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Orginal Article

Olanzapine-induced renal damages and metabolic side effects: the protective effects of thymoquinone

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Abstract

Aim: The goal of the study is to examine the protective qualities of thymoquinone (TQ) against the side-effects of olanzapine (OLZ) in an experimental model in rat kidneys.

Material and Methods: Thirty five female Spraque-Dawley rats were divided into 5 groups (n=7): Control, OLZ, OLZ+TQ-1, OLZ+TQ-2, OLZ+TQ-3. All treatments were administered for two weeks by gavage. Two weeks administration of OLZ (4 mg/kg, once a day for the first week, 8 mg/kg once a day for the second week, p.o.) was given to all groups, except control. TQ was administered (25, 50, 100 mg/kg, once daily) by gastric tube. On treatment day 15, kidney tissues were removed for analysis.

Results: TQ increased the total antioxidant status (TAS) and decreased creatinine (Cr), blood urea nitrogen (BUN), oxidative stress index (OSI) and total oxidant status (TOS) levels significantly ($p<0.05$).

Conclusion: These results revealed that TQ improved the side-effects of OLZ, contributed to the oxygen radical scavenging activity, increased antioxidant activity and had ameliorative effects on recovery of increased serum biochemical and oxidative stress parameters. Thus, these results demonstrated that TQ had protective and antioxidant effects against adverse effects of OLZ in kidney of rats. TQ could be an effective course of therapy to enhance therapeutic efficacy.

Keywords: Thymoquinone; Olanzapine; Adverse Effects; Kidney; Apoptosis.

INTRODUCTION

Second-generation agents (i.e., OLZ) are defined by multi-receptor affinity and offer a variety of therapeutic benefits (1). Second-generation atypical antipsychotics (SGAs), are currently of great interest to clinicians due to their widespread use in clinics. OLZ is one of the most widely prescribed antipsychotic drugs to treat the symptoms of schizophrenia and bipolar disorder but it is often associated with adverse-effects. Additionally, various metabolic disturbances are escorted by its clinical use (2).

Although treatments with atypical antipsychotics are effective in psychiatric diseases the effect of OLZ on the kidneys requires further investigate. Therefore, there is a great interest in developing a better treatment strategy in order to obtain a good therapeutic efficacy without increasing the side-effects. Atypical antipsychotic drugs are linked to kidney damage, new research suggests, causing investigators to call for their use in this population to be reevaluated (3). Medicinal plants nowadays are an important source of drug synthesis (4). The wide utilization of herbal compounds has encouraged scientists to research their impressive effects on health. TQ is a principal active ingredient of the Nigella sativa seeds (5). It has been informed to exhibit various pharmacological activities, such as antihypertensive (6), anti-inflammatory and anti-cancer (7,8), antidiabetic (9) and analgesic properties (10). TQ is also reported to possess strong antioxidant properties. The high biological activity and low systemic toxicity of TQ make it a promising alternative to conventional therapeutic compounds (11). The influence of TQ on OLZ-induced nephrotoxicity has not previously been studied. Therefore, the present study was designed to investigate the possible beneficial impact of oral supplementation with TQ against OLZ-induced renal damage in rats for the first time. To achieve our goal, we performed several biochemical and histological analyses in female rats.

MATERIAL and METHODS

Chemicals

OLZ was obtained from Ali Arif Ilac Sanayi (ARIS), İstanbul,

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Turkey. TQ (purity > 98%) was purchased from Sigma. All the other chemicals used for tests in the present study were of the best analytical grade and were bought from Sigma Chemical Co.

Animals

Thirty five female Sprague Dawley rats were used in the present study. These rats, weighing from 240 to 260 g purchased from the Fırat University Laboratory Animal Production and Research Center. All animal care and follow-up were performed at this Center. The experimental procedures were approved by Fırat University Faculty of Medicine, Laboratory Animals Ethics Committee (Protocol # 2015/26). The rats were housed and kept under standard conditions: 12-h light and 12-h dark periods. Pellet food and tap water were provided ad libitum. OLZ and TQ were administered to rats for 2-weeks.

