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Potential Protective Role of Nigella sativa Linn against Sildenafil Induced Hepatotoxicity and Nephrotoxicity in Adult Male Rabbits

Mofrih M Hegazy[1], Ibrahim A Elhalfawy[2], Mohammad I Shaban[3] and Elsayed Abouelnour[4]

[1] Forensic Medicine and Clinical Toxicology Department, Faculty of medicine, Menoufia University.
[2] Molecular Diagnostics Department, Genetic Engineering and Biotechnology Research Institute, Sadat City University.
[3] Pathology Department, Faculty of medicine, Menoufia University.
[4] Medical Biochemistry Department, Faculty of medicine, Menoufia University.

Egypt.

Abstract

Introduction: *Nigella sativa* is considered to have antioxidant components though it is proposed to have hepatoprotective and nephroprotective effect.

Aim of the study: This study aimed to investigate hepatotoxic and nephrotoxic effects of sildenafil and to evaluate the role of *Nigella sativa Linn* oil in improving these effects and measure testosterone levels.

Materials and methods: Twenty eight male healthy domestic rabbits were randomly divided into 4 groups (7 animals for each) and gavaged by the studied substances for 28 days. Control group received 2ml/kg/day of gum acacia. *Nigella sativa* group received 2 ml/kg/day of *Nigella sativa* oil. Sildenafil group received 26 mg/kg/day of sildenafil citrate. Combined group received *Nigella sativa* oil followed immediately by sildenafil citrate daily in the previous doses.

Results: Sildenafil induced hepatotoxicity and nephrotoxicity as revealed by significant increase in ALT (452.25±60.23 versus 31.67±4.51, P<0.001), AST (183.75±37.21 versus 26.00±4.00, P<0.001), urea (55.00±3.65 versus 30.00±8.72, P=0.001) and creatinine (1.34±0.22 versus 0.83±0.21, P = 0.001) in sildenafil group than controls and histopathologically by cyto-architectural distortions of the hepatocytes and centrilobular hemorrhagic necrosis and renal degenerative and atrophic changes. These toxic effects were ameliorated biochemically and histologically when sildenafil was administered with *Nigella sativa* oil in the fourth group. Moreover, the testosterone levels were improved in the combined group than in sildenafil group (19.46±0.90 versus16.71±1.16).

Conclusions and recommendations: *Nigella sativa* oil has a protective effect against hepatotoxicity and nephrotoxicity of sildenafil and increases testosterone levels in combination with sildenafil.

Keywords | *Nigella sativa*; Sildenafil; Hepatotoxicity; Nephrotoxicity.

Introduction

Sildenafil is used as a specific treatment for erectile dysfunction. The drug acts by inhibiting the phosphodiesterase type 5 (PDE5) enzymes that specifically degrade the cyclic guanosine monophosphate (cGMP), responsible for the nitric oxide induced smooth muscle relaxation in the corpora cavernosa, allows inflow of blood and penile erection . Like many other drugs, sildenafil can be easily procured from across the counter without any prescription of a physician and used by persons without any consideration of the therapeutic doses resulting in severe toxicity (Reeuwijk et al., 2013)

Sildenafil induced hepatotoxicity was reported by some studies either when administered in the form of drug (Maroy, 2003; Maroy et al., 2005) or in herbal supplement containing sildenafil (Nissan et al., 2016). The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure (Graziano et al., 2017). The causal relationship between sildenafil use and liver damage remained uncertain; hepatotoxicity was suggested as being probably related to an ischemic mechanism (Maroy et al., 2005) or generation of reactive oxygen species (Yesmin et al., 2013).

Use of herbal drugs as *Nigella sativa* seed (commonly known as black seed or black cumin) in the treatment of liver diseases has a long tradition, especially in eastern countries (Pal et al., 2011). An

Egyptian study reported that the use of *Nigella sativa* seed had increased the levels of glutathione in lipid peroxidation induced liver damage (EI-Gharieb et al., 2010). Also, *Nigella sativa* are used in folk medicine for treatment and prevention of diseases like asthma, diarrhea and dyslipidemia (Jadhav and Mateenuddin, 2013). Moreover, some clinical and experimental researches have shown many therapeutic effects of *Nigella sativa* extracts such as immunomodulator, anti-inflammatory, anti-tumour and antibacterial agent (Danladi et al., 2013).

