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Original article

## Biological activities of ginger against cadmium-induced renal toxicity

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## ABSTRACT

Our aim was to evaluate the protective and antioxidant effects of ginger extract against cadmium-induced renal toxicity in animal models and to support the use of ginger as anti-renal failure natural remedy. Seventy rats were examined in a 4-week experiment to evaluate the effect of Ginger (*Zingiber officinale*) at doses of 100 and 200 mg/kg body weight on molecular DNA content, antioxidant status, and renal function in rats intoxicated with cadmium at dose of (5 mg/kg) using biochemical and histological analysis. Renal dysfunction, kidney tissue damage, and oxidative effect were evident in cadmium intoxicated rats as estimated by significant increase in (creatinine, urea), decrease in (creatinine clearance and reabsorption rate of urine albumin), increase in MDA, decrease in total antioxidant status (TAC), reduction in DNA content, and histopathological changes of kidneys' tissues compared to control rats. Treatment with ginger resulted in significant restoring of renal function biomarkers, TAC, molecular DNA, and histological improvements which occurs via free radical scavenging and regenerative mechanisms. The activity of ginger was supported by estimation of bioactive phenolic and flavonoids constituents. Twenty-eight polyphenolic compounds were estimated in ginger extract; [6]-gingerol, [6]-shogaol, citral and pyrogallol were the highest amounts in ginger, and supposed to be responsible for its major antioxidant and free radical scavenging activity as shown by In vitro DPPH/ $\beta$ -carotene-linolic acid assay tests. Consequently, ginger extracts could have a potent protective effects against nephrotoxicity induced by various toxicants.

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## 1. Introduction

Cadmium (Cd) is the most disseminated contaminant prevails in all environmental resources including food and cigarette smoke (Sullivan and Krieger, 2001).

The exposure of human to both acute and chronic Cd toxicity occurs through natural contaminated sources such as food, air, water, and industrial products (Duruibe et al., 2007), however the most drastic biological defects results from chronic Cd exposure (Satarug et al., 2004), this is largely relates to its accumulation

in most important biological tissues such as liver, lungs, kidneys, bones, and reproductive organs (Alvarez et al., 2007), and ultimately produces several clinical problems such as renal dysfunction, bone diseases, and hepatic dysfunction (Järup et al., 2000), depending on dose, duration and route of exposure (Obianime and Roberts, 2009).

Previous studies, reported that Cd toxicity promotes the induction of various pathological events among humans and animals via free radical initiation mechanisms which produces active oxidative free radicals from biological components of the cell such as lipids, proteins and DNA (Liu et al., 2008).

The released lipid peroxidation (LPO), thiobarbituric acid reactive substances (TBARS), and hydroperoxides were the major indicators of oxidative tissue damage caused by Cd-toxicity (Swarup et al., 2007).

Most studies concluded that, liver and kidney were the most of sensitive biological organs easily affected by Cd toxicity (Ognjanović et al., 2010a, 2010b). The induction of Cd nephrotoxicity for example produced via many mechanisms including free radicals, cell necrosis, and apoptosis (El-Sharaky et al., 2007).

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Previously, some research works focused on using metals such as zinc, copper, germanium, and selenium as antagonists or antioxidant agents for protection against cadmium toxicity. These metals were shown to effect on the absorption and transmission of cadmium compounds within biological systems through masking and displacing mechanisms (Boscolo et al., 2005; González-Trujano and Navarrete, 2011). However, the use of these metals in high doses may have serious biological effects (Minta et al., 1995).

In recent years, extensive research work performed on herbal plants to produce new sources of alternative and safe antioxidant remedies with minimal side effects against many diseases (Lopez, et al., 2007). Many herbal extracts of natural origin such as green tea, curcumin and black cumin were used as protective agents against Cd toxicity (Hamden et al., 2009; Deevika et al., 2012).

Ginger (*Zingiber officinale*) is one of the most popular food spices known among Asian and African people for long periods (El-Sharaky et al., 2009). It includes versatile range of active constituents such as volatile oils, phenolic, proteolytic enzymes, vitamins, and trace elements (Onwuka et al., 2011). These constituents gave ginger the priority to be used in many diseases as anti-inflammatory and antioxidant modulator (Khaki and Khaki, 2010).

The strong antioxidant and protection abilities of ginger to biological tissues and cell membrane lipids against toxicity occurs via free radical scavenging activity in a dose dependent manner (Farag, et al., 2010; Stoilova et al., 2007). So, this increases its tendency to be used in various experimental models as protective agent against various toxicants (Johari, et al., 2013; Haniadka et al., 2013a, 2013b).

In this regard, the present study conducted to evaluate the protective and antioxidant effects of ginger extract against cadmium-induced renal toxicity in animal models and to support the use ginger as anti-renal failure natural remedy by determining the total polyphenols and free radical scavenging activity of ginger extract in vitro.

