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Effect of *Terminalia chebula* on cadmium-induced nephrotoxicity and lipid profiles in rats

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Cadmium Chloride (CdCl2) can accumulate in kidneys as a toxic metal and cause renal failure. This study was undertaken to evaluate the protective effects of *Terminalia chebula* fruit extract against CdCl2-induced renal failure in rats. Forty male albino rats, of 185 ± 20 g weight, were assigned into five groups (n= 8 each). All groups fed on basal diet. The primary group was negative control group (-ve). Other four groups were administrated CdCl2 (3 mg/kg bw). One of them was served as a positive control group (+ve) and three groups were treated with orally *T. chebula* extract (200, 300, and 400 mg/kg/day), respectively for 28 days. The results indicated that treatment with *T.chebula* fruit extract helpful to alleviate the CdCl2 induced toxicity in kidney by significantly decreased levels of serum uric acid, urea creatinine, and total protein. Oral administration of *T.chebula* fruit extract with (200, 300, and 400 mg/kg/day) to nephrotoxicity rats were showed brought back in serum lipid profiles and hepatic biomarkers, tissue lipid peroxidation (LPO) enzymatic, and non-enzymatic antioxidants to near normal. Moreover, the histological evaluation of kidney approved the amelioration of the previous parameters. In conclusion, the present study suggests that the treatment with *T.chebula* fruit extract is helpful in alleviation the renal injury induced by CdCl2

Keywords: *Terminalia chebula,* cadmium chloride, renal failure, nephrotoxicity, oxidative stress.

INTRODUCTION

Cadmium Chloride (CdCl2) is an environmental contaminant and human carcinogen that passes between various stages of the food chain (Satarug et al., 2017). Contaminated water and food are the most important sources of CdCl2 exposure in non-occupationally and general nonsmoking exposed human population (Chunhabundit, 2016). CdCl2's most dangerous feature is that it accumulates during a lifespan (Adeline et al., 2018). CdCl2 accumulates in the kidneys, human kidney concentrations of cadmium have increased several folds during the last century (Thomas et al.,2009).Acute exposure to CdCl2 is known to produce toxicity in the testes, brain, and liver, while chronic exposure to this toxic metal also leads to bone fractures, osteoporosis, anemia, and renal dysfunction (Aghababaei et al., 2018).The primary underlying mechanisms of CdCl2-induced renal dysfunction are oxidative stress and inflammatory responses (Famurewa et al., 2018).

Various experiments have shown that cadmium causes oxidative damage to cells. This metal has been shown to induce free-radical production, resulting in oxidative deterioration of lipids, proteins, and DNA and initiating various pathological conditions in humans and animals. This has often been regarded as the main cause of its deleterious effect on membrane dependent function (Nordberg, 2009); this increases kidney

susceptibility to cadmium toxicity. Hence, knowledge of the defensive mechanisms against toxin and drug induced organ-toxicities leads scientists to look for biologically active specific compounds from herbal plants that may have intrinsic antioxidant activity and protect certain organs from excessive oxidative stress. Plants hold a major birth in modern medicine as raw materials for some important drug preparations (Sarwat et al., 2011).

Terminalia chebula Reitz. is a flowering perennial tree belongs to the family Combretaceae. In Tibet, *T. chebula* is recognized as the "King of Medicine (Choedon and Kumar,2013). The fruit and bark are the main parts used for medicinal purpose, and have been considered the precious and economical source of unique phytoconsttuents which are utlized widely in the development of drugs against different diseases (Singh and Malhotra, 2017). *T. chebula* is mainly used in traditional medicine for the management of different illnesses as anti-diabetic, antioxidant and prevent ageing and also increase body resistance against disease (Dinesh et al., 2017). It also impedes cardiac injury, hepato protective and is used for the management of kidney disorders (Silawat and Gupta, 2013 and Kalra et al., 2018).The powder fruit's water or ethanol extracts are used to treat oxidative stress-related diseases, as well as cancer diseases (Saleem et al., 2002).

The phytochemical analysis of *T. chebula* shows the presence of several phenols such as gallic acid, tannic acid, ß-sitosterol and chebulic acid. It is also one of the richest sources of ascorbic acid having various pharmacological properties (Kaur and Jaggi, 2010). *T. chebula* and its phytoconsttuents have a therapeutic effect with no toxicity (Akhtar and Husain, 2019).Based on existing evidence, the present study was designed to evaluate the effects of *T.chebula* extract against CdCl2-induced renal dysfunction in rats.

