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Protective Effects of Nigella Sativa and Propolis against Cadmium or Lead Induced Nephrotoxicity: An Experimental Histological and Molecular Study

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ABSTRACT

Background: Water pollution by heavy metals is a dangerous health problem causing multiple system diseases. Natural materials, such as nigella sativa and propolis, appear to offer a good preventive of pollution in comparison to more costly technologies currently in use.

The Aim of The Work: This study aimed to evaluate and compare the potential protective effects of propolis and nigella sativa against the Cadmium and Lead toxicity harmful effects on the kidney structure and functions of adult male rats.

Materials and Methods: Seventy adult male albino rats were chosen as an animal model for this study, divided into seven equal groups [each 10 rats]: Group I, the control group received the standard diet and normal saline [1 ml/kg body weight [BW]/day]; Group II for cadmium [Cd]; Group III for cadmium plus nigella sativa; Group IV for cadmium plus propolis; Group V for lead [Pb]; Group VI for lead plus nigella sativa and Group VII for lead plus Propolis. Each rat received [0.5 ml/rat] of its prepared solution orally every day for 15 days. At the end of the experiment, rats were sacrificed and blood samples were collected for the assessment of kidney functions. Then, the kidney was removed and prepared for histopathological and immunohistochemical examination. Finally, the kidney tissue homogenate was prepared for assessments of renal malondialdehyde [MDA].

Results: Exposure of rats to Cd. chloride and Pb. acetate resulted in a significant increase in serum creatinine, urea, uric acid, and renal MDA levels and induced histopathological alterations in kidney tissue. But concomitant administration of lead or cadmium with nigella sativa or propolis were associated with amelioration of the kidney impairment induced by lead or cadmium.

Conclusion: The natural antioxidants, nigella sativa and propolis, are capable of minimizing the hazardous effects of cadmium chloride or lead acetate on the kidney.

Keywords: Heavy Metals; Lead Acetate; Cadmium chloride; Nephrotoxicity; Nigella sativa; Propolis.

INTRODUCTION

Water contamination by heavy metals represent a serious problem on human health due to growth of food crops on the contaminated soils. Heavy metals accumulated in food crops and ultimately harms the human health [1].

Common pollutants of fresh and waste waters are lead, cadmium, mercury and arsenic. These metals represent a risk to human, animal health and agriculture [2]. These metals are highly toxic, refract biodegradation and easily bioaccumulate and reach different system organs through ingestion of contaminated foods. Then, it could disrupt normal physiology, leading to acute or chronic intoxication which could end by death [3].

Lead [Pb] toxicity was known to cause many diseases leading to illness and death, depending on its amount and duration of exposure as it enters the body by inhaling materials containing lead or by intake of contaminated food and/or water which enters the blood by absorption from the respiratory and digestive system leading to binding with the RBCs circulated to different tissues and stored in bone [4]. Also, Cadmium is a heavy metal represent a public health problem due to its environmental persistence and the long biological half-life [5].

The main pathophysiological mechanism of heavy metal toxicity is the oxidative stress that leads to cellular destruction through the enzymatic depletion by binding to sulfhydryl groups, damage to the lipid bilayer, and nephrotoxicity [6].

The kidneys are more likely to be poisoned by heavy metals [mostly Cd and Pb]. They are the most nephrotoxic metals, known to man, which can lead to progressive renal failure as they have the ability to settle in the kidney proximal tubules and its glomeruli [7]. So, concern has increased in the past years and led to many different policies to reduce the water pollution by heavy metals, including, membrane filtration, chemical precipitation and management of toxicity complications [2].

There is no effective curative treatment for heavy metal toxicity, even with the use of chelating agents. Thus, preventive strategies to heavy metal toxicity are highly recommended [8].

Moreover, it is important to find medication for its complications, especially from natural bases and herbal plants extracts which can be used to decrease or inhibit the risky effects of heavy metals [e.g., cadmium] on different organs [e.g., the kidney, liver, pancreas, spleen and bone] [5].

Nigella sativa is a traditionally natural herb commonly prescribed in the treatment of many human diseases, including those affecting the urinary system. It has a kidney-protective effects due to its antioxidant, anti-inflammatory, immunomodulatory, antiapoptotic, and antifibrotic properties [9].

