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Research Article
Effects of Aqueous-ethanolic Extract of *Nigella sativa* Seeds (Black Cumin) and Vitamin E on Cisplatin-induced Nephrotoxicity in Rat

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Abstract

Cisplatin (cis-dichlorodiamineplatinum II) is a potent antineoplastic agent against several types of tumor. Nevertheless, its clinical utility is limited due to its cytotoxic adverse effects that include nephrotoxicity. Several factors including inflammation, oxidative stress, DNA damage and mitochondrial injury are involved in cisplatin-induced cell injury. *Nigella sativa* and vitamin E possess the anti-inflammatory and antioxidant properties. Accordingly, the present study was designed to investigate the protective effects of hydroalcoholic extract of *Nigella sativa* seeds and vitamin E on cisplatin-induced nephrotoxicity. Forty eight male Wistar rats were randomly divided into 8 groups and treated daily with *Nigella sativa* extract (100 or 200 mg kg^{-1}, i.p.) or vitamin E (100 mg kg^{-1}, i.p.) 1 h before single dose cisplatin injection (6 mg kg^{-1}, i.p.) and continued for 5 days. Serum and urinary biochemical parameters were measured on day 0 and 6. Histopathological examination of the kidney and determining the kidney index were performed on day 6. The results showed that serum urea and creatinine concentrations, as well as urine glucose, kidney index and histopathological damage were significantly increased in cisplatin group compared with control group, while Glomerular Filtration Rate (GFR) and urea clearance were significantly reduced. Similar alterations in biochemical factors were observed in groups that received cisplatin together with *Nigella sativa* extract or vitamin E compared to control group. However, treatment with *Nigella sativa* extract or vitamin E could improve histopathological damages due to cisplatin. In conclusion, *Nigella sativa* extract or vitamin E treatment attenuated the histological alterations induced by cisplatin.

Key words: *Nigella sativa*, acute renal failure, cisplatin, vitamin E, rat

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cisplatin (cis-dichlorodiamineplatinum II) is an effective anti-neoplastic agent used to treat various solid tumors including cancers of the ovary, testis (Jung *et al*., 2009), bladder and tumors of head and neck (Santos *et al*., 2007). Nevertheless, its clinical utility is limited due to its cytotoxic adverse effects that include nephrotoxicity (Atasayar *et al*., 2009). Cisplatin primarily affects the S_3 segment of the proximal tubule. The severity of cisplatin nephrotoxicity is related to platinum concentrations in the kidneys (Kroning *et al*., 2000).

There is an increasing amount of evidence that cisplatin-induced nephrotoxicity is related to oxidative damage resulting from free radicals generation (Mora *et al*., 2003), as several studies have shown that the oxygen free radicals are important mediators of cisplatin-mediated nephrotoxicity (Ali and Al-Moundhri, 2006; Yao *et al*., 2007). Therefore, recent studies have focused on the role of antioxidants in the treatment of cisplatin-induced toxicity and it has been reported that the administration of antioxidants has been efficient in inhibiting these side effects (Ali and Al-Moundhri, 2006; Naziroglu *et al*., 2004).

Nigella sativa (NS), an annual herbaceous plant of the Ranunculaceae, has been shown to contain fixed oil and volatile oil. The volatile oil has been shown to contain 18.4-24% thymoquinone and 46% monoterpenes such as pcymene and a-piene (El Tahir *et al*., 1993). It has been traditionally used in the Middle East, Northern Africa, Far East and Asia for the treatment of various diseases for over 2000 years. Recently, several effects of *Nigella sativa* extracts, including antioxidant, anti-inflammatory, immunomodulatory, antitumor, antidiabetic and hepatoprotective effects have been documented in both clinical and experimental studies (Yaman and Balikci, 2010; Salem, 2005; Ali and Blunden, 2003; Abuelgasim *et al*., 2008). *Nigella sativa* relatively recovered histopathologic properties in the nephrotoxicity induced with cisplatin (Hadjzadeh *et al*., 2012). Vitamin E is the major lipophilic chain-breaking antioxidant presents within cell membranes. Accordingly, the present study was designed to examine the protective effects of hydroalcoholic extract of *Nigella sativa* seeds and vitamin E on cisplatin-induced nephrotoxicity in rats.