MATERIALS AND METHODS

Materials

Fruit

T.chebula Reitz. Family *Combretaceae*, ripen from November to March. The entirely ripe fruits were gathered from the field as soon as they dropped and dried shade. The dried fruit skins were hammered in to small pieces. Fresh fruits of *T.chebula* were obtained from local markets in Egypt.

Chemicals:

CdCl2 as cadmium chloride and other chemicals for histological and biochemical analysis were obtained from Sigma (St Louis, MO, USA). The basal diet was prepared using AIN-93 according to Reeves et al., (1993).

Methods:

Preparation of plant extract:

T. chebula Reitz.shade-dried fruits were taken to prepare the extract. To prepare a fine powder, dried fruits was grinded in an electric grinder. Approximately 890 g of crushed processed material was hauled out with 80% ethanol at a temperature of 60°C to near about 48h (Jami et al., 2014). The extract was lastly deposited in airtight holder at 2–8°C for more uses throughout the study (Hivrale et al., 2013).

Experimental animals:

Forty male albino rats weighted (185 ± 20 g) were procured from Helwan Experimental Animals Station, and they were maintained in an air-conditioned room (26 ± 1°C) with a 12-hour light/12-hour dark cycle. Feed and water were provided for one week for adaptation before the start of experiment (4 weeks). The basal diet was formulated according to Reeves et al. (1993). After adaptation, rats were randomly divided into five groups of eight animals each. The primary group was negative control group (-ve) and fed on basal diet only. The other four groups were subcutaneously administrated CdCl2 (3 mg/ (kg b.w), in 0.5ml of sterile physiological saline (Shibasaki et al., 1994). One group of them was served as a positive control group (+ve). The other three groups were treated with T. chebula extract (200, 300, and 400 mg/kg/day orally), respectively for 28 days (Ekambaram et al., 2018).

The animals were anesthetized by an aesthetic ether at the end of the experimental period. Blood was gathered and the kidney dissected, and washed in ice-cold saline for removal of blood. Tissues were sliced into pieces and homogenized in an appropriate buffer (pH 7.0) in cold condition to give 20% homogenate (w/v). The blood was allowed to clot and serum was separated at 2500 rpm for 15 min and used for various biochemical estimations.

(A) **(B)**

Figure1: Pictures of *Terminalia chebula* fruit

CdCl2 concentration in renal tissue:

Concentrations of CdCl2in renal tissues were estimated utilizing a standard method (Keet al., 2019).

Assessment of nephronprotective activity:

Serum urea nitrogen, uric acid and creatinine were determined according to the described methods (Patton and Grouch, 1977; Fossati et al., 1980 and Larsen, 1972). Serum albumin was estimated by Biuret method (Reinholdm, 1953). Serum cholesterol was determined according to the enzymatic method described by Fossati and Praneipe (1982). Serum triglycerides were calorimetrically determined according to the method described by Wahlefeld, (1974). HDL-c was determined according to the method described by Albers *et al*. (1983), while concentration of VLDL-c was estimated according to the method described by Fruchart, (1982). Low density lipoprotein cholesterol can be calculated as follows: LDL-c = (Total cholesterol)–(HDL-c) –(VLDL-c).

Lipid peroxidation(LPO) and antioxidant biomarkers determinations in kidneys tissue:

LPO was determined by quantifying malondialdehyde (MDA) that formed in terms of thiobarbituric acid reactive substances (TBARS) by the method of Draper and Hadley,(1990). Determination of antioxidant biomarkers' levels as reduced glutathione (GSH) was estimated by Beutler et al., 1963. From other hand, the activities of tissues superoxide dismutase (SOD) and catalase (CAT) were determined calorimetrically according to Spitz and Oberley, (1989) and Aebi (1984), respectively.

Histopathological studies:

For histological studies, the kidney tissues were fixed with 10% phosphate buffered neutral formalin, dehydrated in graded (50-100%) alcohol and embedded in paraffin. Thin sections (5M) were cut and stained with routine hematoxylin and eosin stain for photo microscopic assessment. The initial examination was qualitative for evaluating histopathological lesions in kidney tissue.

Statistical analysis:

The results were expressed as mean ± standard Error (SE) and were analyzed statistically using one-way analysis of variance ANOVA. The results were considered significant at $P \leq 0.05$. Calculations were made on SPSS software version 20 (SPSS Inc., Chicago, Illinois, USA) (Emsley et al., 2010).

