدواء الجنتمايسين قدرة على إحداث قابلية لتناقص تركيز الجلوتاثيون المختزل، و لكن لم يكن هذا التناقص ذو دلالة إحصائية. كما تم ملاحظة أنه قد نتج عن حقن الجنتمايسين تناقص معتبر في تركيز السايتوكروم ب-450، بينما لم تحدث تغييرات معتبرة في نشاط إنزيمات المرحلة الثانية لأيض الدواء(جلوكورونايلترانسفيريز و جلوتاثيون سلفر ترانسفيريز) في كلى الفئران المعالجة بدواء الجنتمايسين، وذلك عند المقارنة بالقيم التي تم قياسها في فئران مجموعة السيطرة و الفئران التي حقنت بالثايموكوينون لوحده أو مجموعة الفئران التي تم حقنها بالثايموكوينون و الجنتمايسين في نفس الوقت. تؤكد هذه النتائج التي تم الحصول عليها، على قدرة الجنتمايسين في إحداث السمية، كما تثبت قدرته في تقليل نشط إنزيمات المرحلة الأولى لأيض الدواء، بدليل تقليله لتركيز السايتوكروم ب-450 في كلى الفئران التي تمت معالجتها.

**الخلاصة:** يمكن أن نخلص من هذهـ الدراسة إلى قدرة مركب الثايموكوينون عند حقنه متزامناً مع دواء الجنتمايسين على إحداث تأثيرات واقية من سمية الجنتمايسين في كلى الحيوانات المعالجة بالإضافة إلى قدرته على رفع تركيز السايتوكروم ب-450 و العودة به للمستوى الطبيعي في كلى الفئران المعالجة.