Since, the majority of drugs administered to animals are eliminated by a combination of hepatic metabolism and renal excretion, the present study was carried out to investigate the toxic effects of sildenafil citrate on the liver and kidneys of adult male rabbits and to evaluate the role of *Nigella sativa* oil in improving these effects through biochemical and histological evaluation and measure serum testosterone levels.

Materials and methods

I: Materials

Nigella sativa oil was used after cold compression of the Nigella sativa seeds. Nigella sativa seeds contain 36%-38% fixed oils, proteins, alkaloids, saponin and 0.4%-2.5% essential oil (Gani and John, 2013). As the essential oil was analyzed using gas chromatography-mass spectrum (GC-MS), many components were detected including thymoquinone (27.8%-57.0%), carvacrol (5.8%-11.6%), p-cymene (7.1%-15.5%), 4-terpineol (2.0%-6.6%), t-anethole (0.25%-2.3%) and longifoline (1.0%-8.0%) (Burits and Bucar, 2000; Gani and John, 2013).

Sildenafil citrate 100 mg tablet (Virecta) from Eva Pharma Pharmaceutical Industries, Egypt was used in this study. Gum acacia was used as suspending media.

II: Methods

This study was conducted on 28 adult healthy male domestic rabbits weighing 1250-1500 g body weight from the 1st to the 29th of May 2016. Animals were fed with a standard laboratory chow and water ad libitum. The rabbits were acclimatized for one week before the experiment started. After that, rabbits were randomly allocated into 4 groups and gavaged by studied substances, 7 animals in each group as follow: Group I: (control group) that received a single daily dose of gum acacia (2ml/ kg/day) for 28 days; Group II (*Nigella sativa*) received (2 ml/kg/day) of *Nigella sativa* oil daily for 28 days (Abdel-Daim and Ghazy, 2015). Group III or sildenafil treated group that received a single dose of one-tenth (1⁄10) lethal dose (LD_{50}) (26 mg/kg) of sildenafil citrate in gum acacia daily for 28 days. Group IV or *Nigella sativa* oil and sildenafil treated group received daily dose (2 ml/kg) of *Nigella sativa* oil and followed immediately by 1⁄10 LD_{50} of sildenafil citrate for 28 days. The therapeutic dose of sildenafil citrate in rabbits was 6 mg/Kg (Lauver et al. 2014) and sildenafil LD_{50} for rat was 500 mg/Kg then it was converted according to Paget table (Abbott et al., 2004).

The study applied the double blind technique for both the administrator of animal feed and materials and the investigators of biochemical and histopathological examinations

Biochemical assessment

On the twenty ninth day of the experiment, blood samples were collected from the neck veins of all rabbits of the studied groups. Blood serum was separated by centrifugation at 3000 rpm for 15 min.

Assay of serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) was done using kinetic UV method, the concentration was calculated using Δ absorbance/minute with factor which was 1746 at 37 ºC (Henderson and Moss, 2001).

Measurement of serum albumin was done using modified bromocresol green colorimetric method. The concentration was determined by measuring the absorbance at 630 nm and comparison with the absorbance of the standard solution (Doumas et al.,1971).

Creatinine was determined spectrophotometrically by the kinetic method (Diamond). The absorbance was read at 30 seconds and 2 minutes later. Creatinine concentration was calculated using standard concentration which is 2 mg/dl (Henry, 1974).

Urea was determined by Berthelot enzymatic colorimetric method. Using urease to hydrolyse urea into ammonia and carbon dioxid. The concentration was determined by measuring the absorbance at 572 nm (Kaplan, 1984).

Testosterone was determined using the LIAISON Testosterone kit and analyzer. The LIAISON Testosterone assay is a direct, competitive, chemiluminescence immunoassay (CLIA) method for quantitative determination of testosterone (Pearce et al.,1989).