In addition, propolis is a natural material that contains phenolic and flavonoid chemicals, which have been found to be able to be a scavenger for free radicals, keeping lipids and other molecules away from oxidative damage and inhibiting lipid peroxidation [10]. Propolis action was thought to be by different mechanisms including chelation or antagonism of heavy metals in order to decrease their production of free radicals, counteracting their oxidative effect and interfering with the reaction of auto-oxidative chain [11].

THE AIM OF THE STUDY

The present study was designed to evaluate and compare the potential protective actions of nigella sativa or propolis, on cadmium or lead-induced nephrotoxicity.

MATERIALS AND METHODS

Preparation of Propolis powder and Seeds of [Nigella sativa L.] extracts & solution:

Propolis powder and Seeds of [Nigella sativa L.] was obtained commercially from the local market of Damietta, Egypt. Seeds of [Nigella sativa L.] identified by a botanical taxonomist at Department of Botany, Faculty of Agriculture Damietta University. The seeds were washed under running tap water, followed by sterilized distilled water and dried at room temperature in the shade for one day then grinded to powder using an electrical blender. The powder sample [1000g] was mixed with petroleum ether [2.0 L] in a closed flask for 24 hours. Thereafter, it was filtered rapidly taking precautions against the loss of the solvent. The etheric extract [EE] was concentrated to dryness in a rotary evaporator under reduced pressure and controlled temperature [50-60°C] until reached the final volume 70 ml. The extract had been freeze at 4°C till further use.

Preparation of heavy metal solutions:

Six different solutions and extracts were prepared according to Embaby *et al.*, Hannan *et al.*, [7, 9] as following:

1- The Cd solution 2.4 $CdSO_4$ g was dissolved in 300 ml DW.

2- The Cd solution 2.4 $CdSO_4$ g+ nigella sativa oil 1.5 ml was dissolved in 300 ml DW.

3- The Cd solution 2.4 CdSO4 g + Propolis was dissolved in 300 ml DW.

4- The Pb solution 12.0 $[CH_3COO]_2$ Pb g was dissolved in 300 ml DW.

5- The Pb solution 12.0 $[CH_3COO]_2$ Pb g + nigella sativa oil 1.5 ml was dissolved in 300 ml DW.

6- The Pb solution 12.0 $[CH_3COO]_2$ Pb g + Propolis [2.0 g] was dissolved in 300 ml DW.

Animals and experimental design

Adult male albino rats were purchased from Faculty of pharmacy, Mansoura Univ. Egypt. Rats were housed in steel mesh cage [5 rats/cage] and maintained for one week acclimatization periods on standard rat diet and free tap water. Rats were kept on a balanced diet throughout the experimental period.

Animal handling was approved by the medical ethical committee, Damietta Faculty of Medicine, Al Azhar University, Egypt [IRB 00012367-21-06-006].

Seventy male adult albino rats were kept in standardized rat cages, with light–dark cycle [12/12] at 22°C ± 2°C and left for 1 week for acclimatization, animals were randomly divided into the groups [10 rats in each group- 5/cage], they received the following treatments once daily orally by gavage for 15 days according to its grouping: Group I, Normal control group received the standard rat chow diet and given normal saline [1 ml/kg body weight [BW]/day], other rats are categorized as follow: Group II, Cadmium solution [0.5 ml/rat]; Group III, [Cadmium + Nigella] sativa oil solution [0.5 ml/rat]] and Group IV, [Cadmium + Propolis] solution [0.5 ml/rat]; Group V, Lead solution [0.5 ml/rat], Group VI, Lead + Nigella sativa solution [0.5 ml/rat] and Group VII, [Lead + Propolis] solution [0.5 ml/rat].

Blood collection, Serum biochemical analyses

At the end of the second week, blood samples were collected from the retro-orbital plexus, centrifuged at 1200 g for 15 minutes. Serum was separated and collected in Eppendorf tubes that was kept at −20 ° C till the time of analysis. The analysis included serum urea, uric acid and creatinine, using the available commercial kits according to manufacturer's guidelines.

Hematoxylin and Eosin [H&E], Masson trichrome and immunohistochemistry:

The rats were sacrificed by cervical decapitation. The kidney was sectioned and specimens were fixed in 10% formalin for 24 h. The specimens were washed by running tap water and immersed in serial dilutions of ethyl alcohol before embedding in paraffin. The sections were cut in 4 µm thickness and stained with hematoxylin and eosin to examine tubulointerstitial injury. Masson trichrome staining was used to assess interstitial fibrosis and Immunostained with caspase 3 to assess the apoptotic changes under the light microscope.

