Original Article

Protective Effects of Black Seed Oil (Nigella Sativa Oil) Against Pulmonary, Renal and Cardiac Toxicity Induced by Nefopam in Albino Rats

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ABSTRACT

Introduction: Pain is a disturbing condition that may increase postoperative patient complains. Moderate to severe postoperative pain require the use of more potent analgesics such as Nefopam, a centrally acting non-opioid analgesic. Despite its common use, the effect of nefopam on the histology of lung, kidney and heart is not well documented.

Aim of the Work: The goal of this work is to explore the changes induced by nefopam on the lung, kidney, and heart tissues and investigate the protective role of black seed oil (Nigella sativa oil) on these tissues.

Material and Methods: Eighteen adult healthy albino rats of both sexes were randomly divided into three groups, 6 rats in each. Group I considered as a control group. Group II received intraperitoneal Nefopam (10 mg/kg body weight) for one month. Group III received black seed oil orally (0.2 ml /kg) through oral gavage one day preceding each intraperitoneal injection of Nefopam for one month period. Lung, kidney and heart of the three groups were removed and prepared for histological examination by light microscope. Morphometric measurements were done to compare some parameters among the groups.

Results: Compared to control, several pathological changes were seen in Nefopam treated rats. Sections of lungs revealed inflammatory cell infiltration as well as emphysematous dilatation of the alveoli. Shrinkage of the glomerular tuft with widening of the urinary spaces was seen in kidney sections. On the other hand, heart section showed sever congestion and haemorrhage of the blood vessels and oedema in between the cardiac muscle fibers. Pretreatment with black seed oil efficiently alleviate the changes induced by Nefopam on the lung, kidney and heart tissue and reverts the abnormal structure to become near normal.

Conclusion: Nefopam induces marked structural changes in the lung, kidney and heart of albino rats. These changes were effectively reversed by pretreatment with black seed oil.

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Key Words: Nefopam, nigella sativa oil, protective, rats.

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INTRODUCTION

Pain is a highly noxious complain experienced by individuals and it has detrimental impacts on the mood and quality of life[1]. Nefopam (Acupan, Silentan, Nefadol, Ajan, fenazoxine) belongs to the non-sedative benzoxazocine class widely used to releife pain following orthopedic, obstetrics and gynaecological operations. Nifopam was developed in the 1960s as a muscle relaxant. However, subsequent clinical trials showed that it has a central analgesic non-opioid efficiency[2]. It is thought that Nefopam induces analgesia through limiting monoamines (serotonin, norepinephrine, and dopamine) reuptake in the central nervous system as well as decreasing glutamate signaling by modifying calcium and sodium channels[3]. Nefopam use is associated with some adverse reactions including nausea, vomiting, headache, blurred vision, drowsiness and urinary retention[4]. Nefopam is given orally in a divided dose ranging from 30–90 mg/day and adjusted according to response. A single intravenous or intramuscular dose of 20 mg can also be used. Due to its wide use, Nifopam gained more attraction from researchers to examine its potential effects on different vital organs[5].

The traditional black seeds Nigella sativa (N. sativa) which yields to the vegetal Ranunculaceae family have been widely consumed as a remedy by various cultures[6]. Seeds and oil are very popular in numerous traditional schemes of medicine and it is thought to be one of the major forms of curative medications in Islamic literature since it has been recommended in Tibb-el-Nabwi (Prophetic Medicine)[7].

Nigella sativa is an annual plant undeviating leaves, its delicate flowers are pink white, or pale blue, it is characterized by numerous black colored funnel shaped seeds. Various names of the plant are branded like black cumin, black caraway seeds and kalajira[8]. The N. sativa seed includes about 40% fixed oil, up to 0.45% volatile oil, alkaloid and proteins while the the nutritional components are proteins, carbohydrates, vitamins, mineral, fats, and essential amino acids[9].

A broad spectrum therapeutic potential of N. sativa have been well recognized previously due to its antioxidant, anti-inflammatory, anticancer and antimicrobial properties[10] in addition to hepatic and renal protective role[11]. It was recommended recently as a supportive medicine in the

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management of Covid-19[12]. In addition, Thymoquinone (TQ), an essential component of black seed oil, has a strong antioxidant potential due to its free radicals scavenging activity[13]. The defensive properties of N. sativa and its main ingredients against some toxic agents in various vital organs like brain, heart, liver, kidney and lung have been reputable[14].

The current study aimed to inspect the effect of prolonged use of Nefopam on the histology of lung, kidney, and heart in a rat model and explore the protective role of black seed oil against possible Nifopam induced toxicity.

MATERIALS AND METHODS

The experimental design was approved by the Medical Research Ethics Committee in the College of Medicine, University of Mosul.

