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Protective effects of resveratrol on testicular oxidative stress induced of MK-801 in mice

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Summary: Recently, it has been discovered that the doses of the MK-801 causing schizophrenia also initiate the oxidative stress in the testis. The current study investigated the protective role of the resveratrol against the MK-801 induced oxidative stress in the testis in mice. The testis weight, the total oxidant-antioxidant status, seminiferous tubules diameter, epithelial height, testicular pathology, and epididymal sperm motility were evaluated. A total of 24 male mice were equally divided into 4 groups so that each group included 6 mice. In the study, Group I (control group) was intraperitoneally received with 0.9% saline (10ml/kg). Group II was i.p. administered with MK-801 (1mg/kg), Group III was treated with i.p. MK-801 (1mg/kg) and resveratrol (40mg/kg), and the Group IV was treated i.p. with resveratrol (40mg/kg). All injections were performed for 14 days. According to the results, in the testis of mice in Group II the oxidative stress was observed. The oxidative stress affected the seminiferous tubules pathologically and decreased the weight of the testis and sperm motility. However, resveratrol protected the MK-801 induced oxidative stress in the testis. Moreover, this dose of the resveratrol increased the sperm motility compared with the controls. In conclusion, MK-801 caused oxidative stress in the testis and resveratrol had a protective effect against this damage.

Keywords: MK-801, oxidative stress, resveratrol, schizophrenia, testis.

Fare testislerinde Mk-801'le indüklenen oksidatif strese karşı resveratrolün koruyucu etkisi

Özet: Günümüzde MK-801'in şizofreniye sebep olan dozlarının testiste oksidatif strese de neden olduğu ortaya çıkmıştır. Bu çalışma fare testislerinde MK-801 kullanılarak ortaya çıkartılan oksidatif strese karşı resveratrolün koruyucu etkisini araştırmak amacıyla yapılmıştır. Testisler ağırlık, toplam oksidan-antioksidan seviyeleri, seminifer tübüllerin çapları ve epitel dokularının yükseklikleri, patolojik ve epididimal sperm motilitesi yönünden değerlendirilmiştir. Bu amaçla 24 fare alınarak grup başına 6'şar fareden oluşan 4 grup oluşturulmuştur. Grup I, kontrolden oluşmuştur ve bu gruba intraperitoneal yolla %0,9 FTS (10ml/kg) verilmiştir. Grup II'ye i.p. yolla MK-801 (1mg/kg), Grup III'e i.p. yolla MK-801 (1mg/kg) ve resveratrol (40mg/kg), Grup IV'e de i.p. olarak resveratrol (40mg/kg) verilmiştir. Uygulamalar on dört gün boyunca sürmüştür. Bu sürenin sonunda testisler çıkartılmış ve yapılan incelemeler neticesinde testiste ikinci grupta MK-801'in oksidatif strese sebep olduğu saptanmış, testis ağırlığında azalma, sperm motilitesinde düşme ve tübüllerde patolojik değişiklikler olduğu görülmüştür. Resveratrolün ise oksidatif strese karşı testisi koruduğu ortaya konulmuştur. Ayrıca resveratrol grubunda kontrole göre sperm motilitesinin arttığı gözlenmiştir. Sonuç olarak MK-801'in testiste oksidatif strese sebep olduğu ve resveratrolün de koruyucu etkisinin bulunduğu ortaya çıkarılmıştır.

Anahtar sözcükler: MK-801, oksidatif stres, resveratrol, şizofreni, testis.

Introduction

The MK-801 is an N-methyl-D-aspartate (NMDA) receptor antagonist in the glutamatergic category and acts by disrupting the Wnt signaling pathway (9, 26). The hypofunction of the NMDA receptor impairs the glutamatergic system and leads to schizophrenia illness (10, 11, 15, 26). Experimentally, the NMDA receptor could be blocked with certain doses of MK-801 (24, 25, 26). Recently, it has been discovered that the 5 days 0.5 mg/kg intraperitoneal (i.p.) dose of the MK-801 has emerged the oxidative stress in the testis because the glutamatergic system units like transporters and receptors are not only placed in the nervous system (14, 16). They are also placed in the several peripheral body parts like adrenal, pituitary, pineal glands, pancreatic islets, retina, liver, kidney, intestine, heart, lung, skeletal muscle and bone marrow (7, 14, 16). The metabotropic glutamate receptors were also found in the human and rat testis (21, 22). In addition to the human and rat, the mice testis has both glutamate transporters and receptors (7).