The images were photographed & the percentage area density of collagen fibres & caspase 3 was measured using a Ray wild E5 microscope with a Ray wild M-300 digital camera with image-analyzing system [Mvi-mage program v12].

Preparation of tissue homogenates

An accurately weighted piece [0.3 g] of kidney tissue sample was homogenized according to Huculeci *et al*. [12] in ice phosphate buffer saline using a Teflon pestle connected to a homogenizer motor [25 strokes per minute at 1000 rpm], the kidney homogenate was diluted to yield 10% [w/v] kidney homogenate, which was centrifuged at 13000 rpm for 30 min at 4 °C to remove cell debris and nuclei. The supernatant was used for biochemical determination of renal malondialdehyde [MDA].

Statistics

Data are represented as the mean ± SD. Means were compared by One-way analysis of variances, followed by Duncan's post hoc test for multiple group comparisons. The lease significant differences [LSD] were the test of choice. The software for social sciences [SPSS] for Windows was used to complete all analysis [Version 21; IBM®SPSS® Inc., Chicago, IL, USA], and P value < 0.05 was considered significant for interpretation of data.

RESULTS

Effects on kidney functions:

Compared to the normal rats, there were marked and significant increase in the level of serum creatinine, urea, uric acid, and renal malondialdehyde [MDA] levels in kidney in animals treated with cadmium/lead for 15 days, while a significant reduction in those levels in rats treated with daily administration nigella sativa/Propolis along with Cadmium/Lead, for 15 days [Table 1].

Effects on renal tissue levels of MDA, Collagen & caspase 3

Serum MDA level of rats treated with HFD was significantly increased in animals treated with cadmium chloride and lead acetate for 15 days, while a significant reduction in those levels in rats treated with daily administration nigella sativa/Propolis in combination with cadmium/lead, for 15 days [Table 2].

Hematoxylin and eosin-stained sections results

The kidney from control rat group showed Group I: The cortex of the kidney of control rats showed normal histological appearance of renal corpuscles, Proximal convoluted tubules and distal convoluted tubules. Both of Group II [Cd-treated rats] and Group V [Pb-treated rats]: showed shrinkage of glomerulus with widening of urinary space, increased vacuolization, damaged and vacuolated PCTs and DCTs with wider lumen. While, Group III, IV, VI&VII [$CdCl_2$ + Nigella Sativa/Propolis treated rats on exposure to Pb/Cd]: showed nearly normal structure, with intact glomeruli and glomerulus membranes, PCTs, and DCTs as observed in the control group. However, some damages in the glomeruli, PCT and DCTs were still present [Figure 1]. Masson Trichrome and immuno-staining were presented in figures [2 and 3].

Table [1]: Assay of the kidney functions in different groups

	Creatinine [mg /dl]	Urea [mg /dl]	Uric acid [mg /dl]
Control	0.49 ± 0.08	23.60 ± 3.14	4.82 ± 0.40
Cadmium[Cd]	1.75 ± 0.14 [a]	52.80 ± 3.29 [a]	6.85 ± 0.45 [a]
Cd+ Nigella	0.91 ± 0.61 [a]	30.20 ± 2.34 [a b]	5.45 ± 0.25 [a b]
Cd+ Propolis	0.98 ± 0.24 [a b]	31.20 ± 3.14 [a b]	5.75 ± 0.45 [a b]
Lead [Pb]	1.68 ± 0.34 [a]	51.60±2.50 [a]	6.42± 0.52 [a]
Lead+ Nigella	1.19±.03 [a b]	29.60±1.04 [a b]	5.12±7.5 [a b]
Lead+ Propolis	1.23 ± 0.05 [a b]	30.08 ± 2.21 [a b]	5.60 ± 0.26 [a b]

Data are shown as mean ± SD; [a] Significantly different from the corresponding control group; [b] Significantly different from the corresponding Cd/Pb exposed group.

Table [2]: Assay of tissue levels of MDA, Collagen and Caspase 3.

