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Review

The role of Nigella Sativa in Amelioration of Cisplatin-Induced Nephrotoxicity in albino rats

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ABSTRACT

Background: Many solid human cancers are treated with chemotherapeutic drugs as cisplatin which was found to induce nephrotoxicity as a known side effect. This study aimed to assess the effects of Nigella Sativa on the induced Cisplatin-nephrotoxicity in rats.

Materials and methods: thirty adult male albino rats were randomly assorted into 3 equal groups (10 rats/each): the first group (control), the second group (received Cisplatin only), and the third group (received Cisplatin plus Nigella Sativa). At the end of the experiment, rats were sacrificed, and blood analysis was done to assay the kidney functions. Also, fresh kidney specimens were split and processed for further tissue and histopathological studies.

Results: Rats exposed to Cisplatin had significantly lower levels of antioxidant system, deteriorated kidney functions and higher levels of markers of free radicals, and apoptosis compared to the control group. While rats exposed to Cisplatin plus Nigella Sativa had higher levels of antioxidant system, restoration of kidney functions and lower levels of markers of free radicals, and apoptosis compared to that in Cisplatin group. The histopathological changes in the rats' kidney on exposure to Cisplatin revealed glomerular dystrophy, tubular degeneration. While rats exposed to Cisplatin plus Nigella had restored the normal structural architecture of the kidney than the only group.

Conclusion: Nigella Sativa alleviates the Cisplatin-induced nephrotoxicity in male rats through its antioxidative mechanism.

Introduction

The kidneys are important organs in the human body which eliminate waste, responsible for filtration control acid and electrolyte balance, and generate hormones that influence the health of other important organs (1).

There are numerous, complex etiologies for the decline in renal function including a number of environmental toxicants, age, diabetes mellitus, and hypertension, as well as drug-induced nephrotoxicity as the kidney is exposed to larger amounts of circulating medicines and/or metabolites than any other organ system, it is therefore more vulnerable to drug-induced harm (2, 3).

The most important factor contributing to renal damage was drug use; specifically, acetaminophen, aminoglycoside, ACEI, cisplatin, penicillin G, and ranitidine were the most important in causing the development of AKI. These drugs may have done this by causing inflammation, acid-base disturbance, electrolyte abnormalities, intrarenal obstruction, and interstitial nephritis (4).

Cisplatin (CIS) is a platinum-based chemotherapy medication that is frequently used to treat many tumors in different ages, including osteosarcoma, neuroblastoma, hepatoblastoma, brast cancers, ovarian carcinoma as well as several types of brain tumors (5). Nephrotoxicity is a known and significant side effect of cisplatin through induction of renal apoptosis, oxidative stress, and DNA damage by accumulation in tubular cells. In addition to causing acute kidney injury (AKI) and exacerbating tubular damage, cisplatin also lowers renal blood flow (6, 7).

Because cisplatin nephrotoxicity is a dose-limiting adverse effect, varying cisplatin dosages result in varying degrees of nephrotoxicity and histopathological alteration. Acute kidney damage (AKI), chronic kidney injury (CKI), or any other clinical renal symptoms could be signs of this nephrotoxicity (8).

Drug induced nephropathy (DIN) has seriously impeded research and development of new drugs. Prior studies have demonstrated that DIN has resulted in the removal of many potentially novel medications from clinical trials, which has a direct impact on the low approval rate (9, 10).

Many preclinical studies have confirmed that the cisplatin-induced nephrotoxicity can be ameliorated by different modalities focusing on its antioxidant and anti-inflammatory mechanisms (11, 12).

Nigella sativa (black cumin), is a well-known spicy herb. Its seeds, in particular, have long been used to treat a wide range of illnesses in people, especially those that affect the kidneys. Its nephroprotective benefits thought to be mediated by antioxidant, anti-inflammatory, immunomodulatory, antiapoptotic, and antifibrotic effects (13, 14).

So, this study was designed to explore the effect of Nigella sativa to ameliorate cisplatin induced nephrotoxicity.