Nefopam (Acupan®) was used as a 20mg/2 ml injectable ampoule (Medisol Lot:H1o8o, France), Black seed oil was purchased from local market as a pure cold pressed oil (8 fl oz 237 ml, Pioneer Company).

Eighteen adult male and female Wistar albino rats of 170-210 gm body weight were randomly distributed into three groups consisting of 6 animals for each group. The animals were acclimatized in animal house of Veterinary College, University of Mosul for a period of one week befor the beginning of the experiments. A standard laboratory pellet foods and tap water were available ad libitum. The weight of all animals in the three groups was recorded at the beginning of the experiment and then recorded again after one month just before sacrificing the animals.

Study groups

Group I, Control group, rats received 0.9% normal saline (vehicle) 2 ml/kg/day by intraperitoneal injection for one month period.

Group II, rats received intraperitoneal injection of Nefopam 10 mg/ kg/day[15] for one month period.

Group III, rats received black seed oil orally in a dose of 0.2 ml/kg/day[16], the oil was giviv 24 hour before each injection of Nefopam for the same period.

At the end of experimental period, the rats were anaesthetized using intramuscular injection of Ketamine (50 mg/kg) and Xylazine (5mg/kg)[17]. Thoracic and abdominal midline incision was performed and the lung, kidney and heart of the three groups was excised and then put in normal saline solution (0.9%) for washing. Specimens were then fixed in a solution of 10% neutral buffered formalin for 24 hours. Paraffin tissue blocks were produced[18] and tissue sections 5 µm thickness were cut from each block and stained with Harris Hematoxylin and Eosin (H&E) and with Masson's trichrome stain[19]. The sections were examined under light microscope.

Morphometric study

Quantitative micro-morphometric measurements were conducted in the Department of Anatomy and Histology, Veterinary College, University of Mosul to compare some parameters among the groups using the color USB 2.0 digital image camera (Scope Image 9.0- China) which was provided with image processing software. Digitized images were captured from randomly chosen non-overlapping fields from each section. The alveolar wall thickness was measured using perpendicular lines drawn across the section of the alveolar walls.The software of camera was calibrated to all lenses of MicroscopeOlympus-CX31 by aid of 0.01mm stage micrometer (ESM11/Japan)

Biochemical analysis

Heart puncture was done to obtaine blood samples then serum was isolated for evaluation of renal function by measuring the level of blood urea using specialized Urea Enzymatic Colorimetric Kit and serum creatinine using Creatinine Colorimetric Kit.

Statistical analysis

The software SPSS version 20 was used for statistical analysis. One-way Analysis of Variance (ANOVA) followed by Bonferroni multiple comparisons was performed to calculate the Mean±SD and to compare the significant changes which was set as $P < 0.05$. P-values less than 0.01 were regarded as high statistical significance while *P-values* less than 0.05 were considered as statistically significant.

RESULTS

The animals of the control group remained, active with good appetite while the animals treated with Nefopam became less exciting with less appetite, group III rats remained alert till the end of the work.No significant change in the body weight in the Nefopam treated group and the group received black seed oil prior to Nefopam as compared to the control group (*P-value* >0.05) (Table 1).

Histological Findings

In the lung, sections obtained from the control group showed regular size and shape of the alveoli and normal terminal bronchioles (Figure 1A) with normal distribution of collagen fibers in the alveolar walls, the wall of the pulmonary vessel and terminal bronchiole (Figure 1B).

In Nefopam treated rats, an aggregates of lymphoid follicles with hyperplasia of lymphatic tissue around the bronchui (Figure 2A) was noted. Congestion of the blood vessles, with permeation of mononuclear inflammatory cell around the terminal bronchioles and blood vessels (Figure 2B) as well as destruction of the alveolar walls and abnormal integration of neighboring alveoli causing emphysematous dilatation(Figure 2C) were evident. The walls of the blood vessles were thickened in comparism to the control rats (Figure 2D). Masson's trichrome stain revealed deposition of collagen fibers around the blood vessles (Figure 2E). Group III (black seed oil prior to Nefopam recipient group) showed more conserved architecture of lung tissue with representative epithelial lining of the terminal bronchiole and less emphysematous

dilatation of the alveoli (Figure 3A). Little collagen fibers were observed around the pulmonary vessels and around the terminal bronchiole appeared green in color (Figure 3B).

In the kidney, the control group rats showed normal architecture and appearance of both renal cortex (Figure 4A) and medulla (Figure 4B). The proximal convoluted tubules (PCT) were lined by cuboidal epithelium with esinophilic cytoplasm and basal nuclei while the distal convoluted tubules (DCT) were lined by cuboidal epithelium with lighter cytoplasm and apical nuclei (Figure 4A). Normal collecting tubules and collectind ducts were also found (Figure 4B).