MATERIALS AND METHODS

Animals: Forty eight male Wistar albino rats (weighing 250-300 g) were obtained from the Animal House, Mashhad University of Medical Sciences (Mashhad, Iran). The animals were housed 4 cage^{-1} under standard temperature (24±2°C), humidity (55±5%) and lighting (12:12 h; light:dark) conditions. Food and water were supplied *ad libitum*. The health status of the rats was monitored daily. All experiments were conducted in accordance with the guide for the care and use of laboratory animals and the study was approved by Mashhad University of Medical Sciences.

Chemicals: Cisplatin (Mylan Company, France) was provided by Omid Hospital Pharmacy (Mashhad, Iran). The injection form of vitamin E, dl-α-tocopheryl acetate (Osvah Company, Iran) was purchased from 22 Bahman Pharmacy (Mashhad, Iran). *Nigella sativa* seeds were obtained from the local herbal market (Mashhad, Iran) and was identified by botanists in the herbarium of Ferdowsi University of Mashhad with herbarium number 293-0303-1. Crushed seeds were extracted by Soxhlet apparatus (Burits and Bucar, 2000). The solvent was removed under vacuum.

Experimental design: Forty eight rats randomly divided into 8 equal groups including 6 animals each:

- **Control group:** The rats received single dose of isotonic saline
- **Cisplatin (CP) group:** The rats received single dose of cisplatin 6 mg kg^{-1} (Ali *et al*., 2006; Francescato *et al*., 2004)
- **NS100 group:** *Nigella sativa* extract (100 mg kg^{-1} i.p.) was injected daily for 5 days (El Daly, 1998; Khan *et al*., 2003)
- **NS200 group:** *Nigella sativa* extract (200 mg kg^{-1} i.p.) was injected daily for 5 days
- **NS100+CP group:** *Nigella sativa* extract (100 mg kg^{-1} i.p.) was injected 1 h before administration of cisplatin and continued for 5 days
- **NS200+CP group:** *Nigella sativa* extract (200 mg kg^{-1} i.p.) was injected 1 h before administration of cisplatin and continued for 5 days
- **Vitamin E group:** Vitamin E (100 mg kg^{-1} i.p.) was injected daily for 5 days (Yasuyuki *et al*., 1992)
- **Vitamin E+CP group:** Vitamin E (100 mg kg^{-1} i.p.) was injected 1 h before administration of cisplatin and continued for 5 days

Drugs and extracts were injected intraperitoneally in the lower right quadrant to avoid injection to the cecum and urinary bladder.

Sampling: Animals were kept separately in metabolic cages and acclimatized for at least 1 day before treatment. Twenty four hours urine output was collected on days 0 and 6 with clean metabolic cages. Blood from retro-orbital plexus was

collected and centrifuged at 4000×g for 10 min for serum separation on days 0 and 6, urine and serum specimens were quickly kept frozen at -20°C until needed for analysis. On day 6, all animals were anesthetized by diethyl ether and the right kidneys were rapidly excised from the body of each animal. Weighed organs were preserved in 10% buffered formalin for histological examinations using hematoxylin and eosin staining, followed by the analysis of tubular damages. In brief, the formalin fixed tissues were dehydrated in graded concentrations of alcohol and xylene followed by embedding in paraffin. The kidney tissue blocks were then cut at 5 µm and stained with hematoxylin and eosin. Photographs from samples were taken by Olympus BX51 microscope. Percentage of kidney damage including necrosis, inflammation, tubular casts, tubular cell flattening and glomerular atrophy pathologically were examined by a pathologist (Badary *et al*., 1997).

Biochemical analysis: Serum and urine urea, creatinine, glucose and albumin concentrations were analyzed by appropriate kits from Pars Azmun company (Karaj, Iran) using Convergys 100 (Germany).

Statistical analysis: The calculations and statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) for windows version 11.5 software. The data were expressed as Mean±SEM. At first, the normality for the data was tested using one sample Kolmogorov-Smirnov test. It was found that total of data fit to normal distribution. Thus, the parametric one-way analysis of variance (ANOVA) test was used for differences between groups followed by Tukey *post hoc* test. Results were considered statistically significant at $p<0.05$.