The MK-801 impairs the glutamatergic system in the testis and induces the oxidative stress. The oxidative stress is the abundant production of the reactive oxygen species (ROS) in the tissue. Accumulation of the ROS impairs the antioxidant system and may damage and cellular injury occur in the tissue (14, 16). Actually, the body already produces reactive oxygen metabolites. In the testis, during the spermiogenesis, the dead and abnormal spermatozoon production causes reactive oxygen metabolites normally. However, if ROS production exceeds certain limits or the antioxidant system is inadequate, tissue damage may occur due to lipid peroxidation. Because of the highly rich polyunsaturated fatty acid content of testicular membranes, the ROS impairs the membrane lipids with initiating the lipid peroxidation (1). Lipid peroxidation in the sperm cell membrane impairs the midpiece of the sperm cell and thus canceled the capacitation and the acrosome reaction (1,6,13).

Resveratrol is a phytoalexin with an antioxidant feature and especially found abundantly in the peanuts and grapes (2, 5). It could be used as anti-oxidant, anti-inflammatory, anti-cancer, anti-viral, anti-aging, anti-diabetic, and cardio-protectant (2, 5, 12, 18). Recent studies have shown that resveratrol could be used successfully as a testicular protectant against oxidative stress (5, 12, 13, 18). It protects the spermatocytes against the lipid peroxidation which appears in the sperm cell membrane and DNA damage by increasing antioxidant enzyme release (5, 18). The resveratrol may be beneficial in testicular dysfunctions and much effective than melatonin, vitamin E and α-phenyl-N-tert-butyl nitrone (17). Meanwhile, the resveratrol improves sperm quality and motility (13).

In the present study, the possible protective role of the resveratrol was aimed to evaluate against the testicular oxidative stress conducted by the chronic dose of MK-801. The previous researches were detected that the 1mg/kg i.p. injections for 14 days is the chronic dose of the MK-801 in mice (24, 25). In this study, the effects of the oxidative stress in the mice testis aimed to understand by measuring the testicular total oxidant-antioxidant parameters, pathology, seminiferous tubule diameter, epithelial height, and epididymal sperm motility.

Material and Methods

Animals: The current study was carried out on 24 male Balb/C mice housed at the Experimental Animal Research Centre of Afyon Kocatepe University following ethical committee approval (Ethical Committee for Experimental Animals, Afyon Kocatepe University, AKUHADYEK-132-16). All mice were placed in the plexiglass cages with a 12/12h light/dark cycle and fed ad libitum with the commercial food pellets and tap water. The room temperature was adjusted to 20-22 ^{0}C.

Groups and dosages: This study was performed on 24 male mice testis. The mice were divided into 4 groups and each group included 6 mice. The Group I was the control and intraperitoneally (i.p.) received with 0.9% saline (10ml/kg) (due to MK-801 (Sigma, St. Louis, MO, USA) dissolved in the saline). Group II was i.p. administered with MK-801 (1mg/kg). The Group III was treated i.p. with MK-801 (1mg/kg) + resveratrol (purchased from Terraternal Pharmaceutical, London, England) (40mg/kg) and the Group IV were treated i.p. with resveratrol (40mg/kg - resveratrol was dissolved in 0.9% saline). The saline, MK-801 and resveratrol doses in this study were selected based on the previous studies (8, 25). All injections were performed for 14 days. In Group III, resveratrol was injected in the morning and MK-801 was injected in the afternoon. After the injections, all mice were sacrificed by decapitation and all testes were collected. All the right testes were separated for the determination of the oxidative stress parameters and the other testis was separated for the histo-morphometric and pathological evaluations.

Morphometric and pathological evaluation: After the sacrification of the mice, all the left testes were weighted and fixed with the 10% buffered neutral formaldehyde solution, totally embedded in paraffin, sliced and stained by Hematoxylin-eosin for the histo-morphometric and pathological evaluations. The diameter and epithelial height of seminiferous tubules were measured using Mshot software loaded to a computer connected to the Olympus BH2 microscope attached Mshot 14 mp camera (23). The measurements were performed under X20 objective.