Group II showed shrinkage of the glomeruli with widening of the bowman's space and congestion of renal vessels with haemorrhage in the interstitial tissue (Figures 5A,B). Focal inflammatory cell infiltration was also very evident (Figure 5C). Dilatation of lumen of renal tubules along with oedema and vacuolations were noticed in the tubular epithelial cells (Figures. 5D,E). Group III showed more conserved architecture of renal tissue and the glomeruli recovered to near normal appearance (Figure 6).

The heart sections of the control group showed the endocardium which lines the chambers of the heart consisting of one layer of squamous endothelial cells arranged on a thin loose subendothelial connective tissues, the cardiac muscles are arranged in layers a complex spiral (Figure 7). A marked congestion and haemorrhage of the blood vessles and interstitial oedema observed in between cardiac muscle fibers (Figures 8A,B) was noted in group II. Group III showed a preserved cardiac tissue with little haemorrhage and congestion of the blood vessels (Figure 9).

Biochemical results

In the current study, the values of renal function tests persisted within normal levels, and there was no statistically significant difference in their measurements neither among the treated nor in the control groups (*P-value* >0.05) (Figure 10).

Morphometric results

As seen in Table 2, the alveolar wall thickness showed very highly significant increase (P=0.001) in the Nefopam treated group (group II) (16 ± 4.1) as compared with the control group (6.3 ± 2.1). Furthermore, the third group treated with black seed oil before Nefopam showed no significant differences in the alveolar wall thickness (5.2 ± 2) compared to the control group (*P* = 0.2) but showed significant differences when compared with group II (*P* = 0.01) (Table 2).

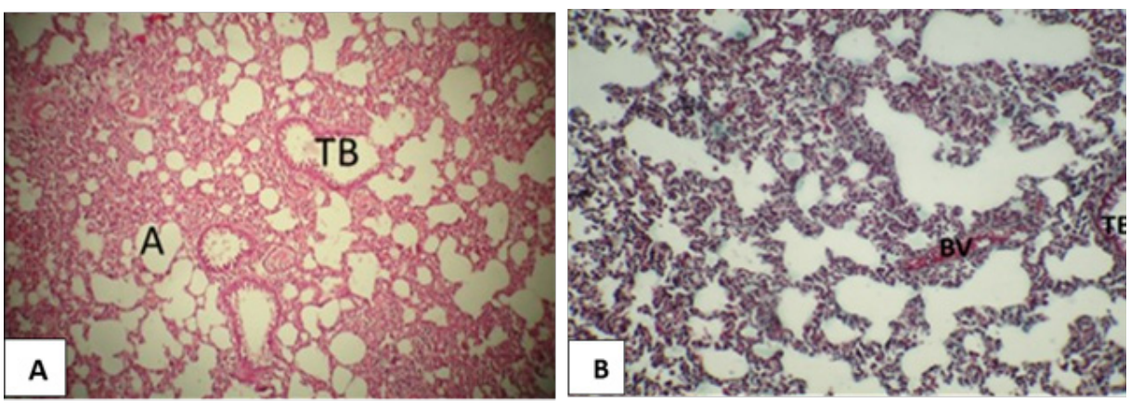

Fig. 1A: Micrograph of the rat's lung of group I(control group) showing alveoli (A) and terminal bronchiole (TB)) H&E X100). Fig. 1B: Collagen in the alveolar walls, around the pulmonary vessels (BV) and terminal bronchiole (TB) (Masson's trichrome X 100).