RESULTS

Effects of *Nigella sativa* extract and vitamin E on cisplatin-induced changes in serum urea and creatinine levels: Cisplatin significantly increased serum urea and creatinine concentrations on day 6 of research in CP group compared to control group ($p<0.001$ and $p<0.01$, respectively, Fig. 1 and 2). Treatment with 70% aqueous-ethanolic extract of *Nigella sativa* and vitamin E together with cisplatin did not significantly change the serum urea and creatinine concentrations compared to cisplatin group.

Effects of *Nigella sativa* extract and vitamin E on cisplatin-induced changes in urine glucose and albumin levels: In CP group, urine glucose significantly increased on day 6 of experiment compared with control group

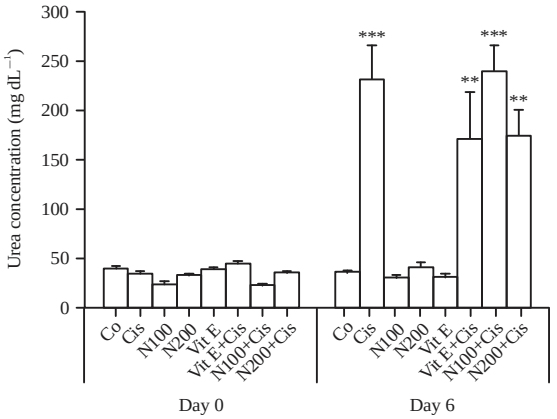

Fig. 1: Serum urea levels in experimental groups. **p<0.01 and ***p<0.001 compared to control group

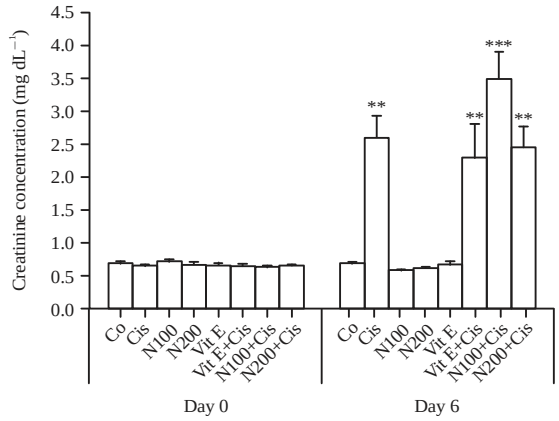

Fig. 2: Serum creatinine levels in experimental groups. **p<0.01 and ***p<0.001 compared to control group

(p<0.001, Fig. 3). Treatment with aqueous-ethanolic extract of *Nigella sativa* or vitamin E together with cisplatin did not significantly change the urine glucose levels compared to cisplatin group. There was no significant change in urine albumin concentration between experimental groups on day 6 of experiment (Fig. 4).

Effects of *Nigella sativa* extract and vitamin E on cisplatin-induced changes in GFR and urea clearance: Treatment with cisplatin significantly decreased GFR as well as urea clearance in CP group compared with control group (p<0.001, Fig. 5 and 6). Treatment of experimental groups with *Nigella sativa* extract or vitamin E together with cisplatin did not change the GFR and urea clearance compared to cisplatin group (Fig. 5 and 6).

Kidney index and pathological examination: The CP group showed a significant increase in Kidney Index (KI) compared with control rats. However, among

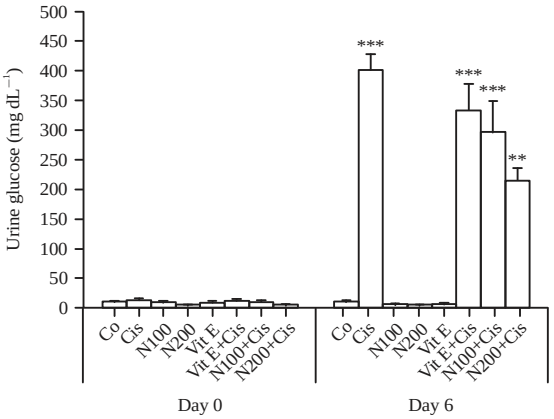

Fig. 3: Urine glucose levels in experimental groups. **p<0.01 and ***p<0.001 compared to control group