Biochemical analyses

Preparation of homogenate: All the right testes were trimmed and the remaining portions (each of 0.1g in weight) were washed with ice-cold 0.9% NaCl and immediately homogenized for oxidative stress analyses. Initially, the tissue was homogenized as follows. Each tissue was separately placed into a homogenizer (IKA T18, Germany), adding 1 mL of the solution containing 10% (w/v) in 0.1M phosphate buffer, pH 7.4, 1mM EDTA and the mixture was homogenized in ice for five minutes with the homogenizer. Then the homogenates were centrifuged (Nüve NF 1000R, Ankara, Turkey) at 3500 rpm/min for 10 min at 4°C. The testis samples prepared for use in the analyses were stored at -80°C, until laboratory analyses.

Measurement of oxidative stress parameters in tissue homogenate: TAS (total antioxidant status) and TOS (total oxidant status) levels which are among the oxidative stress parameters were measured using the kit (Rel Assay, Gaziantep, Turkey) working with the spectrophotometric methods (3, 4). The TAS method is calibrated with a stable antioxidant standard solution,

which is a vitamin E analog and traditionally named as Trolox Equivalent. On the other hand, TOS assay is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidants in acidic medium. TAS and TOS levels were reported as mmol Trolox Equivalent/L and µmol H_2O_2 Equivalent/L, respectively.

Epididymal sperm evaluation: The forward progressive sperm motility percentage was assessed using a phase contrast microscope with a heated stage as described by Sonmez et al. (20). A glass slide was placed on a phase contrast microscope and the stage was warmed up to 37 °C. Then, several droplets of Tris buffer solution [0.3 M Tris (hydroxymethyl) aminomethane, 0.027 M glucose, 0.1 M citric acid] were dropped on the glass slide, and a very small droplet of fluid obtained from left caudal epididymis with a pipette was added to the Tris buffer solution and mixed by a coverslip. The forward progressive sperm motility percentage was evaluated visually under the microscope at 200x and 400x magnifications. The estimation of the sperm motility was performed from three different areas in each sample. The mean of the three successive estimations was accepted as the final motility score.

Statistical analysis: Data obtained from experimental animals were expressed as means and standard deviations and analyzed using one-way analysis of variance (ANOVA) followed by Duncan posthoc test on the SPSS software computer program. A difference in the mean values of $P<0.05$ was considered to be significant.

Results

The mean testis weight, spermatozoon motilities, testicular structures, and total oxidant-antioxidant levels were measured and reported with P values in Table 1 and Table 2. In the present study, in Group II, it was detected that the mean testis weight was significantly decreased compared with the others ($P<0.05$). The resveratrol administration protected the mean testicular weight treated with MK-801 in Group III.

Table 1. Effects of MK-801 (1 mg/kg), resveratrol (RES-40 mg/kg) and RES (40 mg/kg) + MK-801 (1 mg/kg) on mean testis weight, epididymal spermatozoon motility percentage, the diameter of seminiferous tubules and epithelial height of seminiferous tubules.
Tablo 1. MK-801(1 mg/kg), resveratrol (RES-40 mg/kg) ve RES (40 mg/kg) + MK-801 (1 mg/kg) kombinasyonunun ortalama testis ağırlığı, epididimal spermatozon hareketliliği yüzdesi, seminifer tubül çapı ve epitel yüksekliği üzerine etkisi.

Groups	The mean testis weight (g)	Epididymal spermatozoon motility percentage	The diameter of seminiferous tubules (µm)	The epithelial height of seminiferous tubules (µm)
Control	0.227±0.026[a]	71.66±4.08[b]	228±11	63±3
MK-801	0.175±0.43[b]	61.66±9.83[c]	224±7	61±5
MK-801+Resveratrol	0.230±0.029[a]	70.00±6.32[b]	228±10	62±3
Resveratrol	0.236±0.21[a]	81.66±4.08[a]	225±8	59±3
P	<0.011	<0.001	0.856	0.340

Values are mean ± S.D, n=6.
[a,b,c]: In the same column values with different letters show statistically significant differences in mean testis weight and epididymal spermatozoon motility percentage ($P<0.05$)
[a,b,c]: Aynı sütunda farklı harfleri taşıyan ortalama testis ağırlığı ve epididimal spermatozon hareketliliği yüzdesi ($P<0.05$) istatistiksel açıdan önemlidir