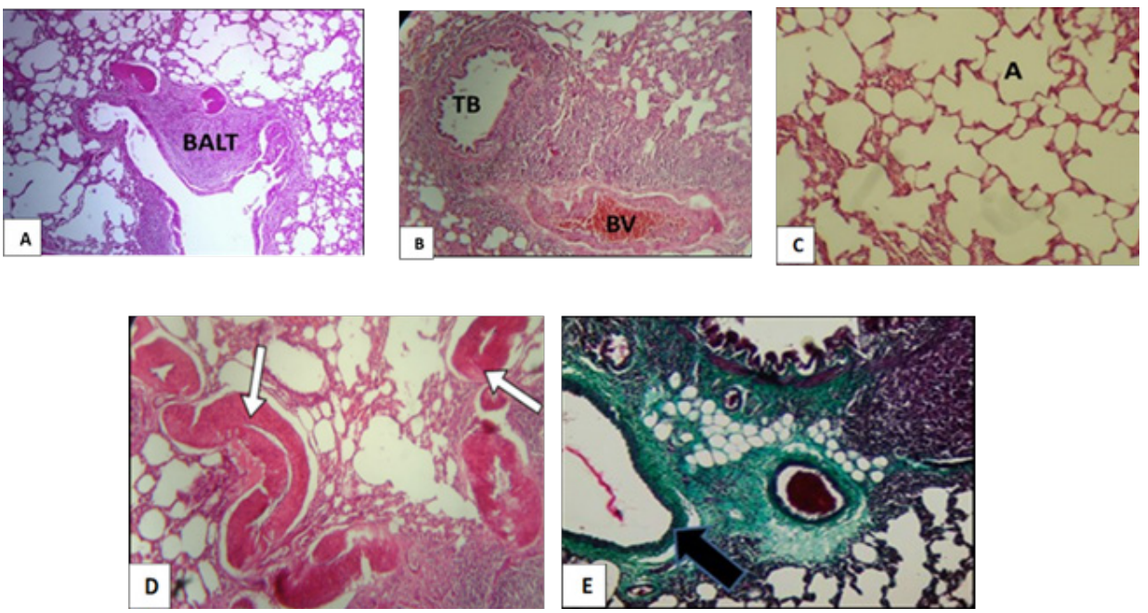

Fig. 2A: Micrograph of the rat's lung of group II revealed hyperplasia of lymphatic tissue around the bronchui (H&E X100). Fig. 2B: Congestion of the blood vessels, infiltration of mononuclear inflammatory cells around the terminal bronchioles(TB)(H&EX100). Fig. 3C: emphysematous dilatation of adjacent alveoli(A)(H&EX100). Fig. 2D: Thickening in the wall of the blood vessels (white arrows)(H&EX100). Fig. 2E: Deposition of collagen fibers (green color) around the blood vessels (black arrow)((Masson's trichrome X 100).

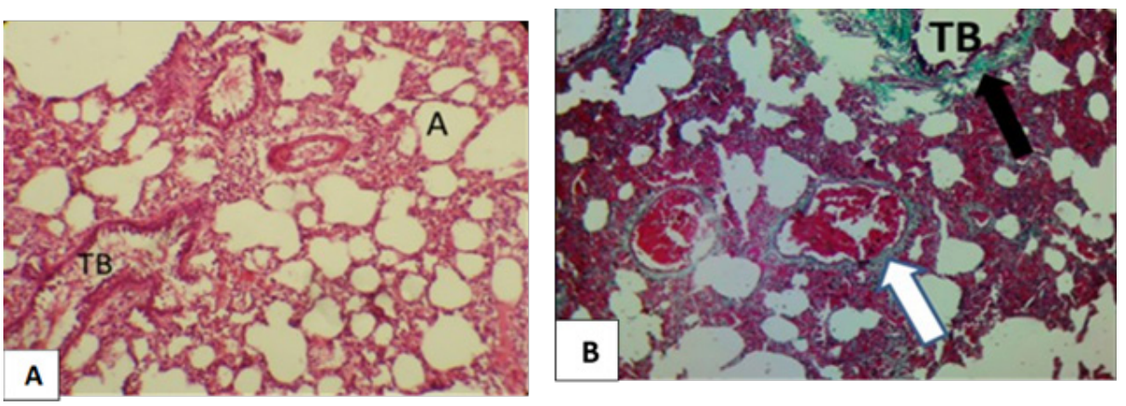

Fig. 3A: Micrograph of the rat's lung of group III revealed normal epithelial lining of the terminal bronchiole (TB) and less emphysematous dilatation of the alveoli (A) (H&EX100). Fig. 3B: Micrograph from lung of group III showing showing green colored little collagen fibers around the pulmonary vessels and around the terminal bronchiole (TB) (black arrows)(Masson's trichrome stain X 100).