Experimental design

In our study, thirty five female Sprague Dawley rats aged twelve weeks old (240-260 g) were used. Rats were randomly divided to five experimental groups (n = 7 each) as follows: group 1, control; group 2, OLZ; group 3, OLZ+TQ-1; group 4, OLZ+TQ-2; group 5, OLZ+TQ-3. Physiological saline solution was given to the first group by gavage once a day. OLZ (4 mg/kg) was given to all groups, except control by the gavage route once daily for the first week. Then OLZ (8 mg/kg) was given to all groups, except control by the gavage route once daily for the second week. TQ (25 mg/kg) was given to OLZ+TQ-1 group. TQ (50 mg/kg) was given to OLZ+TQ-2 group. TQ (100 mg/kg) was given to OLZ+TQ-3 group.

The assigned dosage of powdered OLZ was administered to female Sprague Dawley rats according to a previous report (12). TQ was given by gastric tube daily between 8:00 and 9:00 a.m. TQ dose and duration was chosen according to results from previous study (13).

All compounds were suspended in physiological saline solution and treated by gavage route once a day. Body weights were recorded at the beginning of the study and at the end of the study.

The treatment course lasted 2 weeks for all groups. At the end of the 2nd week of treatment period, rats were decapitated under diethyl ether anesthesia. Kindeys were excised and prior to storage at -80 oC for future use. Blood samples were placed within centrifuges at 3000 g then placed at -80 °C prior to analysis.

Biochemical analysis.

BUN and Cr levels were measured to evaluate the renal function using Hitachi automatic biochemical analyzer 7060 c (Japan) and Roche Diagnostics kits (Mannheim, Germany) by the picric acid method (14).

TAS, TOS and OSI determination

TAS, TOS and OSI levels were measured spectrophotometrically using Erel method. Measurement of TAS and TOS in serum samples was defined by TAS and TOS kit (REL Assay Diagnostics, Gaziantep, Turkey). OSI was calculated using the formula OSI = TOS/TAS (15-17).

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay.

Paraffin block sections (5-6 µm) were taken to slides with poly-L-lysine. ApopTagPlus Peroxidase in Situ Apoptosis Detection Kit (Chemicon, cat no: S7101, USA) was utilized for detection of apoptotic cells in accordance with the manufacturer's instructions for use. In the assessment of TUNEL staining, cells with blue nuclei were normal, while brown nuclear staining was admitted as indicating apoptotic cells. At least 400 cells were counted on each field. Apoptotic index was calculated as a ratio of the TUNEL - positive cell number to the total cell number (normal + apoptotic cells) (18,19).

Statistical Analyses

Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, IL, USA). All data were expressed as mean values ± their standard errors (SEM). Normality for variables in the groups was determined by the Shapiro-Wilk test. ANOVA followed by the LSD post hoc test were used for the comparison of biochemical parameters and total oxidant/antioxidant levels. Significance was considered at the $p<0.05$ level. For histopathological analysis, results were expressed as the means ± standard deviation (SD). The statistical significant difference was determined by ANOVA followed by Tukey's multiple comparison test. Probability values (p) less than 0.05 were considered to be statistically significant.

RESULTS

Effects of OLZ and TQ on biochemical and oxidative stress parameters.

Levels of biochemical parameters in sera were measured and the results are shown in Table 1, Figure 1 and oxidative stress parameters are shown in Table 2, Figure 2. Cr level was significantly increased in the OLZ group compared to the control, OLZ+TQ-1, OLZ+TQ -2 and OLZ+TQ-3 groups ($p<0.05$). Cr levels were significantly increased in the OLZ+TQ-1 group compared to the OLZ and OLZ+TQ-2 groups ($p=0.004$, $p=0.015$ respectively) (Table 1; Figure 1).

BUN levels were significantly increased in the OLZ group compared to the control, OLZ+TQ-1, and OLZ+TQ-2 groups ($p=0.000$, $p=0.000$, $p=0.004$ respectively). BUN levels were significantly decreased in the OLZ+TQ-1 group compared to the OLZ and OLZ+TQ-3 groups ($p=0.000$, $p=0.016$ respectively) (Table 1; Figure 1).

Ameliorative effects of TQ treatment against OLZ administration significantly increased the TAS levels and decreased TOS, OSI levels ($p<0.05$). The control group had a significantly higher TAS levels compared to the OLZ group ($p=0.001$). The OLZ+TQ-1 group had a significantly higher TAS levels compared to the control, OLZ, OLZ+TQ-2 and OLZ+TQ-3 groups ($p=0.000$).