Materials and Methods

Drugs

Cisplatin was acquired from the Greek company Mylan.

Chemicals

We purchased Nigella Sativa oil from the local market and identified by a botanist.

Animals and design of the experiment

This study used thirty adult male albino rats (weighed between 130 and 150 g). The rats were kept in standard metabolic cages (each of five rats), with unrestricted access to rat chow and tap water.

Three equal groups were randomly selected from among the animals: The control group received receiving normal saline (i. p.), the Cisplatin group received cisplatin on the 6th of the experiment, (6 mg/kg BW, i. p.) after receiving normal saline (i. p.) for 11 days. and the Cisplatin plus Nigella sativa group received both and Nigella s. oil (2 ml/Kg BW) orally by gavage for 11 consecutive days and CIS (6 mg/kg BW, i. p.) on the 6th day of the experiment.

Blood and tissue sampling

By the end of the experiment (12th day) animals were sacrificed. Blood samples were taken from the retro-orbital plexus. After centrifuging at 4000 g for 10 minutes, serum was kept at -20 ˚C until analysis. Kidney functions including serum urea and creatinine were analyzed according to the manufacturer's instructions.

Fresh kidney specimens were extracted, preserved in 9% neutral buffer formol, dehydrated in alcohol, cleared in xylol and stained with either Hx. &E. for analysis of the structural changes of the kidney or Masson trichrome stain for detection of the fibrotic changes of the kidney. Another fresh kidney specimens were used for further tissue analysis of oxidative stress parameters: malondialdehyde (MDA), reduced glutathione (GSH) and Catalase (CAT).

Statistical assessment

The Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data, and the results were presented as mean ± standard error of the mean (SEM). A one-way analysis of variance (ANOVA) for multiple comparisons was used to evaluate differences between group means. P less than 0.05 was regarded as significant.

Results

kidney functions

Cisplatin injection deteriorated kidney functions in the form of increased serum levels of creatinine, urea, and uric acid compared to the control group. While, the use of Nigella Sativa Oil plus Cisplatin enhanced those parameters compared to those in CIS-group (Table 1).

Oxidative stress parameters in the kidney

Cisplatin injection increased tissue level of MDA, and decreased tissue levels of reduced glutathione (GSH) and Catalase (CAT) compared to those in the control group. While, the use of Nigella Sativa Oil plus Cisplatin increased tissue level of MDA, and decreased tissue levels of reduced glutathione (GSH) and Catalase (CAT) compared to those in CIS-group (Table 2).

Cisplatin injection deteriorated kidney structure in the form of tubular and glomerular dystrophy compared to the control group. While, the use of Nigella Sativa Oil plus Cisplatin restored those changes compared to those in CIS-group (Figure 1).

Fibrotic changes

Cisplatin injection increased deposition of collagen fibers in the kidney compared to that in the control group. While, the use of Nigella Sativa Oil plus Cisplatin decreased deposition of collagen fibers in the kidney compared to those in CIS-group (Figure 2).

Table 1. Assay of kidney functions in different groups.

Variables	Control	CIS	CIS+ NSO
Creatinine (mg /dl)	0.52 ± 0.49	2.17 ± 0.32a	1.61 ± 0.28b
Urea (mg /dl)	30.41 ± 3.82	60.74 ± 5.87a	37.18 ± 6.40b
Uric acid (mg /dl)	3.91 ± 0.72	8.07 ± 0.19a	4.91 ± 0.39b

CIS: Cisplatin; NSO: Nigella Sativa Oil
[a]Significant change in comparison to the control group at the level of P < 0.05.
[b]Significant change in comparison to the Cisplatin group at the level of P < 0.05.

Table 2. Assay of oxidative stress and antioxidant system in different groups.

Variables	Control	CIS	CIS+ NSO
MDA (µmol/g tissue)	0.394 ± 0.038	2.280 ± 0.561a	0.438 ± 0.027b
GSH (µmol/g tissue)	1.827 ± 0.158	0.489 ± 0.197a	1.509 ± 0.063b
CAT (U/g protein)	2.907 ± 0.231	0.601 ± 0.027a	2.310 ± 0.072b

MDA: malondialdehyde; GSH: reduced glutathione; and CAT: Catalase.
[a]Significant change in comparison to the control group at the level of P < 0.05.
[b]Significant change in comparison to the Cisplatin group at the level of P < 0.05.