Animal painless procedures was conducted with appropriate sedation to avoid pain and stress under general inhalation of ether anaesethia, Collected livers and kidneys from sacrificed rabbits of all groups were prepared for histological examination by fixation in 10% formalin and kept in the fixative overnight. Then, they were dehydrated in an ascending grade of alcohol (70%, 80%, 95% and 100% ethanol for 1 h for each concentration), cleared in xylene and embedded in paraffin wax. Serial sections of 5 mm thickness were obtained using a rotatory microtome. The deparaffinised sections were stained routinely with hematoxylin and eosin reagent. Photomicrographs of

the specimens were obtained using digital research photographic microscope (Ramos-Vara et al., 2017).

Approval

The use of experimental animals was prospectively approved by the Ethical Committee, Faculty of Medicine, Menoufia Unversity.

Statistical analysis

Data was tabulated and statistically analyzed by SPSS Version 20 software (SPSS,
Chicago, IL, USA) on an IBM compatible computer. Descriptive statistics as mean and standard deviation (SD) were used. Analytic statistics: one way analysis of variance (ANOVA) for comparison between the studied groups regarding the quantitative variables followed by (LSD) post hoc test. A P-value ≤0.05 was considered to be statistically significant.

Results

Sildenafil induced hepatotoxicity as revealed by significant higher levels of ALT and AST in sildenafil group than controls (P2 < 0.001 for both). Also, combined *Nigella sativa* with sildenafil treatment attenuated sildenafil induced hepatotoxicity as the values of ALT and AST were significantly lower in the combined sildenafil and *Nigella sativa* group than sildenafil group (P6 < 0.001 and P6 =0.008; respectively). Otherwise, the combined sildenafil and *Nigella sativa* group still had significant higher levels of ALT and AST than controls (P3 = 0.001 and P3= 0.006). There were no significant differences in the mean levels of ALT, AST and albumin in *Nigella sativa* group and controls (P1> 0.05 for all) the values were shown in Table 1.

Albumin levels were significantly lower in sildenafil group than controls (P2=0.001). On the other hand, there was no significant difference in the albumin levels between sildenafil group and the combined group (P6> 0.05) as shown in Table 1.

Regarding levels of serum creatinine and blood urea, there were significantly higher mean levels in sildenafil group than controls (P2 =0.001 for both).There were no significant differences between each of *Nigella sativa* group and the combined group compared with controls (P5> 0.05) as regards the levels of serum creatinine as shown in Table 2.

The combination of sildenafil with *Nigella sativa* had significantly increased the levels of testosterone than sildenafil only (P6 <0.001).

Each of *Nigella sativa* group, sildenafil group and combined group had significantly higher levels of testosterone than controls (P < 0.001 for each).

Also, each of sildenafil group and combined group had significantly higher levels of testosterone than *Nigella sativa* group (P4 = 0.025 , P5<0.001, respectively)

Histopathological changes

Control group: The liver section showed normal histological features with the hepatic lobules showing irregular hexagonal boundary defined by portal tract and sparse collagenous tissues. The hepatic portal veins, bile ductules and hepatic artery within the portal tract were all visible as shown in photomicrograph (1A).

The control sections of the kidneys showed normal histological features. The section indicated a detailed cortical parenchyma and the renal corpuscles appeared as dense rounded structures with the glomeruli surrounded by a narrow Bowman's spaces as shown in photomicrograph (2A).

Nigella sativa group:

Liver section showed normal histological features as shown in photomicrograph (1B)**.**

The kidney sections showed normal histological features as shown in photomicrograph (2B).

Sildenafil group: Section from the liver in sildenafil group showed cyto-architectural distortions of the hepatocytes and centrilobular hemorrhagic necrosis. The central vein showed mild congestion while the bile ducts were normal with scanty perivascular inflammatory infiltrate as shown in photomicrograph (1C).

The kidney sections of animals in group treated with sildenafil revealed mild to moderate distortion of cyto-architecture of the renal cortical structures with mild degenerative and atrophic changes. There were vacuolations appearing in the stroma and loss of renal corpuscles which were less identified and the Bowman's spaces were sparsely distributed as compared to the control group as shown in photomicrograph (2C).