Table 2. Effects of MK-801 (1 mg/kg), resveratrol (RES-40 mg/kg) and RES (40 mg/kg) + MK-801 (1 mg/kg) on total antioxidant status (TAS) and total oxidant status (TOS) of mice. TAS: Total Antioxidant Status, TOS: Total Oxidant Status, g: gram, µm: micrometre
Tablo 2. MK-801(1 mg/kg), resveratrol (RES-40 mg/kg) ve RES (40 mg/kg) + MK-801 (1 mg/kg) kombinasyonunun total antioksidan durum (TAS) ve total oxidan durum (TOS) üzerine etkisi. TAS: Toplam Antioksidan Düzeyi, TOS: Toplam Oksidan Düzeyi, g: gram, µm: micrometre

Groups	Testis TAS (mmol torolox equiv./L) measurement	Testis TOS (µmol H2O2 equiv./L) measurement
Control	0.46±0.08[b]	2.66±0.65[b]
MK-801	0.24±0.06[c]	5.46±1.44[a]
MK-801+Resveratrol	0.61±0.11[a]	2.85±0.46[b]
Resveratrol	0.74±0.15[a]	1.81±0.17[b]
P	<0.001	<0.001

Values are mean ± S.D, n=6.
[a,b,c]: In the same column values with different letters show statistically significant differences in TAS and TOS ($P<0.05$)
[a,b,c]: Aynı sütunda farklı harfleri taşıyan TAS ve TOS değerleri ($P<0.05$) istatistiksel açıdan önemlidir