Structural changes

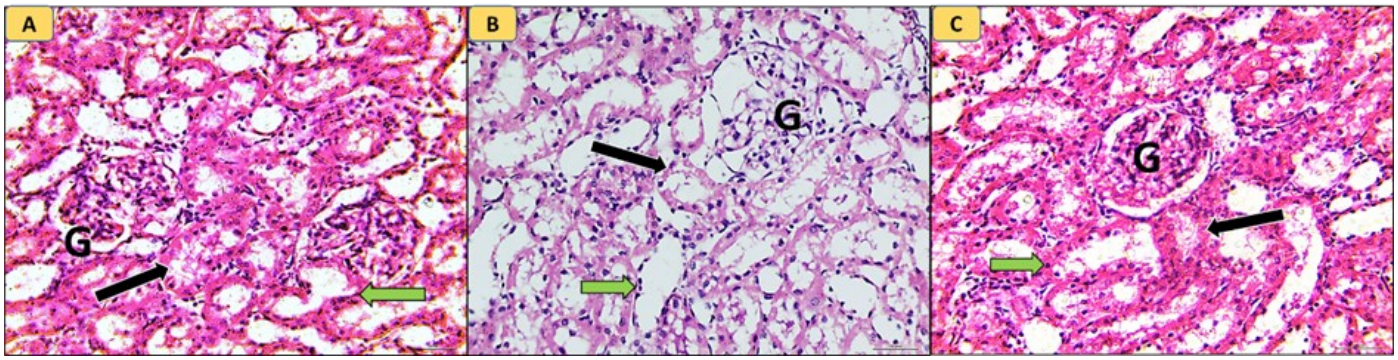


Figure 1. Cisplatin injection in animal group (B) deteriorated kidney structure in the form of tubular (green and black arrows) and glomerular dystrophy (G) compared to the control group (A). While, the use of Nigella Sativa Oil plus Cisplatin in animal group (C) restored those changes compared to those in CIS-group (Hx.E stain X400).

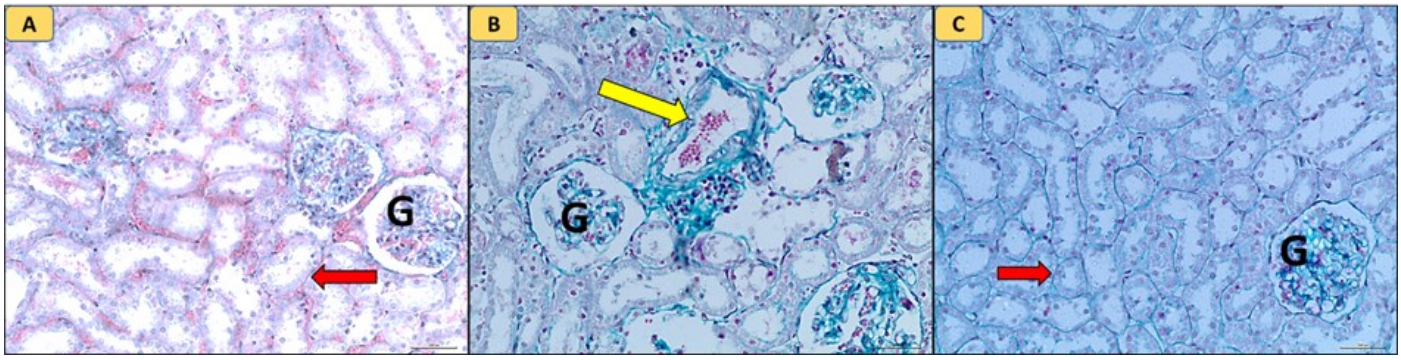


Figure 2. Cisplatin injection increased deposition of collagen fibers in the kidney compared to that in the control group. While, the use of Nigella Sativa Oil plus Cisplatin decreased deposition of collagen fibers in the kidney compared to those in CIS-group (Masson trichrome stain X. 400).