## 2. Materials and methods

### 2.1. Experimental animals

In this study 70 male adult wistar albino rats, weighing (150–200 g) were recruited in this study. The animals were housed and subjected to normal feeding, drinking, and health care mechanisms according to the guidelines of the experimental animal care center, college of applied medical sciences, King Saud Univ., Riyadh, Saudi Arabia. The experiment and the procedures were approved by the Ethics Committee of the Experimental Animal Care Society, Rehabilitation Research Chair (RRC), College of Applied Medical Sciences, King Saud Univ., Riyadh, Saudi Arabia, under file number (RRC-2014-013).

### 2.2. Preparation of ginger ethanolic extract

Two kilograms of fresh ginger rhizomes were purchased from a convenience store (Othaim Markets) in Riyadh, KSA. The fresh ginger rhizomes were extracted in 95% ethanol and a dose of 100 mg/b.w. and 200 mg/b.w. of ginger extract were prepared as previously reported in literature (Bhandari et al., 2005).

### 2.3. Experimental design

Both ginger extract and cadmium chloride (CdCl<sub>2</sub>) were administered orally according to body weight of experimental animals. The animals were classified into seven groups (10 rats/group).

These groups arranged as follows: Group 1 (Control), rats fed on normal diet plus a solution of 2%, Tween-80; Group 2 (Cd-treated), rats treated with 5 mg/kg cadmium chloride for 30 days; Group 3 (Ginger Treated), rats treated with ethanolic-extract of ginger (100 mg/kg body weight for 30 days); Group 4 (Ginger Treated), rats treated with ethanolic-extract of ginger (200 mg/kg body weight for 30 days); Group 5 (Cd plus Ginger), rats treated with (5 mg/kg cadmium chloride plus 100 mg/kg ginger extract for 30 days); Group 6 (Cd plus Ginger), rats treated with (5 mg/kg cadmium chloride + 200 mg/kg ginger extract for 30 days); group 7 (treated with gradual concentrations of ginger; 50 mg to 200 mg/rat). Kidney tissues and blood samples were collected for subsequent histological and biochemical analysis.

### 2.4. Analysis of phenolic compounds in ginger extract

Total phenolic compounds of 100 mg of ginger extract were analyzed at Bio-technology Lab., Plant Pathology Institute, Agricultural Research Center, Giza, Egypt. Analysis was performed with a liquid chromatography “HP1050” equipped with a 4.6 mm × 150 mm ODS C18 column with UV detector and the injection volume was 5 µl. The mobile phase yielded results of 40% methanol: 60% distilled water. The wave length in the UV detector was 230 nm; total run time for the separation was 15 min at a flow rate of 0.60 ml/min according to the proposed method previously reported (Waskmundzka et al., 2007).

### 2.5. Estimation of total phenolic and flavonoid content of ginger extract

Total polyphenols were determined by Folin-Ciocalteu method as described previously (Hamed et al., 2012). The results were obtained from gallic acid calibrated curve and expressed as mg of Gallic Acid Equivalents (GAE)/100 mg of fractions. The total flavonoids were estimated according to the Dowd method as adapted by Lamien-Meda et al. (2008). The amounts of flavonoids in plant fractions were expressed as mg of Quercetin Equivalents (QE)/100 mg of fractions from the calibrated curve.

### 2.6. Estimation of antioxidant activity of ginger extract

#### – DPPH free radical scavenging assay

Spectrophotometric analysis was performed to evaluate the radical scavenging ability of the ginger extract against DPPH as described previously by Brand et al. (1995). Various concentrations from the extracted ginger were prepared in methanol. The concentrations were subjected to the inhibition rate of DPPH radical and the decrease in absorbance was measured at  $\lambda = 517$  nm. The radical scavenging activity was calculated from the equation:

$$\% \text{ of radical scavenging activity} = \frac{(Abs_{\text{control}} - Abs_{\text{sample}}) / Abs_{\text{control}}}{1} \times 100$$

#### – B-Carotene-linoleic acid assay

The antioxidant activity of the ginger extract was measured spectrophotometrically as previously reported (Mothana, 2011). The activity of ginger extracts was recommended by measuring the inhibition rate of peroxidation in linoleic acid system. The antioxidant activity was calculated using the equation:

$$\% \text{ of antioxidant activity} = \frac{(Abs_0 - Abs_t) / (Abs_0 - Abs^*t)}{1} \times 100$$

where Abs<sub>0</sub> and Abs\*<sub>0</sub> are the absorbance values measured at 0 time of incubation for sample extract and control, respectively. Abs<sub>t</sub> and Abs\*<sub>t</sub> are the absorbance values for sample extract and control, respectively, at t = 120 min.