	MDA [nmol/g tissue]	Percentage are of Collagen density %	Caspase 3 density [mm^3]
Control	20.71 ± 3.35	6.17 ± 1.03	3.24 ± 0.62
Cadmium[Cd]	31.75 ± 4.14 [a]	11.21 ± 1.11 [a]	14.56±2.13 [a]
Cd+ Nigella	26.91 ± 1.61 [a b]	8.44 ± 0.82 [a b]	6.25±1.83 [a b]
Cd+ Propolis	27.98 ± 1.24 [a b]	8.64 ± 1.04 [a b]	6.45±1.34 [a b]
Lead [Pb]	30.68 ± 3.34 [a]	10.94 ± 1.61 [a]	13.24±2.61 [a]
Lead+ Nigella	22.19±1.03 [a b]	8.37 ± 0.94 [a b]	17.60±1.029 [a b]
Lead+ Propolis	23.23 ± 1.25 [a b]	8.51 ± 1.17 [a b]	55±7.83 [a b]

Data are shown as mean ± SD; [a] Significantly different from the corresponding control group; [b] Significantly different from the corresponding Cd/Pb exposed group at $p < 0.05$.

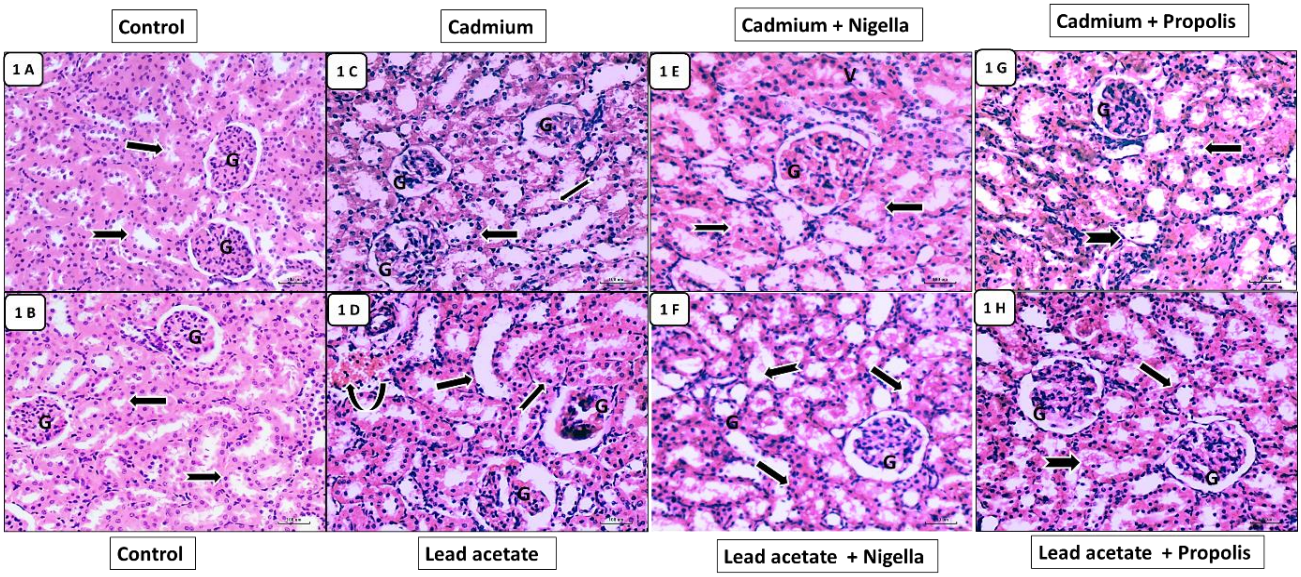

Figure [1]: [A,B] The kidney from control rat group showed: normal histological structure of kidney corpuscles with its glomerulus [G] formed of tuft of capillaries, enclosed in a Bowman's capsule. The Bowman's capsule is formed of two layers, inner visceral and outer parietal layers. Proximal convoluted tubules [Thick arrow] with narrow lumen and lined with simple cubical epithelium. Distal convoluted tubules [notched arrow] with less numerous wide lumen and lined with simple cubical epithelium. [C&D] Cd/Lead-treated rats respectively showed marked tubular dilatation & hemorrhagic congestion [thick, thin notched & curved arrows respectively], shrinkage & rupture of the glomerulus [G] with widened urinary space, hypercellularity and cellular debris. [E-H] Cd/Lead + Nigella Sativa/Propolis treated rats showed near normal structure, intact glomeruli [G] and glomerulus membranes, PCTs, and DCTs [thick & thin notched arrows respectively]. However, some damages in the PCT and DCTs were still observed. A, B: Control group; C: Cadmium group; D: Lead group; E: Cadmium + Nigella sativa group and F: Lead + Nigella sativa group; G: Cadmium + Propolis group and H: Lead + Propolis group. [Hx.&E. X400] Scale bars, 100 µm.