Combined Sildenafil & *Nigella sativa* group:

The liver tissue showed mild cyto-architectural distortions of the hepatocytes as shown in photomicrograph (1D)**.**

The kidney tissue in mixed sildenafil with *Nigella sativa* group showed minimal degenerative changes as shown in photomicrograph (2D).

Table (1): ANOVA test for comparison between the studied groups regarding liver function tests.

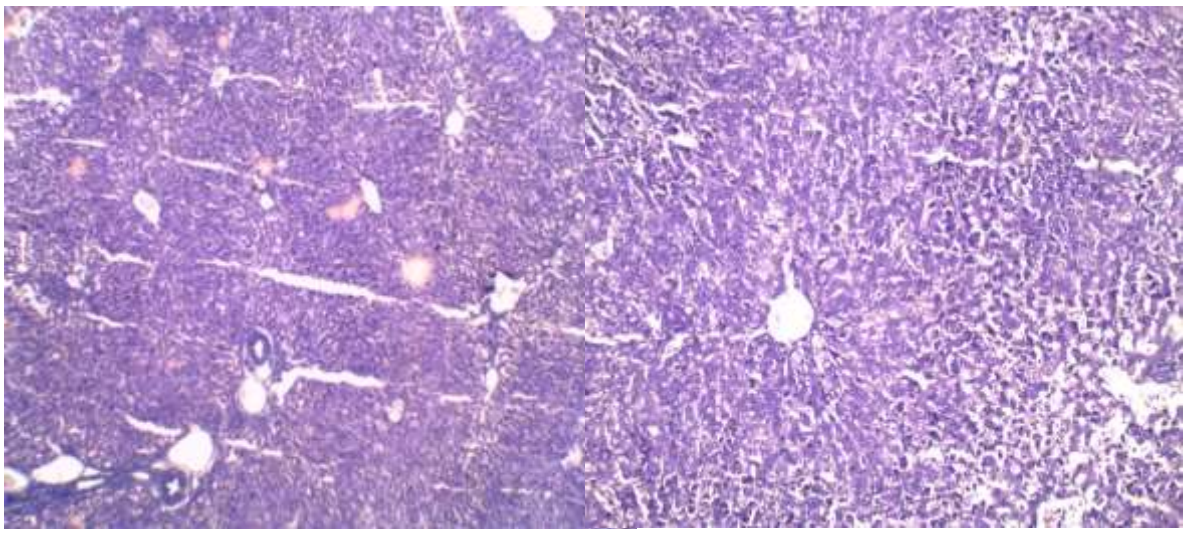
Items	Controls (n=7) Mean±SD	Nigella sativa (n=7) Mean±SD	Sildenafil group(n=7) Mean±SD	Sildenafil and nigella (n=7) Mean±SD	ANOVA test	P-value
ALT (U/L)	**31.67±4.51**	**28.12±3.34**	**452.25±60.23**	**215.67±30.99**	84.44	<0.001* P1=0.120 P2=<0.001* P3=0.001* P4=<0.001* P5=<0.001* P6=<0.001*
AST (U/L)	**26.00±4.00**	**29.07±1.78**	**183.75±37.21**	**109.67±19.66**	30.18	<0.001* P1=0.132 P2=<0.001* P3=0.006* P4=<0.001* P5=<0.001* P6=0.008*
Albumin (g/dl)	**3.50±0.36**	**3.75±0.21**	**2.08±0.17**	**2.27±0.42**	19.41	0.001* P1=0.138 P2=0.001* P3=0.002* P4=<0.001* P5=<0.001* P6=0.452

P1= Nigella group with controls, P2= Sildenafil group with controls, P3= Sildenafil and Nigella group with controls P4= Nigella group with Sildenafil, P5= Nigella group with Sildenafil and Nigella group, P6= Sildenafil group with Sildenafil and Nigella group.