RESULTS

Results illustrates that the treatment with different levels of *T. chebula* extract (orally 200, 300, and 400 mg/kg/day) was effective in alleviating the CdCl2 induced toxicity in kidney by significantly decreased levels of serum uric acid, urea creatinine and total protein as compared to the positive control group. The greatest decrease of kidneys functions are recorded for group which treated with 400 mg/kg/ of *T. chebula* extract (Table 1).

The positive control group showed significant increase in serum levels of (TC, TG, VLDL-c, and LDL-c) and a significant decrease in serum (HDL-c), Compared to the healthy control group which administered $CdCl_2$. Treatment with extract of *chebula* at different levels (orally 200, 300, and 400 mg/kg/day) had significant decrease ($P<0.05$) the levels of TC, TG, LDL-c, and VLDL-c and

significant increment ($p<0.05$) in HDL-c level, compared to the positive group. The greatest decreases of lipid profile are recorded for group which treated with 400 mg/kg/ of *T. chebula* extract (Table 2).

Results showed that positive control group had significant decreased ($p\leq0.05$) the mean value of serum SOD, GSH and CAT, while an increase in the level of MDA compared to normal control group. Treatment with *T. chebula* extract (orally 200, 300, and 400 mg/kg/day) had significant decrease ($p\leq0.05$) the levels of MDA and significant increment ($p\leq0.05$) in SOD, GSH and CAT compared to the positive group (Table 3)

Microscopic examination of normal control group, showed the normal histological structure or renal parenchyma (Fig. A). The kidney of CdCl2-induced rats showed more severe degeneration alteration, vacuolar degeneration of endothelial lining glomerular tufts and epithelial lining renal tubules (Fig. B). In addition, microscopic examination of kidney tissues of rats administrated *T. chebula* extract (200 mg/kg/day) showed congestion of glomerular tufts and granularity of epithelial lining renal tubules (Fig. E).while, microscopic examination of kidneys for *T. chebula* extract (300 mg/kg/day) group showed slight hypertrophy of glomerular tuft as well as mild presence of eosinophilic protein cast in the lumen of some renal tubules (Fig. C).

Table 1: Effect of *T. chebula* extract on injury kidneys functions in rats.

Groups	Uric acid (mg/dl)	Urea nitrogen (mg/dl)	Creatinine (mg/dl)	Total protein (mg/dl)
Control (-ve)	1.73±0.13^{a}	24.45±2.34^{a}	0.77±0.03^{a}	0.63±0.07^{a}
Control (+ve)	2.56±0.10^{d}	51.56±2.46^{d}	1.12±0.02^{d}	2.23±0.10^{d}
***T.chebula* extract (200 mg/kg/day)**	1.84±0.16^{b}	34.66±0.88^{bc}	0.90±0.02^{c}	0.85±0.01^{c}
***T.chebula* extract (300 mg/kg/day)**	1.96±0.12^{bc}	36.63±0.75^{c}	0.85±0.06^{b}	0.72±0.04^{bc}
***T.chebula* extract (400 mg/kg/day)**	1.76±0.15^{a}	29.35±0.67^{b}	0.81±0.03^{ab}	0.68±0.02^{b}

Mean values are expressed as means ± SD.
Means with different superscript letters in the column are significantly different at $P \leq 0.05$.

Table 2: Effects of *T. chebula* extract on serum lipid profiles of CdCl2- induced Renal injury in rats.