### – Total Antioxidant Capacity (TAC)

Serum total antioxidant capacity (TAC) was measured Colorimetric Assay Kit (Catalog #K274-100; BioVision Incorporated; CA 95035 USA). The antioxidant equivalent concentrations were measured at 570 nm as a function of Trolox concentration according to the manufacturer's instructions.

$$Sa/Sv = \text{nmol}/\mu\text{l} \text{ or } \text{mM Trolox equivalent}$$

where Sa is the sample amount (in nmol) read from the standard curve; Sv is the undiluted sample volume added to the wells.

### 2.7. Kidney function tests

Kidney function tests were performed according routine lab methodology previously reported in the literature (Fawcett and Scott, 1960; Teitz, 1987). Urinary albumin was quantified by immunoassay technique using ELISA kit (Cat no., STA-383, Cell Biolabs, Inc., USA). Creatinine clearance as an index of glomerular filtration rate was calculated from serum creatinine and a 24-h urine sample creatinine levels.

### 2.8. Acute toxicity test

Ginger extract was investigated for toxicity studies as previously reported (Organization for Economic Cooperation and Development (OECD), 1999). The extract was supplemented to healthy group of rats (10 rats) orally in drinking water with gradual concentrations (50 mg to 200 mg/rat). Toxic symptoms were observed on the animals directly after the first 4 h of dosing. After 24 h, the survived animals were maintained under daily observations for two weeks.

### 2.9. Histopathological evaluation

Histological and pathological examinations of kidney tissue sample were performed according to recommended routine methods previously reported in literature (Bancroft and Gamble, 2002).

**Table 1**  
Biological activities, total phenolic and flavonoids constituents of ginger extract (mg/100 gm).

Contents/biological activity	Ginger Extract (100 mg)
Phenolic content (mg/100 gm)	26.3
Flavonoids content (mg/100 gm)	9.13
Radical scavenging activity (BCLA; %)	
At cons. of 500 $\mu\text{g}/\text{mL}$	86.7
At cons. 1000 $\mu\text{g}/\text{mL}$	92.3
Total antioxidant activity (DPPH; %)	89.55

**Table 2**  
Phenolic compounds content (mg/g) of ginger ethanol extract using liquid chromatography analysis (HPLC).

Component	Phenolic content (mg/100 g)	Component	Phenolic content (mg/100 g)
Gallic Acid	0.250	Ferulic	0.743
Pyrogallol	15.2	Iso-ferulic	0.08
4-amino-benzoic	0.159	Reversetrol	0.16
3-OH-Tyrosol	1.677	Ellagic	0.12
protocatechuic	0.2461	E- vanillic	0.233
Catechein	0.799	Alpha-coumaric	0.0264
Chlorogenic	2.544	Benzoic	4.95
Catechol	0.766	3,4,5-methoxy-cinnamic	0.34
Epicatechein	0.978	Coumarin	0.592
Caffeine	0.263	Salicylic	1.193
p-OH benzoic	1.22	p-coumaric	0.12
Caffeic	0.7951	Cinnamic	3.5
vanillic	0.34	[6]-shogaol	19.4
[6]-gingerol	24.8	Citral	16.2

### 2.10. Determination of DNA content in kidney

DNA was estimated in kidney tissue samples by using diphenylamine as organic solvent for extraction and the amount of DNA of each sample was measured colorimetrically (Dische and Schwartz, 1937).

### 2.11. Determination of malondialdehyde (MDA)

Malondialdehyde (MDA) was estimated in homogenized kidney tissue samples according a colorimetric standard method previously reported (Utley et al., 1967). The concentration of MDA (nmol/g wet tissue) per tissue samples was measured via absorbance rate of 535 nm. The data were then calculated via standard calibration curve.

### 2.12. Statistical analysis

The data of this study were performed using SPSS version 17. All data were tabulated as mean  $\pm$  SD. The statistical correlation among the studied parameters in treated and control groups was performed by Student's *t*-test.  $P < 0.05$  was considered statistically significant.

## 3. Results

Total phenolic and flavonoids constituents comprise 26.3 mg and 9.13 mg/100 g of ginger extract respectively (Table 1). The active biological constituents of ginger extract were estimated using liquid chromatography. The data showed that [6]-gingerol was the highest amount (24.8 mg/g) followed by [6]-shogaol (19.4 mg/g), citral (16.2 mg/g), and pyrogallol (15.2 mg/g). This was in addition to small amounts of other phenolic compounds as shown in Table 2.

The biological antioxidant activity of ginger was measured in vitro and calculated in relation to the inhibition of linoleic acid oxidation and of DPPH radical scavenging activity. Ginger extract recorded radical scavenging activity (86.7; 92.3 %) at concentrations 500 and 1000  $\mu\text{g}/\text{mL}$  respectively. Whereas the same extract reported antioxidant activity with mean of (89.55%), according to the  $\beta$ -carotene bleaching rate of ginger extract as shown in Table 1.