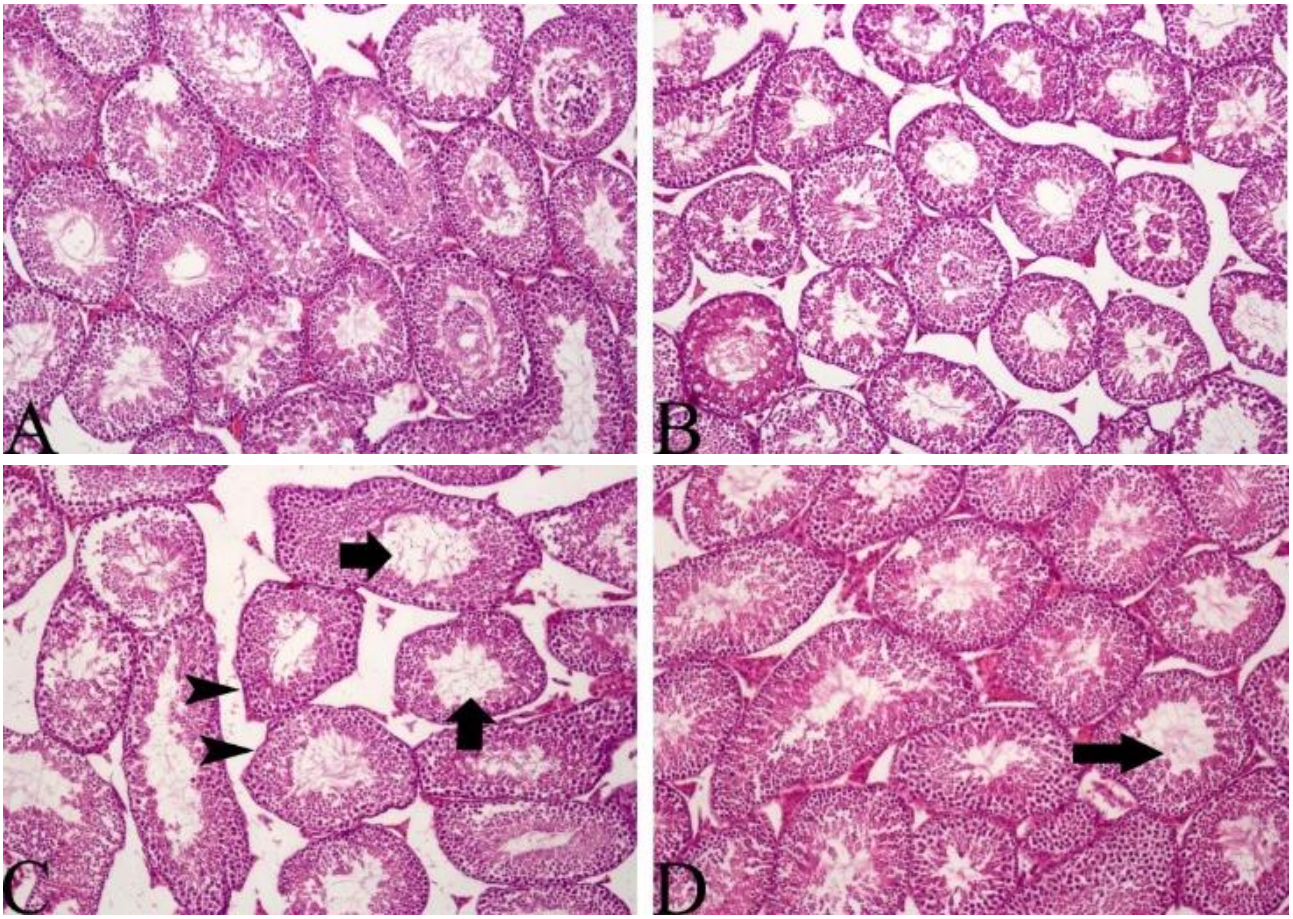

Figure 1. Effects of MK-801 (1 mg/kg), resveratrol (RES-40 mg/kg) and RES (40 mg/kg) + MK-801 (1 mg/kg) on histopathological changes in the testis of mice. A. Control group B. Resveratrol treated group. C. MK-801 treated group, Arrow: Necrobiotic and degenerative changes in the epithelial cells of the seminiferous tubules and decrease in the number of the spermatozoid, Arrowhead: Disorganisation in the basement membrane of the seminiferous tubules D. MK-801+Resveratrol treated group, Arrow: Decrease in the number of the spermatozoid Hematoxylene and eosine (10x)
Şekil 1. Fare testislerindeki histopatolojik değişiklikler üzerine MK-801(1 mg/kg), resveratrol (RES-40 mg/kg) ve RES (40 mg/kg) + MK-801 (1 mg/kg) kombinasyonunun etkisi. A. Kontrol grubu B. Resveratrol grubu C. MK-801 grubu, Ok: Seminifer tübül epitel hücrelerinde dejeneratif ve nekrobiyotik değişiklikler ve spermatozoid sayısında azalma, Ok başı: Seminifer tübül membranında disorganizasyon D. MK-801+Resveratrol grubu, Ok: Spermatozoid sayısında azalma Hematoksilen-eozin (10x)

The oxidant and antioxidant parameters showed statistical differences in Group II compared with the controls. The testicular TOS levels in other groups except Group II did not differ from each other statistically. However, TOS level in Group II was 5.46±1.44 and it was significantly increased when compared with the other groups and the TAS level in the Group II was lower than the others. So, this is clear that the oxidative stress was increased in Group II, compared with the controls and the resveratrol was protected the testicular tissue against the oxidative stress by raised the antioxidant activity in the testis ($P<0.05$). Meanwhile, it was realized that the antioxidant capacity in Group III and IV were also higher than the Group I.

When the diameter and epithelial height of seminiferous tubules were measured no statistical significance found between the groups. Moreover, pathologically, the tubules and the spermatozoids were in their normal posture in the Group I. However, the tubules and the spermatozoids were seen to be affected by the MK-801 administration. The necrobiotic and degenerative changes in the tubular epithelial cells and a decrease in the number of the spermatozoid were detected in Group II and only a decrease in the number of the spermatozoid was detected in group III. Therefore, the administration of resveratrol reduced the degenerative and harmful effects of the MK-801 in the testis (Figure 1).

The percentage of sperm motility in the groups were observed and it was revealed that the sperm motility was significantly reduced in Group II and was significantly increased in Group IV when compared to Group I ($P<0.05$).

Discussion and Conclusion

In the present study, it was aimed to evaluate the protective role of the resveratrol against the testicular

oxidative stress conducted by the chronic dose of MK-801. The excessive amount of reactive oxygen metabolites in the tissue causes oxidative stress. Actually, the reactive oxygen metabolites are already produced by the internal organs of the body while they are running and for example, in the testis small amount of oxidation is necessary for normal sperm production. Meanwhile, the balance between the oxidant and antioxidant system is protected by the antioxidants produced by the body. The chemical agent MK-801 impairs the oxidant-antioxidant system balance and thus oxidative stress appears in the tissue. One of the main points of this study is to catch the ratio of this impairment. In fact, there are various measurement tools that measure the tissue oxidative stress in the tissue. However, the TAS-TOS kit is a useful method to make a decision for the determination of the oxidation in the tissue. There are only a few studies investigated the testicular injury and protective roles of some antioxidants against the oxidative stress induced by MK-801 on the laboratory animals (14, 16). According to literature, this may be the first study researched the antioxidant protection of the resveratrol against the MK-801 induced testicular oxidative stress in the mice.