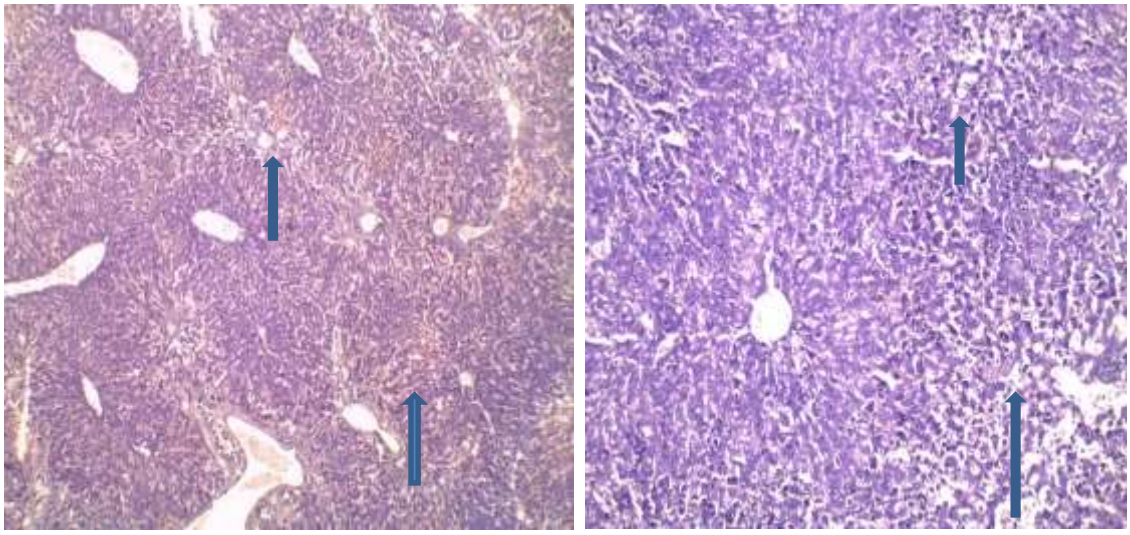
Table (2): ANOVA test for comparison among the studied groups regarding kidney function tests and testosterone levels.

Parameters	Controls(n=7) Mean±SD	Nigella sativa(n=7) Mean±SD	Sildenafil(n=7) Mean±SD	Sildenafil and nigella(n=7) Mean±SD	ANOVA test	P-value
Urea (mg/dl)	30.00±8.72	29.79±7.97	55.00±3.65	37.33±3.06	2.94	0.118 P1=0.963 P2=0.001* P3=0.058 P4=<0.001* P5=0.038* P6=<0.001*
Creatinine (mg/dl)	0.83±0.21	0.99±0.03	1.34±0.22	1.00±0.10	2.01	0.205 P1=0.069 P2=0.001* P3=0.077 P4=<0.00* P5=0.804 P6=0.003*
Testosterone(ng/ml)	10.75±1.25	15.30±1.14	16.71±1.16	19.46±0.90	111.43	<0.001* P1=<0.001* P2=<0.001* P3=<0.001* P4=<0.025* P5=<0.001* P6=<0.001*

P1= Nigella group with controls, P2= Sildenafil group with controls, P3= Sildenafil and Nigella group with controls P4= Nigella group with Sildenafil, P5= Nigella group with Sildenafil and Nigella group, P6= Sildenafil group with Sildenafil and Nigella group.