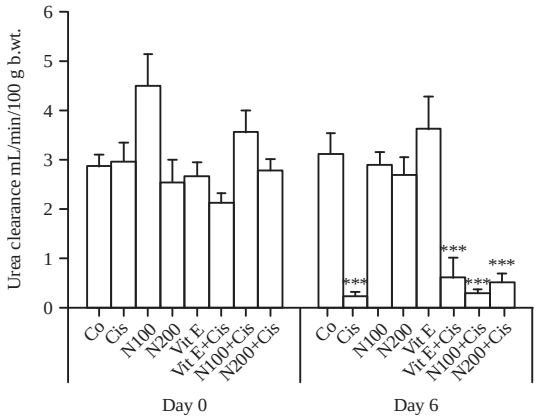

Fig. 6: Urea clearance in experimental groups. ***p<0.001 compared to control group

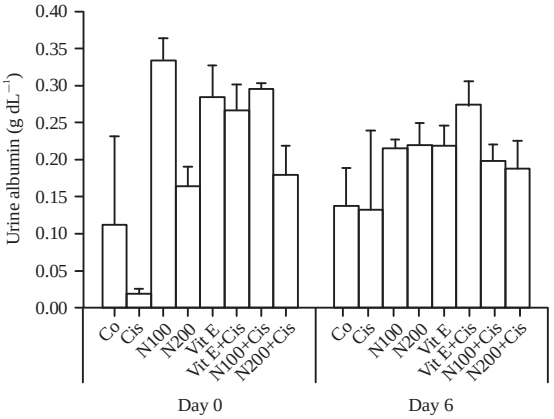

Fig. 4: Urine Albumin levels in experimental groups

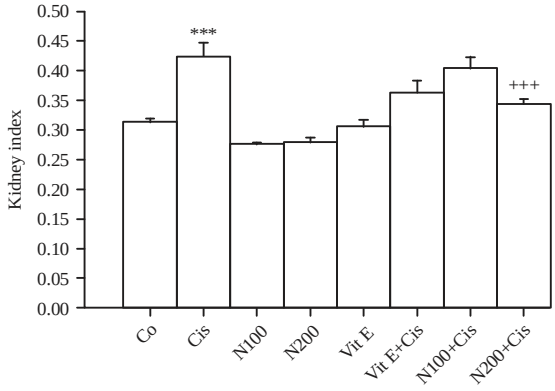

Fig. 7: Kidney index in experimental groups. ***p<0.001 compared to control group and $^{+++}$p<0.001 compared to cisplatin group

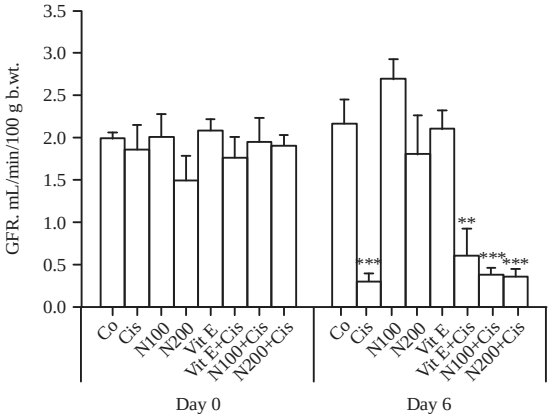

Fig. 5: Glomerular Filtration Rate (GFR) in experimental groups. **p<0.01 and ***p<0.001 compared to control group

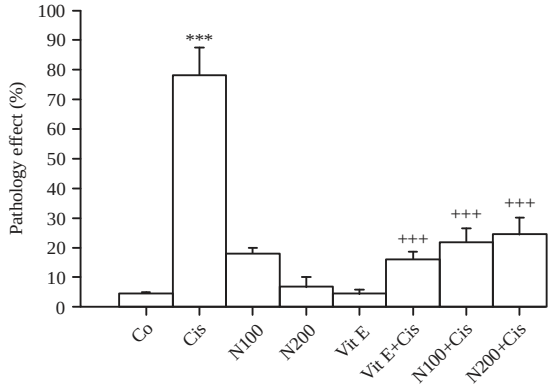

Fig. 8: Percentage of kidney damage in experimental groups, ***p<0.001 compared to control group and $^{+++}$p<0.001 compared to cisplatin group

experimental groups, NS200+CP group presented a significant reduction in KI in comparison with the CP group (Fig. 7).