The OLZ+TQ-3 group had a significantly lower TAS level compared to the control and OLZ+TQ-1 groups ($p=0.013$, $p=0.000$ respectively).

TOS levels were significantly higher in the OLZ group

compared to the control, OLZ+TQ-1, OLZ+TQ-2 and OLZ+TQ-3 groups (p<0.001).

The OLZ+TQ-1 group had a significantly lower TOS level compared to the control, OLZ, OLZ+TQ-3 group (p=0.003). OSI levels were significantly higher in the OLZ group compared to the control, OLZ+TQ-1 and OLZ+TQ-2 groups (p=0.005, p=0.003, p=0.007 respectively) (Table 2; Figure 2).

Table 1. Levels of serum biochemical parameters for all groups

Parameters	Control	OLZ	OLZ+TQ-1	OLZ+TQ-2	OLZ+TQ-3	p
Cr (mg/dL)	0.48±0.00 ^{b,d,e}	0.54±0.01 ^{a,c,d,e}	0.45±0.00 ^{b,d}	0.38±0.01 ^{a,b,c}	0.42±0.04 ^{a,b}	0.000
BUN (mg/dL)	16.14±0.91 ^{b,e}	22.00±0.95 ^{a,c,d}	15.83±1.55 ^{b,e}	17.71±0.74 ^{b}	19.80±0.58 ^{a,c}	0.001

Each group represents the mean ± SEM for seven rats. ^{a}p < 0.05 vs control group; ^{b}p < 0.02 vs OLZ group; ^{c}p < 0.03 vs OLZ+TQ-1 group; ^{d}p < 0.04 vs OLZ+TQ-2 group; ^{e}p < 0.05 vs OLZ+TQ-3 group. Abbreviations: OLZ, olanzapine; TQ, thymoquinone; Cr, creatinine; BUN, blood urea nitrogen; OLZ+TQ-1, OLZ+25 mg/kg TQ; OLZ+TQ-2, OLZ+50 mg/kg TQ; OLZ+TQ-3, OLZ+100 mg/kg TQ. 4 mg/kg once a day for the first week, 8 mg/kg once a day for the second week of OLZ was given to all groups, except control group