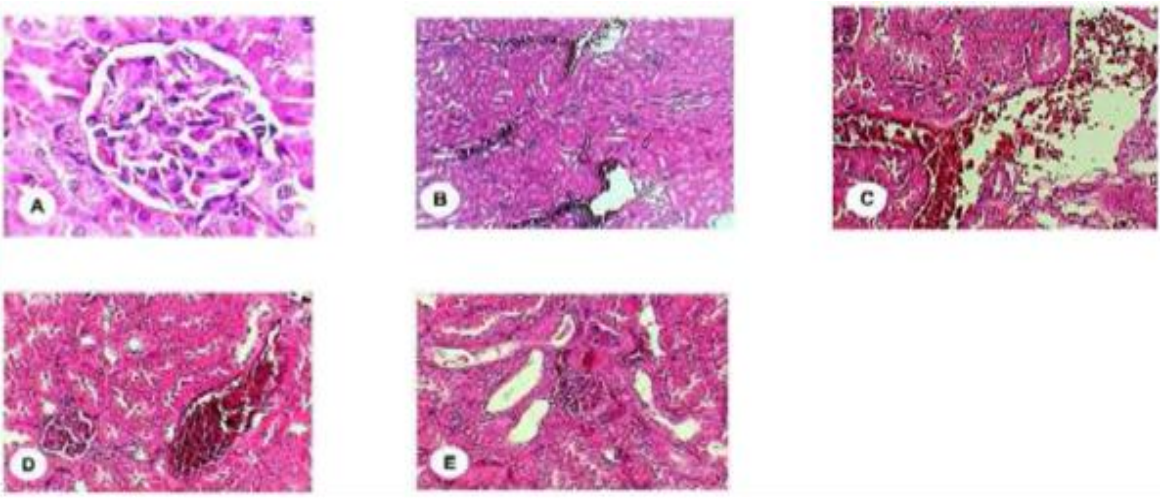
Groups	TC (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
Control (-ve)	80.31±2.14^{a}	62.34±1.88^{a}	49.26±2.98^{a}	18.59±1.85^{a}	12.46±0.38^{a}
Control (+ve)	144.42±1.98^{d}	118.25±2.11^{d}	29.95±1.58^{d}	90.82±1.79^{e}	23.65±0.42^{c}
***T.chebula* extract (200 mg/kg/day)**	101.12±1.52^{c}	91.03±2.17^{c}	32.51±1.53^{cd}	50.41±2.13^{d}	18.20±0.43^{b}
***T.chebula* extract (300 mg/kg/day)**	92.46±1.25^{b}	76.27±1.93^{bc}	38.53±1.10^{c}	38.68±1.97^{c}	15.25±0.39^{ab}
***T.chebula* extract (400 mg/kg/day)**	86.11±1.96^{ab}	68.61±1.99^{a}	42.77±0.97^{b}	29.62±1.62^{b}	13.72±0.40^{a}

Mean values are expressed as means ± SD.
Means with different superscript letters in the column are significantly different at $P \leq 0.05$.

Table 3: Effect of *T. chebula* extract on kidneys tissues lipid peroxide (MDA, GSH, SOD and CAT) of CdCl2-induced renal injury in rats.

Groups	MDA (µmol)	GSH (µmol)	SOD (U /mg)	CAT (U /mg)
Control (-ve)	3.01±0.04^{a}	15.61±2.12^{c}	28.37±1.26^{d}	42.12±2.42^{d}
Control (+ve)	6.12±0.02^{c}	8.55±2.71^{a}	11.64±1.56^{a}	21.13±1.98^{a}
***T. chebula* extract (200 mg/kg/day)**	3.42±0.02^{b}	9.43±2.23^{ab}	22.36±1.37^{c}	27.52±2.30^{b}
***T. chebula* extract (300 mg/kg/day)**	3.13±0.03^{a}	11.74±2.67^{b}	15.28±1.41^{b}	36.21±1.99^{cd}
***T. chebula* extract (400 mg/kg/day)**	3.96±0.03^{b}	12.81±2.01^{b}	18.17±1.32^{bc}	31.11±2.27^{c}

Mean values are expressed as means ± SD.
Means with different superscript letters in the column are significantly different at P ≤ 0.05.



Figures2: b Histopathological alterations in the kidney of control and treated animals
A. Kidney microscopic examination of normal control rat group, showing the normal histological structure; B. Kidney's tissue microscopic examination of CdCl2 treated control rats showing gross necrosis of nephrocytes with nuclear pyknosis, marked vascular degeneration and congestion; C. Kidney's cells microscopic examination of CdCl2+ *T. chebula* extract (300 mg/kg/day) treated rat, showing good histological structure near to normal architecture of kidney cells. D. Kidney's cells microscopic examination of CdCl2+ *T. chebula* extract (400 mg/kg/day) treated rat, showing mild structure for kidney's tissue. E. Kidney microscopic examination of CdCl2+ *T. chebula* extract (200 mg/kg/day) treated rats showing marked improvement in vacuolar degeneration of focal nephrocytes over induced control group

In same context, histological structure of kidney tissues of *T. chebula* extract (400 mg/kg/day) treated rats showed apparent normal histological structure (Fig. D).

DISCUSSION

Nephrotoxicity is one of the major limitations associated with the use of several pharmacological agents. The present study provided more supporting evidence supporting the role of oxidative stress in the pathogenesis of CdCl2--renal toxicity. Moreover, our findings revealed the relation between antioxidant properties of *T. chebula* extract and its protective effects against nephrotoxicity and oxidative

damages caused by the CdCl2. In agreement with our results, antioxidant property of *T.chebula* has been found to protect kidneys too against nephron toxins including cadmium chloride (Yadav et al.,2019).