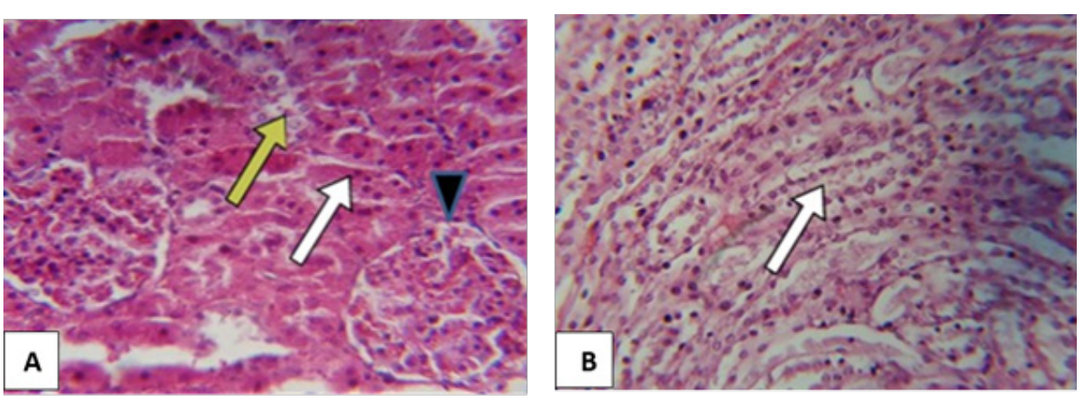

Fig. 4A: Micrograph of the rat's kidney of group I revealed renal corpuscles (arrow head), proximal convoluted tubule (white arrow), distal convoluted tubule (yellow arrow) (H&EX100). Fig. 4B: Renal medulla containing collecting tubule (white arrow)(H&EX100).

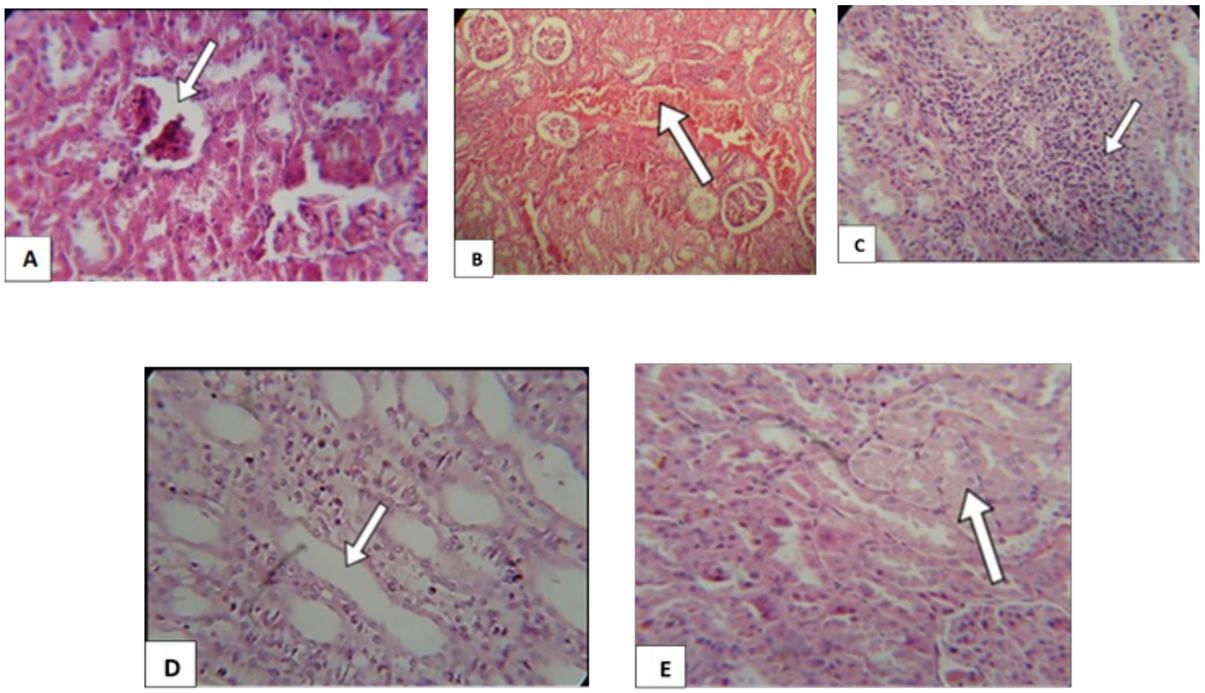

Fig. 5A: Micrograph of the rat's kidney group II showed shrinkage of the glomeruli with widening of the bowman's space (white arrow)(H&EX100).Fig. 5B:Congestion of renal vessels with haemorrhage in the interstitial tissue (white arrow)(H&EX100).Fig. 5C:Focal inflammatory cell infiltration (white arrow) (H&EX100). Fig. 5D: Dilatation of lumen of renal tubules (white arrow)(H&EX100).Fig. 5E:Oedema and vacuolations in the tubular epithelial cells(white arrow)(H&EX100).

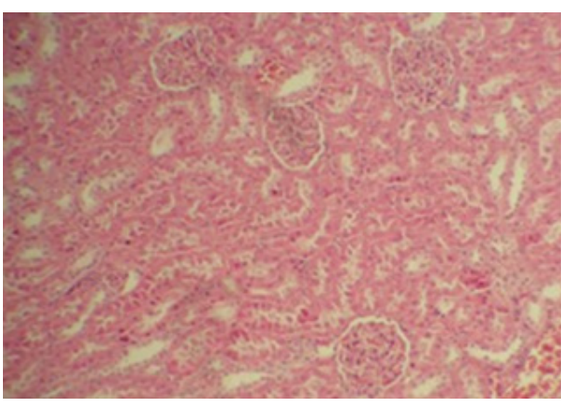

Fig. 6: Photomicrograph of the rat's kidney of group III showed more conserved architecture of renal tissue) (H&EX100).