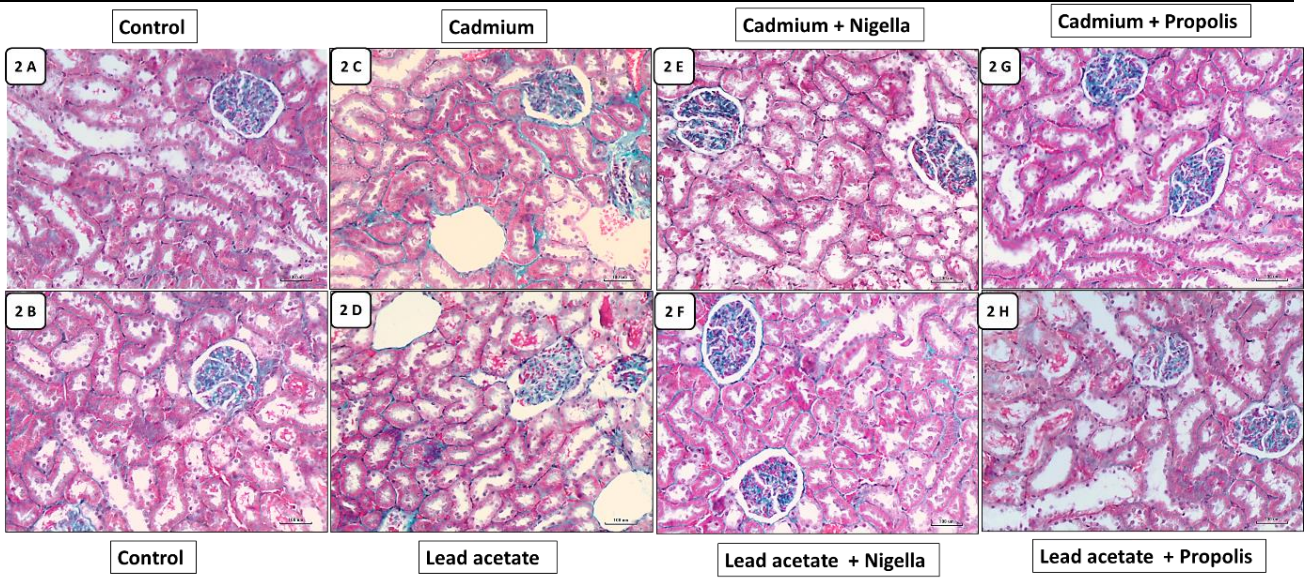

Figure [2]: Nigella sativa/Propolis reduces collagen deposition and tubulointerstitial fibrosis in a rat model of Lead/Cadmium induced renal injury. A, B: Control group; C: Cadmium group; D: Lead group; E: Cadmium + Nigella sativa group and F: Lead + Nigella sativa group; G: Cadmium + Propolis group and H: Lead + Propolis group. [Masson Trichrome stain X400] Scale bars, 100 µm.