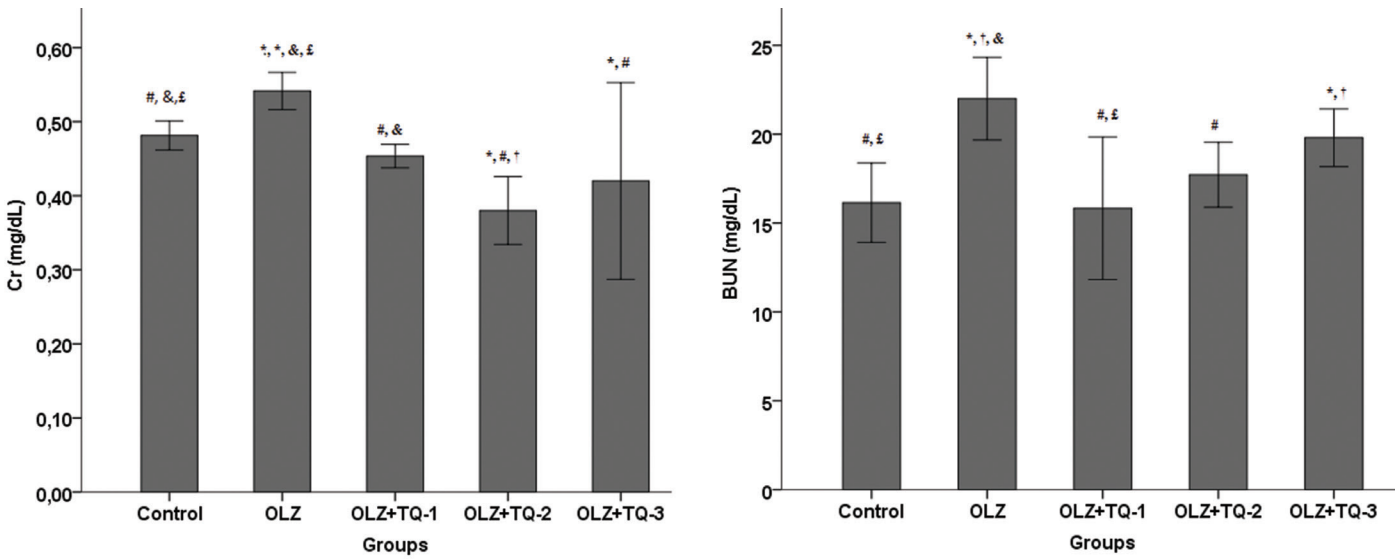

Figure 1. Effects of olanzapine, thymoquinone, and their coadministration on the kidney level of creatinine and blood urea nitrogen in rats after two weeks. Values are expressed as mean ± SEM of seven animals. ANOVA followed by the LSD post hoc test were used. * p < 0.05 versus control; # p < 0.05 versus OLZ-treated rats; † p < 0.05 versus OLZ+TQ-1 treated rats; & p < 0.05 versus OLZ+TQ-2 treated rats; £ p < 0.05 versus OLZ+TQ-3 treated rats. Abbreviations: OLZ, olanzapine; TQ, thymoquinone; Cr, creatinine; BUN, blood urea nitrogen; OLZ+TQ-1, OLZ+25 mg/kg TQ; OLZ+TQ-2, OLZ+50 mg/kg TQ; OLZ+TQ-3, OLZ+100 mg/kg TQ. 4 mg/kg once a day for the first week, 8 mg/kg once a day for the second week of OLZ was given to all groups, except control group.

Table 2. Comparison of serum oxidative stress parameters among the groups.

Parameters	Control	OLZ	OLZ+TQ-1	OLZ+TQ-2	OLZ+TQ-3	p
TOS (µmol/L)	9.90±1.66 ^{b,c}	17.46±1.98 ^{a,c,d,e}	5.24±0.80 ^{a,b,e}	7.70±0.33 ^{b,e}	12.43±0.56 ^{b,c,d}	0.000
TAS (mmol/L)	1.83±0.24 b,^{c,e}	0.76±0.19 ^{a,c}	3.38±0.26 a^{b,d,e}	1.31±0.1$^{6\,c}$	0.96±0.23 ^{a,c}	0.000
OSI (AU)	0.54±0.61 ^{b}	4.21±1.79 ^{a,c,d}	0.15±0.02 ^{b}	0.65±0.10 ^{b}	1.62±0.37	0.018

Each group represents the mean ± SEM for seven rats. ^{a}p < 0.01 vs control group; ^{b}p < 0.01 vs OLZ group; ^{c}p < 0.01 vs OLZ+TQ-1 group; ^{d}p < 0.03 vs OLZ+TQ-2 group; ^{e}p < 0.03 vs OLZ+TQ-3 group. Abbreviations: OLZ, olanzapine; TQ, thymoquinone; TAS, total antioxidant status; TOS, total oxidant status; OSI, Oxidative stress index; OLZ+TQ-1, OLZ+25 mg/kg TQ; OLZ+TQ-2, OLZ+50 mg/kg TQ; OLZ+TQ-3, OLZ+100 mg/kg TQ. 4 mg/kg once a day for the first week, 8 mg/kg once a day for the second week of OLZ was given to all groups, except control group. AU: Arbutrary Units

Evaluation of apoptosis in kidney tissues.

The results of the apoptotic index are shown in Table 3, Figure 3.

Using TUNEL assay to detect apoptotic renal tubular cells in the kidney sections, the control (Figure 3A) group demonstrated only a few TUNEL-positive cells. The number of TUNEL-positive cells markedly increased in the OLZ (Figure 3B) group compared with the control, OLZ+TQ-1, OLZ+TQ-2 and OLZ+TQ-3 groups (p<0.05). OLZ+TQ-1 (Figure 3C), OLZ+TQ-2 (Figure 3D) and OLZ+TQ-3 (Figure 3E) groups were similar and demonstrated rare TUNEL-positive cells.

Treatment with TQ (OLZ+TQ-1, OLZ+TQ-2 and OLZ+TQ-3 groups) (Figure 3C, 3D and 3E) diminished the number of TUNEL-positive cells as compared with the OLZ group (p<0.05).