The tested animal administrated varies doses of ginger extract (50–200 mg/kg). The data of acute toxicity test showed no toxicity and lethality ( $\text{LD}_{50}$  value = 0) observed up to 200 mg/kg of ginger extract in the animals.

Table 3 shows the effect of cadmium and ginger administration on relative body and kidney weights of studied animal groups. In cadmium treated group, there was significant ( $P < 0.01$ ) decrease

**Table 3**

Effect of ginger extract on body weight, kidney weight, and the levels of kidney Function biomarkers in cadmium chloride intoxicated experimental rats.

Group	Parameters					
	Final weight (g)		Kidney function			
	Body	Kidney	Creatinine (mg/dl)	Urea (mg/dl)	Urine albumin (mg/24 h)	Creatinine Clearance
Control (normal diet)	185 ± 2.21	0.49 ± 0.016	0.48 ± 0.08	22.45 ± 1.54	0.13 ± 0.03	0.6 ± 0.04
Cd (5 mg/kg)	153 ± 2.7**	0.78 ± 0.02**	1.35 ± 0.12**	89.6 ± 6.7**	1.63 ± 0.13**	0.21 ± 0.02**
Ginger (100 mg/kg)	189 ± 1.9**	0.46 ± 0.12**	0.46 ± 0.1**	21.9 ± 1.23**	0.12 ± 0.06**	0.56 ± 0.05**
Ginger (200 mg/kg)	195 ± 1.3**	0.42 ± 0.16**	0.43 ± 0.12**	20.8 ± 1.3**	0.11 ± 0.02**	0.58 ± 0.03**
Cd (5 mg/kg) + Ginger (100 mg/kg)	168 ± 2.1**	0.73 ± 0.06**	1.0 ± 0.10**	28.3 ± 2.3**	0.63 ± 0.03**	0.32 ± 0.03**
Cd (5 mg/kg) + Ginger (200 mg/kg)	175 ± 1.8**	0.68 ± 0.04**	0.68 ± 0.14**	25.6 ± 1.4**	0.25 ± 0.04**	0.39 ± 0.04**

All values represent mean ± SD. \* P < 0.05. \*\*\* P < 0.001. Student's *t*-test.

\*\* P &lt; 0.01.

**Table 4**Effect of ginger extract on renal lipid peroxidation, Total antioxidant capacity, and DNA content as kidney fibrotic marker in CdCl<sub>2</sub> -intoxicated experimental rats.

Group	MDA (nmol/dl)	TAC (nmol/mM Trolox eq.)	DNA content (µg/106 cells)
Control (normal diet)	10.7 ± 2.3	8.9 ± 2.8	0.075 ± 0.1
Cd (5 mg/kg)	45.7 ± 6.9**	3.7 ± 1.2**	0.047 ± 0.6**
Ginger (100 mg/kg)	10.2 ± 2.0**	9.1 ± 2.75**	0.076 ± 0.2**
Ginger (200 mg/kg)	9.7 ± 2.3**	9.5 ± 2.9**	0.077 ± 0.2**
Cd (5 mg/kg) + Ginger (100 mg/kg)	35.8 ± 3.7***	6.5 ± 2.8***	0.058 ± 0.7***
Cd (5 mg/kg) + Ginger (200 mg/kg)	26.4 ± 2.5***	9.2 ± 1.8***	0.069 ± 0.5***

All values represent mean ± SD. \* P &lt; 0.05.

\*\* P &lt; 0.01.

\*\*\* P < 0.001. Student's *t*-test.

in body weight and increase ( $P < 0.01$ ) in kidney weight of rats compared with normal control group (Table 3). However, treatment of Cd-treated rats with different doses (100 mg/kg and 200 mg/kg) of ginger extract significantly ( $P < 0.01$ ) restored the body and kidney weight towards normal ranges as compared to Cd treated group. Whereas, normal rats treated with ginger extracts (100 mg/kg; 200 mg/kg) showed significant ( $P < 0.01$ ) increase in body and kidney weight compared to control group.

Also, Table 3 showed that CdCl<sub>2</sub> administration produced significant ( $P < 0.01$ ) increase in the levels of serum creatinine, urea, and decrease in creatinine clearance with excessive excretion of albumin through urine of cadmium treated group compared to normal rats. Whereas, in groups administrated ginger extract at doses of 100 and 200 mg/kg either alone or with cadmium treatment showed significant reduction ( $P < 0.01$ ) in the levels of serum creatinine, urea, and decrease in the excretion rate of albumin through urine of treated rats along with an increase in creatinine clearance. However, the improvement was significantly ( $P < 0.01$ ) higher in rats treated with 200 mg/kg ginger compared with 100 mg/kg ginger treated and cadmium intoxicated groups (Table 3).