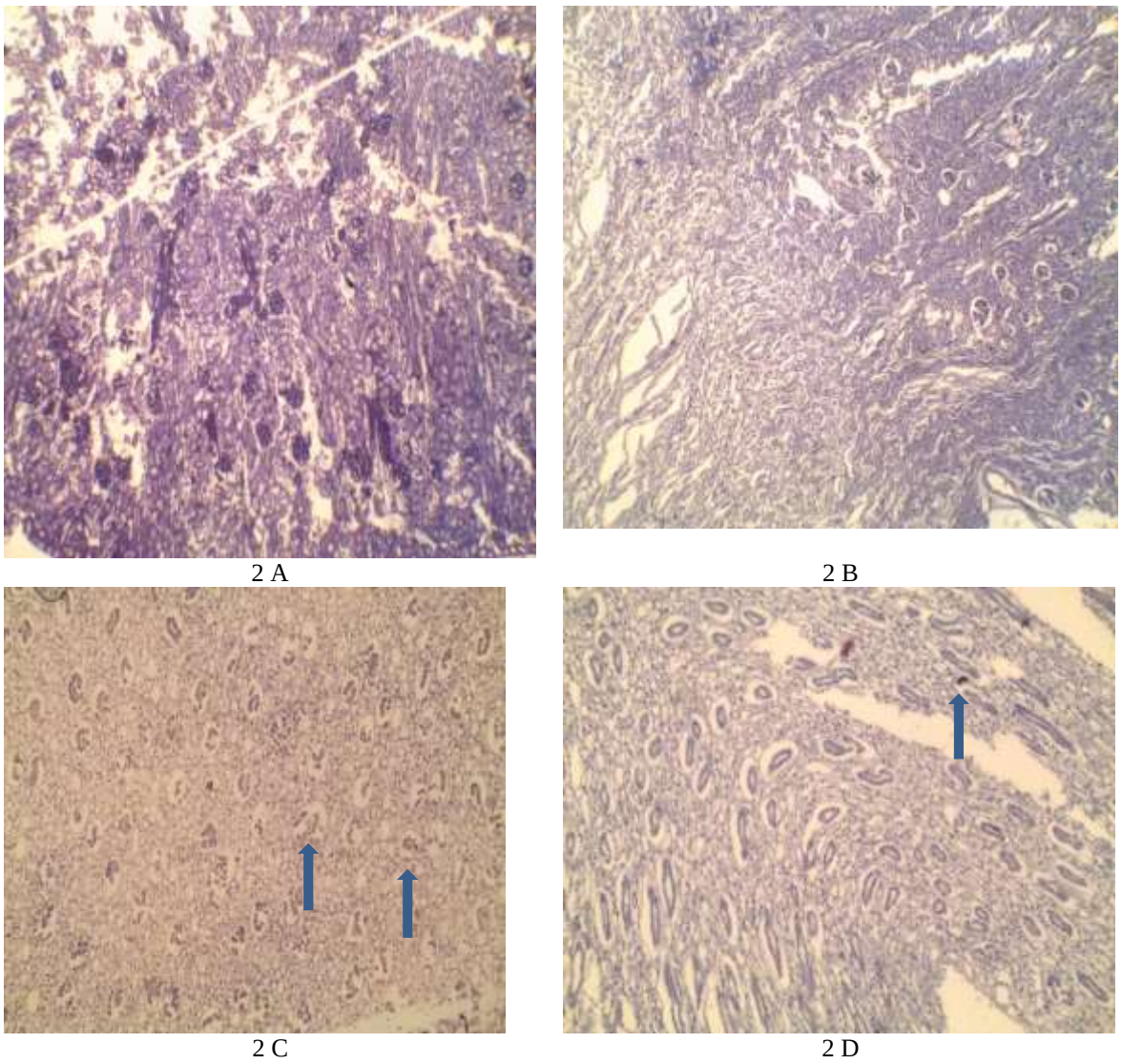


1 A 1 B



1 C 1 D

Photomicrograph (1): Section from the liver in control group (1 A), Nigella group (1 B), sildenafil group (1 C) and combined Nigella and sildenafil group (1 D)



2 A 2 B

2 C 2 D

Photomicrograph (2): Section from the kidney in control group (2 A), Nigella group (2 B), sildenafil group (2 C) and combined Nigella and sildenafil group (2 D)

Discussion

In the present study, sildenafil citrate induced hepatotoxicity as revealed by higher mean levels of ALT and AST as well as lower levels of albumen in sildenafil group associated with centrilobular hemorrhagic necrosis of the liver cells. These effects may be due to the generation of reactive oxygen species and inflammatory response. Moreover, sildenafil can cause lysosomal enzymes leakage and cytoplasmic degeneration caused by cell membrane disturbance (Hashish, 2016).

These results were coincided with Victor et al. (2015) who concluded that chronic administration of sildenafil caused significant alteration in liver functions as evident in the increased serum concentration of liver enzymes and bilirubin. Also, Eweka and Eweka (2011) found atrophic and degenerative changes in adult Wistar rats that received 1.43mg/kg body weight of sildenafil citrate.