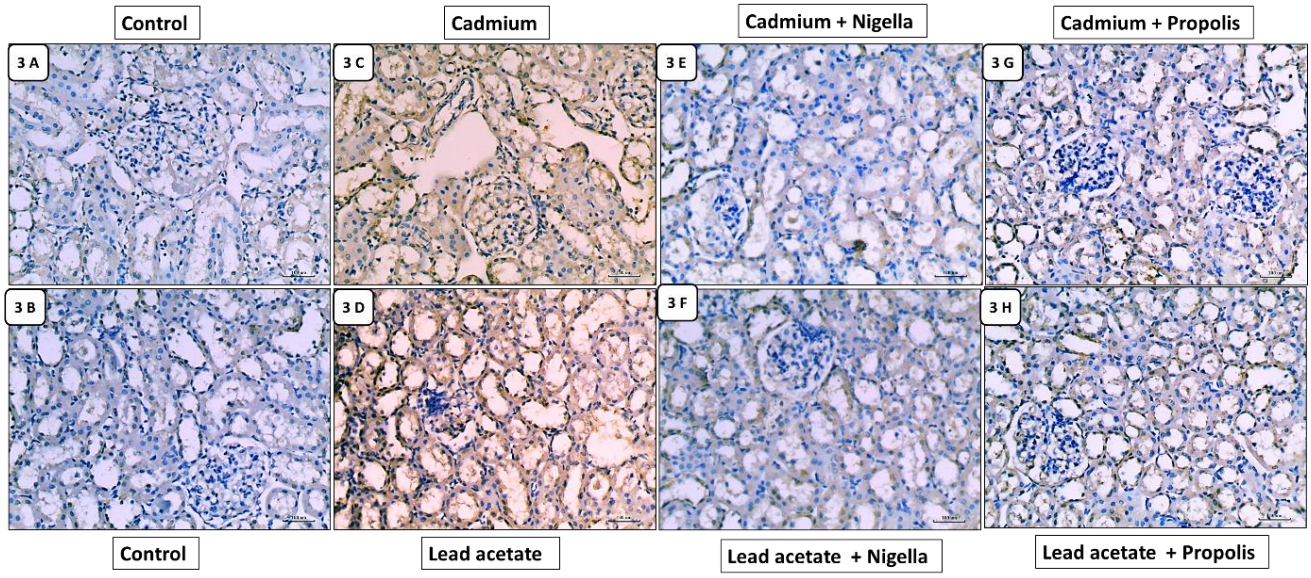

Figure [3]: **Photomicrographs of Immunostained kidney sections for caspase-3** showing no or weakest expression of caspase-3 in control group [A,B]; marked expression of caspase-3 in both Lead/Cadmium groups [C,E]; weak expression of caspase-3 in treated groups with Nigella sativa/Propolis group [D,F]. A, B: Control group; C: Cadmium group; D: Lead group; E: Cadmium + Nigella sativa group and F: Lead + Nigella sativa group; G: Cadmium + Propolis group and H: Lead + Propolis group [Anticaspase 3 immunostaining X400] Scale bars, 100 µm.

DISCUSSION

The heavy metals toxicity has become a public health concern due to exposure to occupational & environmental sources causing environmental and public health problems as acute or chronic metal exposure induce severe organ injury and even death [13].

Cadmium and lead are toxics that represent a threat to human, animal, and plant health. They indirectly increase oxidative stress, while acting through other toxico-dynamic mechanisms [14]. Thus, evaluating the toxicity caused by heavy metals and medications urge more researchers to find natural products with strong antiradical properties to protect biological organisms from oxidative injury induced by generation of free radicals [15]. However, the defense mechanisms are still indistinguishable. So, we meant to assess the effectiveness of nigella sativa and propolis against cadmium/ lead induced renal toxicity, by their antioxidant and several defense mechanisms.

In this study, serum urea, creatinine, and tissue levels of MDA were evaluated to assess kidney functions. The information got indicated a significant increase in kidney indices; urea, uric acid, creatinine and MDA following Lead/CdCl2 exposure which indicate a severe kidney injury triggered via Lead/CdCl2. These changes are in agreement with findings of recent researchers' work who documented that Lead/Cd exposure lead to severe kidney injury documented by alterations in renal functions and increased tissue level of MDA [14].

On the other hand, exposure to low doses of Cd/Pb given as a single dose [0.005 mg Cd/L and 0.01 mg Pb/L],

through drinking water, did not induce any changes in MDA levels in mice kidneys [16]. The possible explanations for the different results are: difference in study design, exposure mode, dose, animal strain as well as the applied chemical form of metals.

The alteration of urea and creatinine levels represent an indicator of renal impairment and excretory function, even after a single administration of heavy metals. The renal impairment might also be caused by the associated hypertension, which induce renal damage [17].

At the structural level, this study indicated that exposure to Lead/Cd induced marked damage of renal glomeruli and tubules. Proximal tubules are the mainly affected tubules. It is the site of maximum absorption. Thus, heavy metal toxicity led to renal impairment with marked elevation of renal damage indicators. Similar to our findings, revealed structural changes in the rat kidney after exposure to Lead/Cd in the form of mild congestion of blood vessels, tubular dilatation, vacuolations, hemorrhagic congestion, glomerulus dilatation, hyper-cellularity and cellular debris [13, 18].