Discussion

Cancer ranks among the leading causes of death worldwide (15). Due to the fact that prevalence and fatality rates are not drastically declining, the present therapeutic approaches are inadequate (16).

For the treatment of many cancers, chemotherapy is the most often utilized approach. But it is associated with the most harmful consequences. Cisplatin, either by itself or in combination, is one of the most widely used anticancer drugs. When using it, nephrotoxicity is the most frequent and upsetting adverse effect (6, 17).

In this study we aimed to asses the nephropathic changes induced by cisplatin in albino rats and detect the possible enhanced effects of combination of nigella sativa with cisplatin.

BUN and creatinine (Cr) are the two most prominent indicators of kidney damage or malfunction (18). The present study's findings showed that the Cisplatin group's serum urea, uric acid and creatinine concentrations were considerably increased in comparison to the control group. In agreements to this finding numerous studies have documented increased creatinine and BUN levels following cisplatin treatment (19, 20).

Proximal tubules followed by the glomeruli and distal tubules are where cisplatin is primarily deposited (21). So, we examined the structural changes occurred in those regions. The current study found that Cisplatin injection in animal group deteriorated kidney structure in the form of tubular and glomerular dystrophy as well as marked collagen deposition compared to the control group. In consistence with this finding, Cisplatin causes histological alterations that vary greatly in severity. The proximal tubules, where cisplatin is primarily deposited, or the distal tubules and glomeruli are the most affected sites in different studies (22, 23).

Numerous mechanisms have been proposed to explain the pathophysiology of cisplatin-induced nephrotoxicity, such as vascular damage, apoptosis, free radical production, toxic metabolites, and a strong inflammatory response (21, 23-25).

There is evidence that cisplatin increases serum urea and creatinine concentrations by decreasing glomerular filtration rate (GFR), which may be caused by reactive oxygen species (ROS) being produced in afferent and efferent arterioles and increased resistance as a result. In addition, ROS promote the synthesis of vasoconstrictor chemicals such as thromboxane, isoprostane, and endothelin, which lower GFR and cause glomerular vasoconstriction (26). The measurement of lipid peroxidation by MDA illustrates the processes by which ROS are produced in tissue injury (23).

Consistent with many other studies (27, 28), the present study, Cisplatin injection increased tissue level of malondialdehyde (MDA), and decreased tissue levels of reduced glutathione (GSH) and Catalase (CAT) compared to those in the control group. By lowering the amounts of antioxidant enzymes, cisplatin causes lipid peroxidation products and reactive oxygen species (ROS) to build up inside cells, which causes oxidative stress and harmful illnesses (29).

Antioxidants that scavenge ROS of both internal and external origin can help prevent or lessen oxidative stress (30). So, we used Nigella sativa to alleviate the oxidative stress effects and we found that the use of Nigella Sativa Oil plus Cisplatin increased tissue level of MDA, and decreased tissue levels of reduced glutathione (GSH) and Catalase (CAT) compared to those in CIS-group. Similar to this findings, several researches revealed that in comparison to those in the CIS-group, the use of Nigella Sativa Oil plus Cisplatin raised tissue levels of MDA and decreased tissue levels of reduced glutathione (GSH) and catalase (CAT) (31, 32).

The ameliorative effects of nigella sativa in combination with cisplatin could be explained by these antioxidative action by removing free radicals, these antioxidative enzymes prevent harmful damage and shield cells from ROS (32, 33).

Finally, from the above results this study reveal that Nigella Sativa could Ameliorate the Cisplatin-Induced Nephrotoxicity in albino rats.

Conclusion

Nigella Sativa alleviates the Cisplatin-induced nephrotoxicity in male rats through its antioxidative mechanism.

Disclosure

None to be disclosed.

Conflict of interest

None.

Data sharing plans

Data will be available upon request.

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