Also, in normal rats treated with the same ginger doses showed significant ( $P < 0.01$ ) improvement in biomarkers of kidney function compared to control non-treated rats (Cd-treated group).

The oxidative free radical initiation activity of cadmium induced renal toxicity was represented with MDA and total antioxidant capacity (TAC) as oxidative stress markers (Table 4). The comparison between these parameters is conversely related. There was significant increase ( $P < 0.01$ ) in MDA and decrease ( $P < 0.01$ ) in TAC of cadmium treated rats compared with control group. However, these oxidative damage effects of cadmium on kidney tissues were restored with ginger administration at doses of 100 and 200 mg/kg. The protective action of ginger towards oxidative damage induced as result of cadmium toxicity was supported by significant increase ( $P < 0.001$ ) in TAC and decrease ( $P < 0.001$ ) in MDA levels in kidney of ginger treated rats compared to CdCl<sub>2</sub> intoxicated group (Table 4).

Also, DNA content of renal cells was estimated as molecular marker of oxidative renal tissue damage induced by cadmium tox-

icity on molecular level (Table 4). There was significant decrease ( $P < 0.01$ ) in DNA content in cadmium treated rats compared to control group. However, supplementation of ginger extract at doses of 100 and 200 mg/kg to cadmium intoxicated rats caused significant improvement of renal tissue cells via increasing DNA content ( $P < 0.001$ ) as compared with intoxicated group. Similarly, when the same ginger doses applied in non toxicated normal rats, the data showed significant improvement in DNA content of renal cells compared with control group (Table 4), confirming the preventive action of ginger in normal cases.

The protective effect of ginger against cadmium toxicity was evaluated in kidney tissue using histological examinations as shown in Fig. 1–7. Normal renal cortex, tubules, parenchyma, and glomeruli medulla were observed in the kidney of control rats (Fig. 1) and ginger extract alone at doses of 100 and 200 mg/kg (Figs. 2 and 3). In animals treated with cadmium showed congestion of the cortical blood vessels, focal replacement of the renal parenchyma with numerous lymphocytes infiltrates, and dilation of glomeruli (Figs. 4 and 5). In groups treated with Cd along with ginger extracts at doses of 100 mg/kg (Fig. 6) and 200 mg/kg (Fig. 7) showed regeneration and restore of glomeruli; renal tubules, and cells.