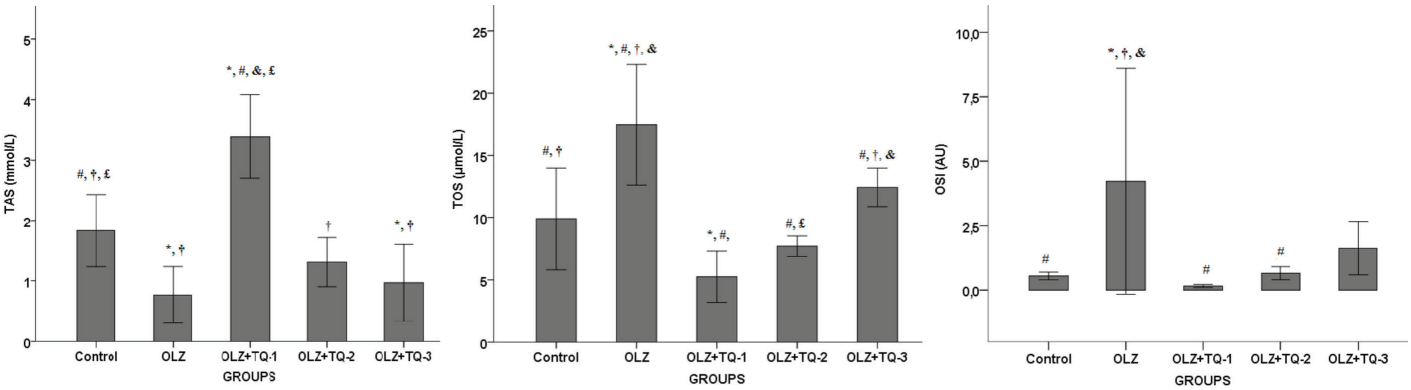

Figure 2. Effects of olanzapine, thymoquinone, and their coadministration on the levels of TAS, TOS and OSI in rats after two weeks. Values are expressed as mean ± SEM of seven animals. ANOVA followed by the LSD post hoc test were used. * p < 0.05 versus control; # p < 0.05 versus OLZ-treated rats; † p < 0.05 versus OLZ+TQ-1 treated rats; & p < 0.05 versus OLZ+TQ-2 treated rats; £ p < 0.05 versus OLZ+TQ-3 treated rats. Abbreviations: OLZ, olanzapine; TQ, thymoquinone; TAS, total antioxidant status; TOS, total oxidant status; OSI, Oxidative stress index; OLZ+TQ-1, OLZ+25 mg/kg TQ; OLZ+TQ-2, OLZ+50 mg/kg TQ; OLZ+TQ-3, OLZ+100 mg/kg TQ. 4 mg/kg once a day for the first week, 8 mg/kg once a day for the second week of OLZ was given to all groups, except control group. AU: Arbutrary Units.

Table 3. Effects of olanzapine and thymoquinone on apoptotic index (%) in rat kidneys	
Control	5.33±1.36[b,d]
OLZ	31.16±3.60[a,c,d,e]
OLZ+TQ-1	12.66±1.50[b]
OLZ+TQ-2	14.40±2.30[a, b]
OLZ+TQ-3	13.66±3.20[b]

The apoptotic index of all the groups. Values are mean ± SD for seven rats in each group. a: Significant from control; b: Significant from OLZ; c: Significant from OLZ+TQ-1; d: Significant from OLZ+TQ-2; e: Significant from OLZ+TQ-3 (p ≤ 0.05). Abbreviations: OLZ, olanzapine; TQ, thymoquinone; OLZ+TQ-1, OLZ+25 mg/kg TQ; OLZ+TQ-2, OLZ+50 mg/kg TQ; OLZ+TQ-3, OLZ+100 mg/kg TQ. 4 mg/kg once a day for the first week, 8 mg/kg once a day for the second week of OLZ was given to all groups, except control group. The extent of TUNEL staining was scored semiquantitatively as 0 (no), 1 (light), 2 (medium), and 3 (intense)