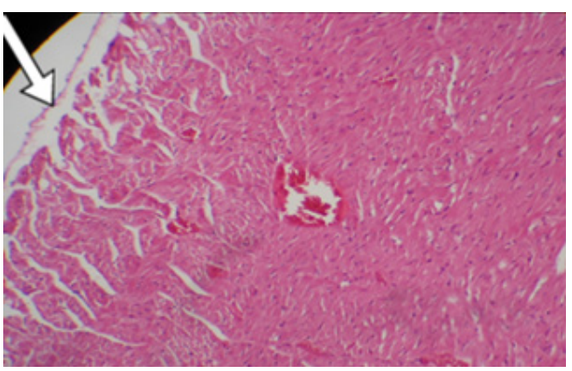

Fig. 7: Photomicrograph of the rat's heart of the control group showed single layer of squamous endothelial cells rest on a thin subendothelial layer of loose connective tissues (white arrow), cardiac muscles are arranged in a complex spiral (H&EX100).

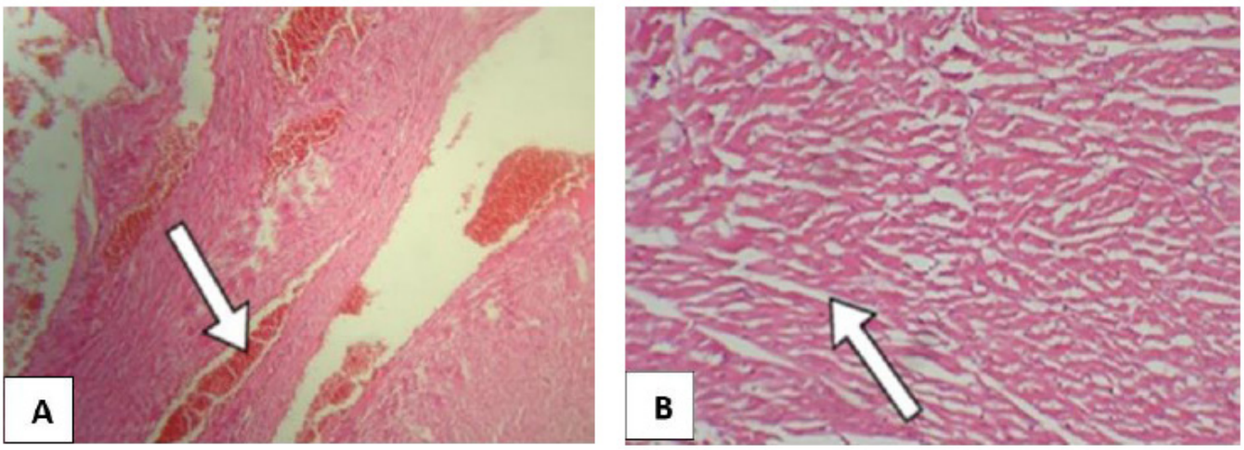

Fig. 8A: Micrograph of the rat's heart of showed marked congestion and haemorrhage of the blood vessles(white arrow). Fig. 8B: Interstitial oedema observed in between cardiac muscle fibers (white arrow)(H&EX100).

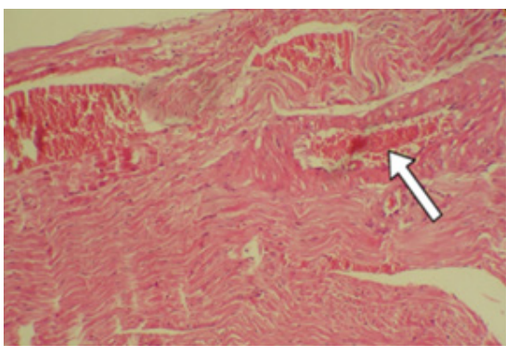

Fig. 9: Micrograph of the rat's heart of group III showed a preserved cardiac tissue with little haemorrhage and congestion of the blood vessels (white arrow) (H&EX100).