Pathological examination also showed a significant enhancement of renal injury in CP group (Fig. 8 and 9)

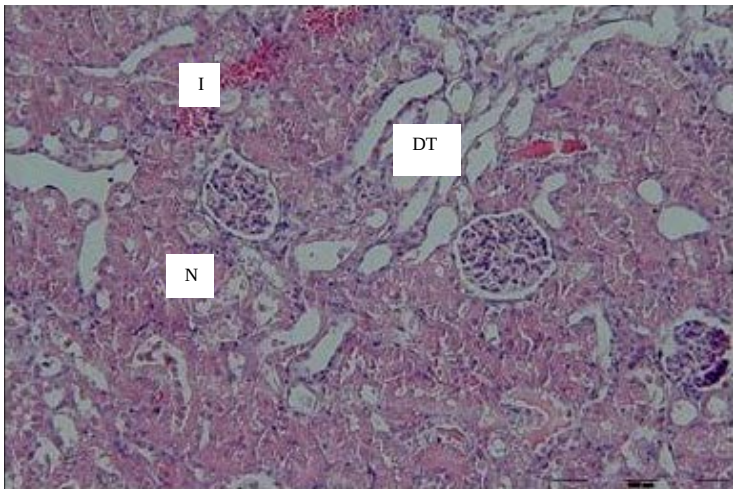

Fig. 9: Photographs of the cortical areas in cisplatin group with a magnification 200× (hematoxylin-eosin staining). Necrosis (N), vascular congestion and inflammation (I) and dilated tubular space (DT) have been shown

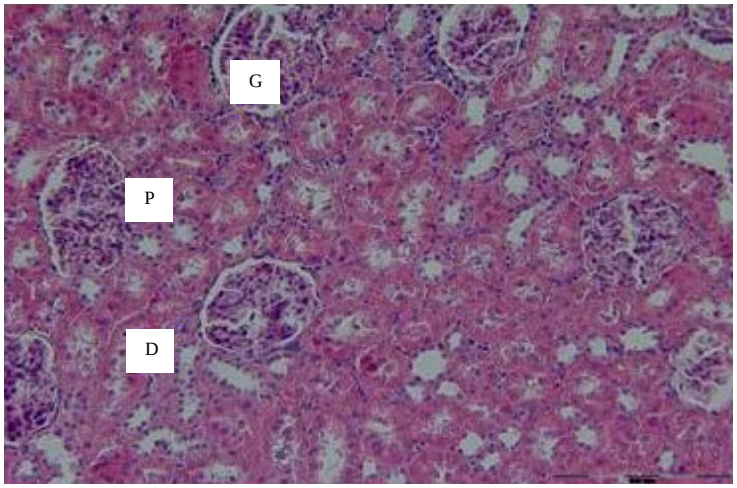

Fig. 10: Photographs of all cortical areas in control group with a magnification 200× (hematoxylin-eosin staining). Glomeruli (G), proximal (P) and distal (D) tubules are observed

compared with control rats (Fig. 8 and 10). However, there was a significant reduction in kidney damage in vitamin E+CP, NS100+CP and NS200+CP groups comparing with the CP group (Fig. 8).

DISCUSSION

In the present study, the biochemical and histological data showed that a single dose of cisplatin (6 mg kg^{-1} i.p.) led to renal failure; serum urea and creatinine levels, as well as urine glucose were significantly increased, while urea and creatinine clearance were significantly decreased in cisplatin group compared to control group on day 6 of the experiment. Furthermore, the kidney index and renal tissue damage was significantly increased in the group receiving cisplatin compared to control group. This result are consistent with the previous studies (Atasayar *et al*., 2009; Francescato *et al*., 2004; Mansour *et al*., 2002; Yadav *et al*., 2010) and confirms the kidney damage caused by cisplatin.

Increased serum urea and creatinine concentrations, as well as decreased urea and creatinine clearance could be resulted from the effects of cisplatin on renal vascular endothelial cells and glomeruli. Production of inflammatory mediators and reactive oxygen species due to cisplatin, leads to bulging of the vascular endothelial cells and the reduction of filtration coefficient (Nissenson, 1998). Khan *et al*. (2007)

have also suggested that the cisplatin can reduce renal blood flow. On the other hand, tubular cast formation by cisplatin leads to obstruction of renal tubules and increase of tubular hydrostatic pressure, this leads to decrease in glomerular hydrostatic pressure and filtration rate; subsequently the serum urea and creatinine concentrations are increased.