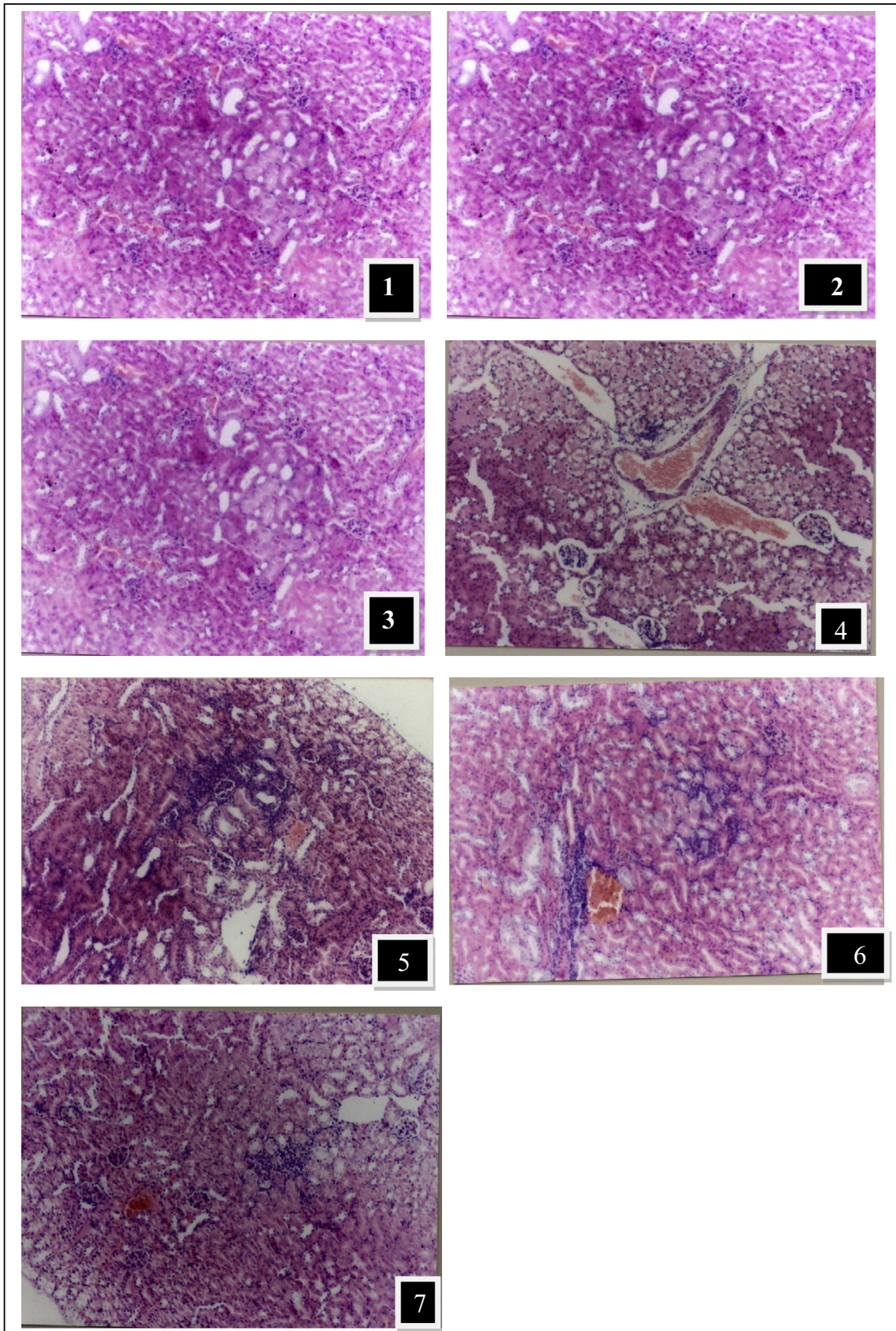
#### 4. Discussion

Cadmium and its derivatives considered one of the most dangerous toxic compounds adversely effect on the health of living organisms (Patra et al., 2011). It was reported that exposure to cadmium compounds increase the generation of free radicals which produces oxidative damage of many biological tissues (Liu et al., 2008). It was reported that liver and kidney are the most sensitive organs towards cadmium toxicity (Liu et al., 2010).

The accumulation of cadmium in human organs contributes with many pathological diseases including renal dysfunction (Arisawa et al., 2007).

So, studying the mechanism of toxicity induced by toxins and drugs encourage more scientists to search for new biologically





**Fig. 1–7.** photos of hematoxylin and eosin stained sections of kidney tissues showing the protective effect of ginger extract against cadmium toxicity. (1) Normal control; (2) Ginger treated (100 mg/kg); (3) Ginger treated (200 mg/kg); both group 1,2, and 3 showing normal renal cortex, tubules, parenchyma, and glomeruli; (4 and 5) Cadmium treated group showing congestion of the cortical blood vessels and focal replacement of the renal parenchyma with numerous lymphocytes infiltrates, and dilation of glomeruli. (6) Cadmium + Ginger treated (100 mg/kg); (7) Cadmium + Ginger treated (200 mg/kg). Ginger treated groups (6 and 7) showed regeneration and restore of glomeruli; renal tubules, and cells [H & E 120 $\times$ ].

active constituents from herbal plants which could have intrinsic antioxidant activity to protect biological systems from free radical oxidative damage (Sarwat et al., 2011).

Our study aimed to evaluate the potency of ginger extract at different doses against cadmium induced renal toxicity, through estimation of renal function biomarkers, histological and oxidant-antioxidant status of kidney tissues along with DNA content of renal cells as markers for oxidative tissue damage.

The current study showed high levels of polyphenolic (26.3 mg) and flavonoid (9.33 mg) compounds with high antioxidant and anti-free radical scavenging activity for ginger. It was reported that food products of plant origin are enriched with higher amounts of phenolic and polyphenolic compounds. These compounds supposed to have remarkable antioxidant and nephroprotective activities (Shan et al., 2005). Also, another research work supported that food containing higher amounts of flavonoids reduce susceptibility to certain human diseases (Policegoudra et al., 2011).

In the present study, the active biological constituents and free radical scavenging activity of ethanolic ginger extract were estimated using liquid chromatography, DPPH, and  $\beta$ -carotene tests. From the studied sample of ginger extract, only 28 of active phenolic constituents were identified. 6-gingerol were the highest amount (24.8 mg/g) followed by 6-shogaol (19.4 mg/g), citral (16.2 mg/g), and pyrogallol (15.2 mg/g). This was in addition to small amounts of other phenolic compounds.

Most recent phytochemical studies reported the presence of zingerone, shogaols, gingerols in addition to numerous other active compounds in ginger (Haniadka et al., 2013a, 2013b; Palatty et al., 2013). Also, gingerol (polyphenol) was identified as the major active component of fresh ginger rhizome in addition to volatile oils such as mono sesquiterpenes; camphene, beta-phellandrene and curcumin (Policegoudra et al., 2011). These compounds support the ginger as natural antioxidants to play a pivotal role in the chemoprevention of diseases resulting from free radical oxidative stress.