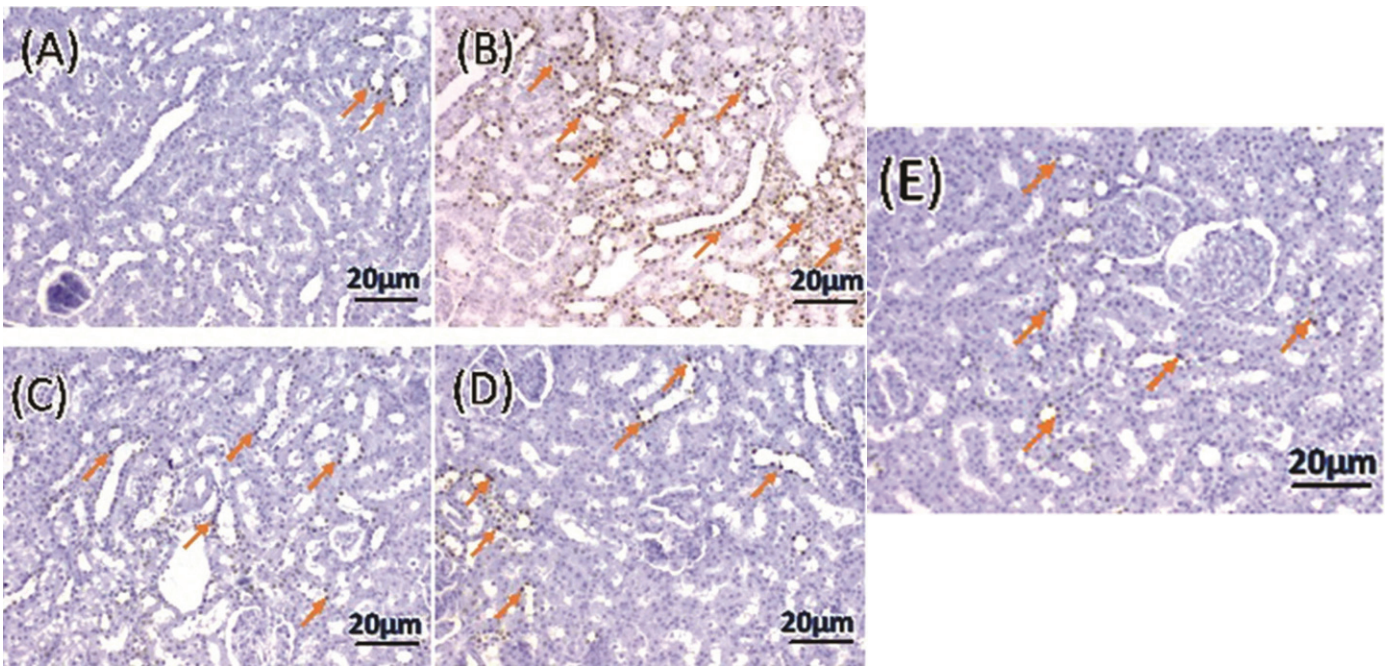

Figure 3. Representative photomicrographs of TUNEL staining in all five groups (scale bars=20 µm), showing: (A) Group 1 (control) only few TUNEL-positive cells (arrow); (B) Group 2 (OLZ) a lot of TUNEL-positive cells (arrows); (C) Group 3 (OLZ+TQ-1), (D) Group 4 (OLZ+TQ-2) and (E) Group 5 (OLZ+TQ-3) similarly rare TUNEL-positive cells (arrows). This analysis was exerted in at least eight areas of each kidney section (two sections/animal), and the sections were analyzed at 400× magnification. The evaluation of TUNEL staining was exerted based on the extent of the staining of apoptotic cells. The extent of TUNEL staining was scored semiquantitatively as 0 (no), 1 (light), 2 (medium), and 3 (intense).

DISCUSSION

Antipsychotic drugs are very much essential in the management and treatment of various mental illnesses. Although they have many beneficial effects, they are also not devoid of serious side effects (20). OLZ is an atypical antipsychotic drug used for the treatment of schizophrenia and bipolar disorder. Despite OLZ showed heavy metabolic side effects, among SGAs, it is efficaciously prescribed in the treatment of psychotic diseases (21). Many authors proposed a co-treatment between OLZ and compounds that regulate its metabolic side effects. Natural compounds, antioxidant and radical scavenger, might prevent and treat diseases (22). Therefore, health community interested to natural compounds that work either alone or cooperatively (23).