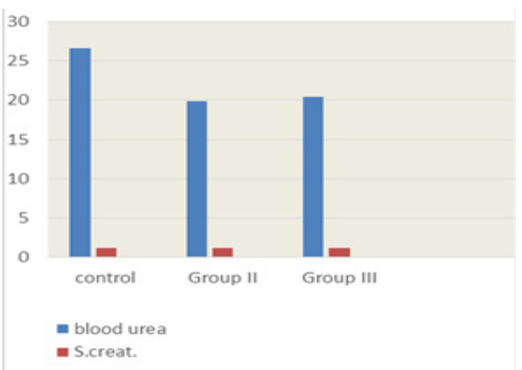

Fig. 10: Blood urea and serum creatinin values in the three animale groups. Results are presented as mean ±SD

Table 1: Body weight of rats before and after injection in each experimental group (Data expressed as mean±SD

Groups	N	Body weight Before injection	Body weight after injection	*P-values*
Control (I)	6	200±2	210±3	0.21
Nefopam (II)	6	210.5 ±3	220.5±3	0.1
Nefopam +N.Sativa (III)	6	180 ±1.5	200±1	0.2

Table 2: Morphometric quantities of the alveolar wall thickness for the control and experimental rats

Groups	No.	Alveolar wall thickness (µm)	*P-values*
Group I (control)	6	6.3 ± 2.1	0.001**
Group II (Nefopam)	6	16 ± 4.1	0.1
Group II (Nefopam)	6	5.2 ± 2	0.01*

**: $P = 0.001$ (I versus II), $P = 0.2$ (I versus III),
*: $P = 0.01$ (II versus III)

DISCUSSION

Nefopam is a non-narcotic analgesis that has been widly used recently to alleviate postoperative pain. Despite this wide use, very little is known about its effect on different organ systems. In the present study we compared the histological findings in the lung, kidney and heart tissues after prolonged use of nefopam to control. In addition, the protective effect of N. sativa on these tissues were examined. While there was no changes in weight and behavior af animals treated with nefopam when compared to controls, a very evident histological and morphometric changes were documented.

Evedent blood vessel congestion and inflammatory cell infiltration in the Nefopam treated group can be correlated to the oxidative tissue damage and release of vasodilator substances with subsequent stasis of the blood in the dilated vessels. Similar to the findings by Mousa Y[20] who indicated that oxidative stress amplified the analgesic activity of nefopam in chickens. This oxidative stress can also explain the emphysematous changes noted in the lungs of these rats secondary to insufficient secretion of surfactant material by pneumocytes type II cells. This reduced surfactant will promotes rupture and communication of the neighboring alveoli. This is in

accordance with Fischer *et al*; 2011[21] findings who stated that oxidative stress, protease-antiprotease imbalance and inflammation are a unique pathogenic triad exhibited as emphysema in chronic obstructive pulmonary disease (COPD). However, new researchers suggested that destruction and/or remodelling of alveolar macrophages might induce emphysematous changes as occur in cigarette smoking[22]. The deposition of collagen fibers in rat's lung of Nefopam treated group might be mediated by generation of reactive oxygen species with consequent activation of fibroblast and synthesis of collagen fibers. Similar changes previously observed in chronic lung pathology which necessitate dietary antioxidants supplementation[23].

The shrinkage of the glomeruli and widening of the bowman's space observed in group II together with widening of the bowman's space might be explained due to a drop in the aerobic metabolism followed by low intracellular pH, dysfunction of the Na+/K+ pump with swelling of glomerular epithelial lining and consequent glomerular contraction. Such findings are comparable with Utiel F *et al*.[24] who studied the effects of tramadol the kidney of albino rats. Dilated renal tubules and vacuolations of the tubular epithelial cells agree with similar changes conveyed by Djerada Z *et al*., 2014[25]. Conversely our finding disagree with the study of Jamal N *et al*., 2020[26] who mentioned that the frequency of detrimental effects of Nefopam on the vital organs increases with higher doses and prolonged duration of intake with no significant changes in renal histological structure and function. Vacuolations of tubular epithelial cells noticed in group II is probably due to deterioration of blood flow and subsequent oxidative damage to renal tubular cells which is in agreement with previous findings shown after prolonged use of Morphine[27].

Moreover, oxidative stress can explain the vascular congestion and haemorrhage and myocardial interstitial oedema observed in the group treated with Nefopam. This will cause ischemia and necrosis in the vascular wall then vasodilatation and leakage of blood through the damaged wall due to altered microvascular permeability[28,29].

Concomitant administration of black seed oil with Nefopam revealed a substantial protection with approximatly normal appearance of lung tissue which might be due to a substantial decrease in the inflammatory markers particularly by impeding T-cell proliferation in rat's lung[30].