In the present study, ethanolic ginger extract showed remarkable antioxidant activity against both DPPH and  $\beta$ -carotene tests (89.55 % and 92.3 %) respectively. The obtained results suggested that the phenolic constituents of ginger have the capability to suppress the chain reactions of lipid peroxidation via free radical scavenging mechanism. The data of our study were in line with others who reported that ginger extracts have free radical scavenging effects against superoxide, hydroxyl, nitric oxide in vitro (Höferl et al., 2015). Similarly, most phytochemicals of ginger like zingerone and [6]-Gingerol are shown to scavenge various free radicals such as superoxide, peroxy radicals, and inhibition the production of nitric oxide (NO) and generation of inducible nitric oxide synthase (iNOS) in all biological systems (Shin et al., 2005; Ippoushi et al., 2003).

Previous study reported that exposure to Cd was responsible for many specific clinical disorders in renal function (Jin et al., 2004).

In the present study, there was significant decrease in body weight gain and increase in the weight of kidney following four weeks of Cd exposure. The data obtained matched with other reports which suggested inhibition of growth following cadmium toxicity (El-Demerdash et al., 2004). The loss of weight may be related to significant decrease in protein content and severe diarrhea. Whereas, hypertrophy and nephrotoxicity caused by CdCl<sub>2</sub> accumulation in the kidney were the most causes of the increase in the weight of kidney along with decrease in total body weight (Chieko et al., 1981; Karmakar and Chatterjee, 1998).

However, in current study, treatment with ginger extracts at doses of 100 and 200 mg/kg increased the body weight and restored kidney weight to normal range compared to Cd induced rats. In our experimental model the data also reported that ginger extract at doses 200 mg/kg is not toxic (LD50 = 0) and proved to be

very safe to humans as expected. The improvement in body and kidney weights may be related to the antioxidant and free radical scavenging ability of ginger. According to the presence of oxygen groups in ginger constituents, it behaves like a ligand and prevents cadmium accumulation within kidney via complexation mechanism (Telisman, et al., 2007). Also, it was proposed that vitamin content of ginger especially vitamin A, B6, and retinoids, play a vital role in body growth, fat reserves, and protein synthesis (Ali et al., 2008; Goyall, and Kadnur, 2006). Similarly, phenolic compounds of ginger may increase appetite and stimulate the feeding control in the central nervous system followed by body weight gain (Goyall, and Kadnur, 2006).

In the present study, serum creatinine, creatinine clearance, urine albumin, and urea were estimated to assess renal glomerular function. The data obtained showed significant increase in renal markers; creatinine, urea, urine albumin along with decrease in creatinine clearance following four weeks of Cd exposure. The change in the levels of serum renal biomarkers represents renal damage caused by Cd as previously reported in literature (Bekheet et al., 2011). These data were supported with others who reported that cadmium toxicity induced tubular necrosis or loss of the brush border and damage in the small tubules of kidney (Wang et al., 2009). In the same manner, the increase in excretion of albumin supports that cadmium toxicity induced dysregulation of renal proximal tubule which prevents reabsorption of glomerular-filtered albumin (Gena et al., 2010). In addition to that, the elevated blood urea and lower creatinine clearance caused by cadmium toxicity may be related to disorder in protein catabolism as result of increase in the synthesis of arginase enzyme involved in urea production (Tormanen, 2006), and glomerular functional disturbances such as lower filtration rate which results in poor creatinine clearance in cadmium intoxicated rats (L'Azou et al., 2002).

In this study, the administration of ethanolic ginger extract at doses of 100 and 200 mg/kg showed significant improvement in renal function by decrease in the levels of urea and creatinine along with increase in creatinine clearance and reabsorption of glomerular-filtered albumin. The data obtained suggest a pivotal anti oxidative and chelating effect of ginger against Cd nephrotoxicity, and that the administration of this plant extract alone has no effect on the levels of renal function markers proving the safe use of this plant on kidneys.

The potential effect of ginger extract was related to the antioxidant and nephroprotective activities of its phenolic and flavonoid compounds (Shan et al., 2005; Policegoudra et al., 2011). Our data matched with others who reported significant decrease in BUN among experimental animals following administration of ginger extract for 20 day (Masuda et al., 2004). These support the importance of ginger as therapeutic herbal remedy to manage renal function in patients with uremia as previously reported in literature (Maghsoudi et al., 2011).

Previous reported concluded that the release of cadmium within cells is responsible for production of oxidative free radicals, lipid peroxidation, reduction of antioxidant enzymes, protein cross-linking, and DNA damage, collectively -induced cell death or apoptosis (Brennan, 1996). It was proposed that renal toxicity is attributed with abnormal production of oxidative free radicals which in turn activates renal cell damage (Assadi, 2012).