Nephrotoxicity is an adverse effect of OLZ, and the current study was made an attempt to study the effect of TQ on OLZ-induced nephrotoxicity in rats. In other studies also, OLZ-treated rats showed nephrotoxicity and this may be due to oxidative stress (24). TQ; antioxidative and cytoprotective effects have been shown in experimental drug-induced toxicity studies such as gentamicin nephrotoxicity (25), acetaminophen hepatotoxicity (26) and doxorubicin cardiotoxicity (27).

Kidneys perform a main role in the elimination of toxic substances procedure. The kidneys possess extraordinary ability for filtration, secretion, and reabsorption. Therefore they are more likely to be exposed to toxic materials. Recently numerous studies focused on the kidneys role for elimination of toxic substances and their effects on renal functions (28).

Treatment with the atypical antipsychotic, OLZ, led to significant increases in the formation of free radicals under all study conditions (29). Studies also showed that OLZ is able to influence the expression of antioxidant activity. In accordance with previous studies, there was a decrease in antioxidant capacity and an increase in oxidant levels after OLZ administration in our study (30). On the other hand, previous studies reported that TQ acted as a strong free radical scavenger (31,32). The useful effects of TQ, obtained in the present study, are very likely due to its strong antioxidant properties. Also, in a study by Ragheb et al., TQ exerts considerable antioxidant activity, free radical scavenging properties and augments the activity of antioxidant enzyme in different tissues (33). Our examination showed that under the treatment conditions used OLZ is able to increase formation of free radicals in rat blood, which can be attenuated by TQ. Interestingly, based on our findings TQ was able to improve oxidative stress caused by the OLZ in rat.

Several adverse outcomes attributed to atypical antipsychotic drugs are known to cause renal damage. Cr and BUN were the classical standards to evaluate renal damage (34). Accordingly, Hsu et al. demonstrated the observation of elevated Cr in an atypical antipsychotic drug administration (35). The current study demonstrates that OLZ exposure produced a significant increase in the levels of Cr and BUN indicating damaged structural and functional kidney integrity. Increased nephrotoxicity indicators (Cr and BUN) and degenerative changes in kidney tissuesmay point to the contribution of mitochondrial dysfunction and energy depletion. Consistent with these observations, the beneficial effects of TQ were identified in the prevention of renal tubular damage and dysfunction. In addition, oral supplementation of TQ demonstrated the restoration of the elevated Cr and BUN to the normal levels (36). TQ co-treatment ameliorated these changes in all doses, with an especially obvious effect in high doses. These results are supported by data in the literatüre (37).

The OLZ-induced renal damage was approved by histopathological analysis of rat renal sections. Apoptosis, a specific form of cell death, which happened in various tissues under certain circumstances, clearly differs from necrosis (38). Our study exhibited a significant decrease in the number of apoptotic renal cells of TQ-treated rats. Accordingly, TQ has a remarkable protective effect against OLZ-induced renal damage. Consequently, TQ significantly improved renal oxidative damage and apoptotic cell death. Our results are consistent with Mahmoud et al. who report the anti-apoptotic effect of TQ in various kidney damage models (39). OLZ induced remarkable changes in renal architecture as demonstrated by extension of capsular space and tubular degeneration. Treatment of TQ inverted these renal structural and functional abnormalities. These toxic effects were effectively prevented by antioxidant, TQ, administration. In the 3 doses we applied in our study, 25 mg/kg TQ was found to provide the maximum protective effect on kidneys. This situation demonstrated that TQ could protect against OLZ induced kidney damage. This reno-protective effect of TQ was previously reported in various experimental models of kidney damage (40).

In conclusion, our study demonstrated that TQ had a protective effect against OLZ-induced renal damage and apoptotic cell death in the kidneys of rats. The antioxidant and anti-apoptotic activities can be considered the basic factors responsible for the nephroprotective effect of TQ. Therefore, TQ displayed a potential therapeutic choice to prevent renal tissue damage and dysfunction. Hence, TQ may be a clinically encouraging agent in OLZ-induced renal damage and its metabolic side effects. Further investigations should be undertaken to analysis the possible effect of TQ on renal damage in human and animal models.

Declaration of Conflicting Interests: The authors declare that there are no conflicts of interest.

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