These results also showed that urine glucose was increased after treatment with cisplatin. Several studies (Kim *et al*., 2001; Kishore *et al*., 2000) have shown that cisplatin can decrease the gene expression of aquaporines and reduce their density in the proximal tubule and descending thin sections of henle, leading to increase of sodium and glucose excretion and urine output. Cisplatin can also damage the tubular cells and lead to dysfunction of cell membrane pumps, including sodium-potassium pumps. This results in decrease in sodium reabsorption and sodium-dependent glucose reabsorption so that their urinary concentrations are increased (Khan *et al*., 2007; Kim *et al*., 1995; Kishimoto *et al*., 2006).

However, as shown in results, groups receiving 70% aqueous-ethanolic extract of *Nigella sativa* together with cisplatin and vitamin E together with cisplatin, showed the same results for biochemical parameters as cisplatin group. In the other words, separate treatment with *Nigella sativa* extract and Vit. E had no effect on biochemical factors. These results are in favour of Zaoui *et al*. (2002) and Hadjzadeh *et al*. (2012) studies, which have reported that treatment with *Nigella sativa* seeds extract did not decrease the blood urea and creatinine levels. However, in contrast with these findings, El Daly (1998) have reported that the injection of black seed soaked extract at half an hour before cisplatin for 5 days decreased the serum urea and creatinine, In another study, it was found that the black seed oil could decrease the serum urea and creatinine and tubular injury (Uz *et al*., 2008). The reason that *Nigella sativa* extract had no effect on renal biochemical parameters is not clear, but it may be in part due to the dosage of the *Nigella sativa* extract or its time-course action on biochemical parameters. Cisplatin-induced renal nephrotoxicity is a quick process that begins through the apoptosis initiating reactions in the cell in the 1st h of injection (Wu *et al*., 2005). Therefore, the protective factors like *Nigella sativa* extract and also vitamin E should be used in proper dose before or along with the induction of nephrotoxicity.

As mentioned, treatment with cisplatin also led to renal tissue damage as evidenced by increase in kidney index and the percentage of tissue damage. However, cisplatin groups receiving 100 and 200 mg kg^{-1} of *Nigella sativa* extract and vitamin E separately showed lower kidney index and the percentage of tissue damage compared to cisplatin group. It has been shown that cisplatin leads to weight loss (Ali and Al-Moundhri, 2006) and kidney weight gain (Badary *et al*., 1997) in rats, therefore, the kiney index was increased in the group receiving cisplatin. Weight loss could be caused owing to the adverse effects of cisplatin on food absorption in digestive system, as well as on renal tubules by impairing the water absorption, leading to dehydration of rats (Khan *et al*., 2003). It has been reported that the intermittent infusion of 3 or 5 mg kg^{-1} cisplatin for 5 days led to the tubular damage, particularly in the proximal tubule, eliminating brush borders and tubular cast formation (Noori and Mahboob, 2010; Abdelmeguid *et al*., 2010).

It has been demonstrated that cisplatin induces oxidative stress in renal tubular cells through reactive oxygen species (Jordan and Carmo-Fonseca, 2000). The interaction of reactive oxygen species with cellular components may result in damage to DNA, proteins and lipids. *Nigella sativa* possesses potent free radical scavenging and antioxidant properties (Ramadan *et al*., 2003). Therefore, it seems that the protective effect of *Nigella sativa* extract and vitamin E on kidney tissue damage may be in part mediated by their antioxidant and free radical scavenging properties.

CONCLUSION

The results of biochemical and pathological studies confirmed that cisplatin led to acute renal failure. Also, the present study showed that 70% aqueous-ethanolic extract of *Nigella sativa* at doses of 100 and 200 mg kg^{-1} and vitamin E at dose of 100 mg kg^{-1} 1 h before cisplatin for 5 days had a partial effect on biochemical factors. However, *Nigella sativa* extract and vitamin E at mentioned dosages, could improve renal tissue damage due to cisplatin. The different effects of *Nigella sativa* on biochemical and histopathological parameters could be in part due to time course action on kidney functional improvement. Further assessment about the dosage of *Nigella sativa* extract and duration of treatment as well as the mechanism of its action are suggested for future studies.

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