Our results of the present study showed significant increase in kidney MDA as lipid peroxide marker and decrease in total antioxidant capacity (TAC) as marker of antioxidant status following four weeks of cadmium treatment. The data were in line with others who reported the decrease in antioxidant status such as SOD and CAT in kidney and increase in oxidative free radicals following cadmium toxicity (Ognjanović et al., 2010a; Renugadevi and Prabu, 2010), the increase in oxidative free radicals of lipid peroxidation



(LPO) produces significant changes in antioxidant enzymatic proteins and lipids of biological membranes which in turn produce tissue cell damage and nephrotoxicity (Messaudi, et al., 2009).

The potential protective effect of ginger extract at doses 100 and 200 mg/kg against kidney dysfunction and change in haemostatic balance of oxidant-antioxidant status induced by cadmium intoxication in this study may be related to active biological constituents of ginger which possess higher antioxidant and free radical scavenging efficiency (Hamed et al., 2012). The improvement in antioxidant status in kidney tissues following ginger administration which noticed by the increase in TAC as collective marker of antioxidant profile may be due to the active phytochemicals present in ginger such as gingerols, shogaols and other related bioactive phenolic compounds as shown previously (Haniadka et al., 2013a, 2013b; Palatty et al., 2013).

The production of reactive oxidative radicals promotes damage of cells and release of LPO radicals, alteration in biological proteins and nucleic acid structure (DNA). The imbalance between oxidant-antioxidant status increased the oxidative damage of DNA (Cooke et al., 2003).

In the present, DNA content of renal cells was estimated as a marker of oxidative renal tissue damage induced by cadmium toxicity on molecular level. There was significant decrease in DNA of renal cell treated with cadmium compared to control group. It was reported previously that cadmium can interfere with gene expression, signal transduction, and DNA repair processes (Bertin and Averbek, 2006; Schwerdtle et al., 2010), via generation of reactive oxidative radicals which promote inhibition of Na, K-ATPase, and activate cellular DNA fragmentation which leading to the induction of necrosis and apoptosis (Mao et al., 2011; Valverde et al., 2001).

The results of this study revealed a protective effect of ginger against free radical oxidative damage caused by cadmium intoxication. There was improvement in DNA content in ginger treated rats at doses of 100 and 200 mg/kg following exposure to cadmium toxicity for four weeks. This may be due to higher antioxidant, free radical scavenging, and chelating activity of polyphenolic and flavonoid constituents of ginger. The data matched with others who reported a protective effect of [6]-Gingerol, the major bioactive constituent of ginger against DNA damage via ( $\cdot\text{OH}$ ) radical scavenging through hydrogen atom ( $\text{H}^\cdot$ ) transfer mechanism (Lin et al., 2014). Also, it was reported that ginger oil showed a promising protective effect against oxidative DNA damage induced by  $\text{H}_2\text{O}_2$ , and concluded that ginger acts a scavenger of oxygen radical (Lu et al., 2003). In addition, ginger constituents have been observed to attenuate oxidative cell death and prevent genotoxicity induced by toxicants (Lee et al., 2011; Yang et al., 2011).

In relation to histological modifications observed in the kidneys, we can conclude that cadmium toxicity cause tissue damage via progressive tubular damage whereas the proximal tubules were sensitive to cadmium toxicity as a result of their high reabsorptive activity (Rodrigo and Bosco, 2006).

The generated oxidative free radicals in kidney tissue especially the glomerulus and tubular epithelial cells stimulate NF $\kappa$ B which triggers the release of cytokines, chemokines, adhesion molecules leading to inflammation of renal tissues which in turn resulting in fibrosis, glomerular damage, and tubule interstitial damage (Ohno, 2011). Our histological observations supported both the biochemical and DNA analysis, and confirmed that ginger (*Zingiber officinale*) has a protective and curative activity against Cd-nephrotoxicity. Whereas, the improvement in kidney tissues as reported by histological examinations were in agreement with the improvement in kidney functional markers, and significantly supports the potential protective role of ginger against cadmium induced renal toxicity.

Finally, the results of our study clearly indicate that, ginger treatments at doses of 100 and 200 mg/kg significantly hamper Cd-nephrotoxicity and prevent renal tissue and DNA damage. This significantly related to the free radical scavenging and chelating activity of ginger bioactive constituents such as phenolic, flavonoid, and vitamin A.

In conclusion, the data concluded that ginger significantly protects renal cell dysfunction; decrease the severity of tubular cell, and DNA damage caused by cadmium intoxication via antioxidant and free radical scavenging activity. Thus, ginger ethanolic extract is implied and proposed to be useful in reducing nephrotoxicity induced by various toxicants. But more research studies are necessary to establish its clinical uses.

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## Competing interests

The authors declare that they have no competing interests.

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