The reversed renal changes in the group recieving black seed oil prior to Nefopam agree with previous reports that Thymoquinone (TQ), the active component of N. sativa oil produced a dose-dependent improvement of the renal toxicity induced by aminoglygoides and prevents renal failure[31]. However, TQ significantly decreased lipid peroxidation and restores the inflammatory markers toward normal values in rats treated with Doxorubicin[32]. Furthermore, our findings settles with other workers who mentioned that co-administration of N. sativa seeds improved the biochemical parameters and might be clinically valuable in mercury intoxication[33].

A preserved cardiac tissue is due to potentially protective effects of N. sativa against chemical toxins. Similarly N. sativa oil completely normalized cardiac damage induced by cyclophosphamide and cyclosporine via reducing lipid peroxidation and improving the activity of the antioxidant enzymes[34].

Furthermore, similar protection of other vital organs like liver, brain, gastrointestinal, and reproductive system obtained by N. sativa against intoxication provoked by ethanol, toluene, and CCl4 have been exposed through multiple mechanisms including anti-inflammatory, antioxidant, free radical scavenging, inhibition of apoptosis and regulation of genes expression[35].

CONCLUSION

This study demonstrated that Nefopam has detrimental effects on the lung, kidney and heart of albino rats. Pretreatment with N. sativa oil attenuates pulmonary, renal and cardiac toxicity induced by Nefopam mainly through its active ingredients, thymoquinone which has been reported to decrease oxidative stress and lipid peroxidation and improve antioxidant enzyme activity. Further clinical researches are required to verify the antidotal properties of N. sativa in human intoxications.

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CONFLICT OF INTERESTS

There no conflicts of interest.

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الملخص العربى

التاثيرات المحمية لزيت حبة البركة (نيجلا ساتيفا) ضد السمية الرئوية, الكلوية , والقلبية التي يحدثها عقار النيفوبام في الجرذان

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يهدف هذه العمل الى معرفة التغييرات النسيجية في الرئة والكلية والقلب التي يحدثها الحقن داخل الصفاق لعقار النيفوبام ودور زيت الحبة السوداء(نيجلا ساتيفا) في التخفيف من هذه االتغيرات. أجريت هذه الدراسة على ثمانية عشرمن ذكور واناث الجرذان البالغة والتي قسمت عشوائيا الى ثلاث مجاميع متساوية ستة جرذان في كل منها.المجموعة الاولى هي مجموعة السيطرة,المجموعة الثانية اعطيت عقار نيفوبام ١٠ ملغرام لكل كيلوغرام عن طريق الحقن داخل الصفاق ولمدة شهر.المجموعة الثالثة اعطيت زيت الحبة السوداء عن طريق التزقيم الفموي ٢٤ ساعة قبل كل حقن داخل الصفاق من عقار النيفوبام ولمدة شهر واحد ايضا. اخذت نماذج من نسيج الرئة والكلية والقلب من الجرذان وتم تحضيرها للفحص النسيجي بالمجهر الضوئي.تم صبغ الشرائح النسيجية باستخدام صلغة الهيماتوكسيلين والايوسين وكذلك صبغة الماسون تراكروم وفحصها بالمجهر الضوئي.قورنت بعض المعطيات مابين المجاميع الثلاثة باستخدام مقاييس مورفوميترية نسيجية.اظهرت النتائج وجود تسرب الخلايا الالتهابية حول الاوعية الدموية وحول القصيبات الهوائية في نسيج الرئة,احتقان الاوعية الدموية وازدياد في سمك جدرانها مع انتفاخ الحويصلات الهوائية,بالمقارنة مع مجموعة السيطرة.بينما اظهر نسيج الكلية انكماش في الخصل الكبيبية, احتقان الاوعية الكلوية, نزف في النسيج الخلالي ,تسرب الخلايا الالتهابية, توسع النبيبات الكلوية وتنكس فجوي في النسيج المبطن لها. اظهرت الشرائح النسيجية لنسيج القلب وجود احتقان ونزف في الاوعية الدموية مع وذمة مابين االالياف العضلية القلبية. المعالجة الاولية باستخدام زيت الحبة السوداء يخفف وبكفاءة التغيرات التي يحدثها عقار نيفوبام في نسيج الرئة ,الكلية والقلب ويعيد جميع التغيرات غير الطبيعية الى مايقارب الطبيعي. اظهرت النتائج الشكلية زيادة ملحوظة في سمك جدران الحويصلات الهوائية في جرذان المجموعة الثانية وعدم وجود اختلاف ملحوظ في المجموعة الثالثة بالمقارنة مع مجموعة السيطرة.نستنتج من ذلك ان عقار نيفوبام يحدث تغييرات تلركيبية ملحوظة في انسجة الرئة والكلية والقلب والتي من الممكن ان تعود الى الطبيعي عن طريق تناول زيت الحبة السوداء.