In contrary to our findings, Tripathi and Srivastav [19] found no structural changes of the rat kidney, treated with 5 mg/kg/day $CdCl_2$ for 2 weeks. This may be linked to the timing, dosage, route, the number or animal strain.

In the present study, we assessed the renal fibrosis through detection of collagen content in the kidney, we found excessive deposition of collagen in the extracellular matrix [ECM] in kidney tissue after exposure to Lead/Cd. Similar to our study, several studies found that collagen fibers were increased in glomeruli and interstitial tissue in Masson trichrome-stained kidneys of Lead/Cadmium exposed rats in drinking water [20, 21].

The excessive deposition of collagen in our study indicate the renal fibrosis which is a pathological sign associated with the destruction of renal tissue indicating chronic damage. The damage of renal cells induces an inflammatory response in the kidney tissue. So, exposure to heavy metals results in excessive deposition of collagen in the extracellular matrix [ECM], which induce chronic damage in kidney structure [22].

The lead/$CdCl_2$ induced nephrotoxicity has been reported by previous studies. It manifested as renal dysfunction, increased oxidative stress, and histo-pathological changes [23, 24]. MDA is the principle byproduct of lipid peroxidation. It can destruct different biological macromolecules. It is used as an indicator heavy metal-induced nephrotoxicity [25]. The oxidative stress was a suggested mechanism of the heavy metals induced nephrotoxicity in our study which was confirmed by significant increase of MDA levels after exposure to Lead/Cd. These results are in line with a previous study reported a significance MDA increase in plasma after single oral dose of cadmium [26].

Also, apoptosis is the suggested second phenomenon caused by Lead/Cd exposure which was reflected in the current work by significant increase of Caspase-3 [apoptotic marker] after cadmium or lead exposure. Previous studies demonstrated that, lead or cadmium exposure induced apoptosis in renal tissues [cortex and medulla were affected] [27]. Similarly, other in-vivo and in-vitro studies [28-30] confirmed the cell apoptosis induced by exposure to cadmium or lead in different body organs such as the testis, the liver, and the kidney. The underlying mechanisms include significant production of ROS, destruction of the mitochondrial membranes with reduction of its potential, significant release of apoptotic factors, and caspase-3 activation, disturbance of calcium homeostasis with increased calcium ion concentration leading to stress on the endoplasmic reticulum; and activation of different apoptosis induction pathways.

Caspase-3 has a chief role in the intrinsic mitochondrial-mediated apoptosis pathway [31]. The treatment with Nigella sativa in combination with exposure to Cadmium/ lead, revealed a marked ameliorative effect, thereby protecting the kidney as it was noticed by the statistically decrease in serum urea, creatinine, tissue level of MDA histomorphological architecture of the studied kidney. Several other studies have reported the ameliorative effects and potential pharmaco-therapeutic effects of N. sativa to offer protections against toxic heavy metals such as lead and cadmium [32, 33]. The protective properties of N. sativa were thought to be through antioxidant, anti-inflammatory and anti-apoptotic properties that make it a potential therapeutic remedy for the treatment of induced nephrotoxicity [34].

In our study we also found that propolis has a good nephroprotective effect on exposure to heavy metal toxicity as manifested by improvement in kidney structure and functions. To our knowledge, no previous studies were reported on the nephroprotective effects of propolis on exposure to heavy metal toxicity. Similar to our results propolis was found to have a nephroprotective effect in gentamicin-induced oxidative Stress and hepatorenal damages [35] and in rpirubicin-induced nephrotic damage [36], which may be due to its powerful antioxidant activity as it is rich with flavonoids capable of scavenging free radicals, thus it protects the plasmalemma from lipid peroxidation [37].

In conclusion, cadmium/lead induced kidney toxicity and it was most likely caused by oxidant/antioxidant imbalance and apoptotic pathway in the kidney, as it was associated with elevated tissue level of MDA & caspase 3 in the kidney but, nigella sativa or propolis are proved to be natural nephroprotective that efficiently relieve the nephrotoxicity due to heavy metal exposures through antiapoptotic and antioxidant activities & further studies are recommended on low dose exposure to heavy metals.

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