On the other hand Iyanda (2014) revealed that there were significantly high levels of ALT and alkaline phosphatase (ALP) in fake sildenafil citrate-exposed rats which could be attributed to hepatic damage but not in genuine sildenafil citrate exposed group. These results could be due to the use of smaller dose of sildenafil (25 mg/kg body weight of rats) than which was applied in the present study.

Nigella sativa oil improved the histological picture of liver necrosis and the indices of hepatotoxicity as both ALT and AST levels were significantly lower in combined sildenafil and Nigella group than sildenafil group. However, their levels were still higher than controls. These results coincided with the previous studies of Turkdogan et al. (2001) and Muneer et al. (2013) who found that, the seed extract of *Nigella sativa* improved the histological picture and the indices of oxidative status of the liver.

The hepatoprotective effects of *Nigella sativa* were explained in previous studies by the antioxidant activity that reduces hepatoxicity as one of the active principles of Nigella sativa is nigellone (dithymoquinone) which has antioxidant activity (Gani and John, 2013). Moreover, Yesmin et al. (2013) reported that nigellone was a hepatoprotective agent against carbon tetra chloride induced liver fibrosis by prevention of lipid peroxidation through the decrease in

malondialdehyde and increase in antioxidants preventing liver damage.

In the present study degenerative and atrophic changes in the kidneys were observed in sildenafil treated group and were associated with higher levels of urea and creatinine indicating nephrotoxicity. On the other hand, in the combined sildenafil and *Nigella sativa* group, urea and creatinine levels were nearly similar to control group and associated with minimal degenerative changes in the kidney. This reflects the protective effects of *Nigella sativa* oil for sildenafil induced nephrotoxicity.

On the other hand the use of therapeutic dose of sildenafil (0.5 mg/kg/day P.O for 14 days) before induction of renal failure by potassium dichromate in rats may reduce or delay the emergence of potassium dichromate nephrotoxicity (Salama et al., 2016). Moreover Morsy et al. (2014) revealed the protective effects of sildenafil against gentamicin-induced nephrotoxicity possibly, in part, through their antioxidant activities which were verified histopathologically.

Testosterone levels in the present study were significantly elevated with the administration of *Nigella sativa* as sildenafil either alone or in combination with *Nigella sativa* oil than controls. These results were coincided with Spitzer et al. (2013) who found that, the administration of an optimized dose of sildenafil to men with erectile dysfunction and low baseline serum testosterone increases serum testosterone levels likely by a direct action on the testes. Also, Andric et al. (2010) revealed that administration of sildenafil to rats stimulates the expression of steroidogenic acute regulatory protein and protein kinase G1 which was responsible for increase in serum testosterone levels; moreover, phosphodiesterase 5 was identified in Leydig cells (Scipioni et al., 2005).

Moreover, the testosterone levels were significantly increased by combination of sildenafil with *Nigella sativa* in the combined group than in sildenafil group and *Nigella sativa* group. *Nigella sativa* may enhance the effect of sildenafil in raising the testosterone levels.

These results were in agreement with the previous studies of Haseena et al. (2015) and Paradin et al. (2012) who found a significant increase in the testosterone levels in *Nigella sativa* treated rats. The mechanism of increasing testosterone levels by *Nigella sativa* is still controversy. The study of Gromadzka-Ostrowska et al. (2002) showed that the unsaturated fatty acids stimulate the activity of 17 β-hydroxysteroid dehydrogenase, which is the most important key enzyme in the testosterone biosynthesis pathway. These unsaturated fatty acids were present in the chemical composition of *Nigella sativa* (Nickavar et al., 2003).

Moreover, in the present study, *Nigella sativa* may indirectly enhance testosterone levels by improving liver pathology because testosterone levels may be lowered by chronic diseases (Morris and Channer, 2012).