The oxidative stress in the testis depended on MK-801 firstly reported by the Ozyurt et al. (2007). Ozyurt et al. (2007) and then Parlaktas et al. (2008) were showed the increased oxidative stress parameters in the testicular tissue. In the present study, the testicular measurement of the oxidative stress value in Group II was increase parallel to the findings of these authors. Moreover, in Group III, the addition of the resveratrol against the MK-801 as a protective antioxidant agent seems to be beneficial and protectant. Because resveratrol administered mice in Group III, the TOS value stay close to Group I's level. While the TOS level was decreased, the TAS level was increased in the resveratrol injected groups. The resveratrol threw down the oxidative stress by enhanced the antioxidant activity in the tissue. Additionally, it seems that the powerful antioxidant activity of the resveratrol, tracking the antioxidant activity of the Group III and IV also better than the Group I.

Ozyurt et al. (2007) and Parlaktas et al. (2008) were reported that the MK-801 injected rats' spermatogenesis and normal tubular epithelium was affected. The seminiferous tubules and cells are degenerated and disorganized. According to the findings of these two researchers, administration of the melatonin hormone to the rats protected the testicular tissue and injections of the CAPE prevented the degeneration of the germinal cells and atrophy of the tubular epithelium in the testicular tissue. In another study on the rabbit bucks, MK-801 injection was caused a significant decrease in sperm number, antioxidant parameters and pathological changes in testis. Dietary supplementation of vitamin E, vitamin C, and olive pomace ameliorated the related parameters in the testis (19). In the present study, the emerged oxidative stress sourced by the MK-801 decreased the testicular weight same as previous studies (14, 16). However, the resveratrol was protected the organs loss of weight and kept it near in the Group I's limit. The necrobiotic and degenerative changes in the tubular epithelial cells and a decrease in the number of spermatozoids were detected in Group II. In Group III, only a decrease in the number of spermatozoids was detected. So, the resveratrol protected the testicular tissue against the necrosis and degeneration in the Group III. Meanwhile, the chronic dose of MK-801 injections didn't cause the tubular shrinkage and epithelial loss in the testis.

There are several studies investigating the healing effects of the resveratrol on the testicular tissue. In a study conducted by Reddy et al. (17) the cisplatin-induced testicular toxicity was investigated. The authors reported that the resveratrol improved the injury in the testicular tissue and also spermatogenesis. In another study (12), the protective effect of the resveratrol was observed in the varicocele testis. The varicocele had many negative effects on the testis parameters like volume, abnormal sperm amount and motility. The resveratrol as a protectant was given in a daily dose (300mg/kg by gavage) to the animals from 42 to 100 days of age. At the end of the applications, a reduction of the harmful effects of the varicocele was observed in the resveratrol group. Another research (5) reported that the 5 mg/kg i.p. a dose of resveratrol during 3 weeks alleviated the testicular oxidative stress in diabetic mice. Moreover, the resveratrol (20 mg/kg by gavage daily for 4 weeks) improved the oxidative stress and testicular dysfunctions induced by depression (18).

In the present study, it was revealed that the 40 mg/kg dose of resveratrol increased the progressive sperm motility against the Group I. In a study (13), the 10 mg/kg dose of resveratrol protected the testis from the oxidative stress; however, this dose did not affect the sperm motility. But in another recent research, the asthenospermia sperm samples were collected from the obese peoples and the 2.5, 6, 15, 30, 50 and 100 µmol/l resveratrol was added into the spermatozoa's medium. The 2.5, 6, 15, 50 and 100 µmol/l doses of resveratrol did not alter the progressive sperm motility while 30 µmol/l dose of resveratrol notably improved the progressive motility (2).

In conclusion, the results of the present study demonstrate that resveratrol was effective for the inhibition of the oxidative stress induced with MK-801 in mice testes. The resveratrol protected the testicular tissue against the oxidative stress, pathological injuries, and also sperm motility. Furthermore, in Group IV the resveratrol increased the motility of the spermatozoon than the control group.

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