In conclusion: Sildenafil intake may have hepatotoxicity and nephrotoxicity and *Nigella sativa* oil has a protective role in sildenafil induced hepatotoxicity and nephrotoxicity as revealed by biochemical and histopathological findings, moreover *Nigella sativa* may enhance the effect of sildenafil in raising the testosterone levels. So *Nigella sativa* oil is recommended to be combined with sildenafil intake in erectile dysfunctions also, future studies are recommended to confirm these results.

Conflict Of Interest

There is no conflict of interest

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الملخص العربي

الدور الوقائي المحتمل لحبة البركة ضد التأثير السام لعقار السيلدينافيل على كبد وكلى ذكور الأرانب البالغة

مفرح محمد حجازي[١] و ابراهيم عبده الحلفاوي[٢] و محمد ابراهيم شعبان[٣] و السيد صابر ابو النور[٤]

مقدمة: نظراً لاحتواء حبة البركة على مكونات مضادة للأكسدة لذا فمن المحتمل أن يكون لها دوراً وقائيا ضد التأثيرات السامة لبعض العقاقير التي قد تؤثر على الكبد و الكلى.

الهدف من البحث: دراسة التأثيرات السامة لعقار السيلدينافيل على كل من الكبد و الكلى و دور حبة البركة في الوقاية من هذه التأثيرات وقياس مستوى التستوستيرون.

مواد و طرق البحث: تم تقسيم ثمانية وعشرون من ذكور الأرانب المنزلية إلى ٤ مجموعات (٧ حيوانات لكل منها) بطريقة عشوائية وتم اعطائهما المواد محل الدراسة عن طريق الفم يومياً لمدة ٢٨ يوماً. المجموعة الضابطة تم اعطائها ٢ ملي /كجم من معلق الصمغ العربي .مجموعة حبة البركة تلقت٢ ملي / كجم من زيت حبة البركة. مجموعة السيلدينافيل تلقت٢٦ مجم /كجم من عقار السيلدينافيل. مجموعة حبة البركة و السيلدينافيل تلقت زيت حبة البركة و السيلدينافيل بنفس الجرعات السابقة. في نهاية البحث تم سحب عينات دم لقياس وظائف الكبد و الكلى كما أخذت عينات من الكبد و الكلى لفحص الأنسجة.

النتائج: أظهرت النتائج حدوث تأثيرات سامة لعقار السيلدينافيل على كل من الكبد و الكلى حيث ارتفعت نسبة الأنزيمات الكبدية ALT (452.25±60.23 versus 31.67±4.51, P<0.001) و AST (183.75±37.21 versus 26.00±4.00, P<0.001) و كذلك مادة بولينا الدم (55.00±3.65 versus 30.00±8.72, P=0.001) و الكرياتينين (1.34±0.22 versus 0.83±0.21, P = 0.001) ارتفاعاً ذو دلالة إحصائية في مجموعة السيلدينافيل عنها في المجموعة الضابطة و قد صاحب هذا تغييراً في أنسجة كلا من الكبد (تشوهات في شكل الخلايا مع وجود نزيف) و الكلى (ضمور و تحلل بالأنسجة). و قد قلت هذه التغيرات الكيميائية و الهستوباثولوجية عند إعطاء السيلدينافيل مع حبة البركة في المجموعة الرابعة بالإضافة إلى ارتفاع في مستوى هرمون الذكورة (التستوستيرون 1.16±16.71versus 0.90±19.46) في هذه المجموعة.

الإستنتاجات و التوصيات: لزيت حبة البركة تأثير وقائي ضد التأثيرات السامة لعقار السيلدينافيل على الكبد و الكلى كما يزيد مستوى التستوستيرون عند إعطائهم معاً. لذا يوصى بمزيد من الدراسات للتأكيد على هذه النتائج و تناول حبة البركة مع عقار السيلدينافيل للوقاية المحتملة من سميته على الكبد و الكلى.

١ قسم الطب الشرعي و السموم الإكلينيكية- كلية الطب - جامعة المنوفية.
٢ قسم المشخصات الجزيئية و العلاجيات- جامعة مدينة السادات
٣ قسم الباثولوجي- كلية الطب - جامعة المنوفية.
٤ قسم الكيمياء الحيوية - كلية الطب - جامعة المنوفية.