Several specific clinical complications in renal dysfunction are associated with administration of $CdCl_2$ (Prozialeck and Edwards, 2012). The present study reported that serum renal markers of urea, uric acid, creatinine and total protein, was increased with administration of $CdCl_2$. Serum increasement of these indicators represent biomarkers for renal dysfunction. Other results reported similar findings (Hagar and Al Malki, 2014 and Famurewa et al., 2018). Serum urea increasement may be due to an increase of pyurines and concentrations of free radicals in the body. Also the occurrence of oxidative stress cause oxidation of proteins and amino acids(Manna et al., 2005). The reason for the significant increase in serum creatinine concentration may be due to non-filtration of creatinine from the blood through renal glomeruli due to damage and damage caused by glomeruli due to oxidative damage to cadmium chloride, allowing the release of creatinine in the blood (Adefegha et al., 2015). The decrease of proteins in the cadmium chloride group can cause effect-free radicals resulting from oxidative stress leading to nephropathy and increasing the amount of albumin through the glomerular glands (Guyton and Hall, 2006).

Administration of *T. chebula* extract protect the kidney function from CdCl2intoxication as indicated by significant restoration of serum urea, uric acid, creatinine and total protein. The present study corroborates with the results of Thiruchelvi et al., (2012) and Singh et al.,, (2018) reported that treatment with *T.chebula* significantly decreased the levels of serum urea, urine albumin, creatinine, total protein and significantly restored the creatinine clearance in CdCl2 treated rats when compared to *T.chebula* treated rats. Marked reduction in these levels might be due to the presence of *T.chebula* antioxidant substances, such as its flavonoids and alkaloids (Prasad et al., 2006).

Yadav et al., (2019) indicated that the administration of *T.chebula* at either (198, 300 or 600 mg/kg) for week significantly decreased the mercuric chloride induced increase BUN and serum creatinine levels. Ali et al., (2019) recommended that plant extract having defensive potential to nephrotic cell. All our above findings indicated that plant extract not showed adverse effects and are non-toxic for therapeutic purposes.

Singh et al., (2018) indicated those diabetic rats which treatment with T. chebula seed methanolic extract showed a significant reduction in the serum LDL, VLDL cholesterol, and triglycerides and a significant increase in HDL cholesterol levels when compared with diabetic control rats. This result is in line with our result. Also, Kim et al., (2011) and Sotoudeh et al., (2019) reported significant improvement in plasma lipid profile in diabetic rats which treated with *T. chebula* extract. Moreover, Akram et al., (2019) concluded that aqueous and ethanol extracts of roots of *T. chebula* possess anti - hyperlipidemic activities. This effect and great benefit of *T. chebula* should be taken into consideration in light of the prevention of cardiovascular diseases.

Oxidative stress arises from an imbalance of antioxidants and free radicals that are involved in cellular injury (Rahimifard et al.,, 2014). Naturally, cadmium can cause oxidative stress and this mechanism has long been thought to play a major role in CdCl2-induced kidney damage (Famurewa et al., 2018). Our studies in this regard showed that renal LPO were increased in response to treatment with CdCl2. Such modifications proved the incidence of oxidative stress in renal tissue (Korkmaz and Kolankaya, 2013).Also, MDA levels have been reported to be positively correlated with the magnitude of cellular toxicity (Kurutas, 2016). GSH, SOD and CAT also play a critical role in the maintenance of the oxidative / antioxidant balance in the cells (Ghanbari et al., 2016).

Our results indicated that the administration of (200, 300, and 400 mg/kg/day orally) of *T. chebula* extract significantly attenuated the renal oxidative stress induced by CdCl2as evidenced by decreases in MDA levels and rises in GSH, SOD and GPx levels. Based on the results of this study and others (Miller et al., 2010; Prathapan et al., 2014andSotoudehet al., 2019), we believe the protective effects of *T. chebula* on the nephron may be due to antioxidant andanti-inflammatory efficacy (Sawardekar and Patel, 2015).

Mahesh et al., (2009) concluded that supplementation of T. chebula on kidney in aged rat's decreases oxidative stress in aged rats by alleviating LPO by scavenging of free radicals and increasing antioxidant activity. Singh et al., (2018) and Yadav et al., (2019) conclude that the seeds of *T.chebula* reduce the risk of oxidative stress and ameliorate kidney damage.

Changes in classic biomarkers of glomerular dysfunction, such as serum creatinine are typically

not seen in early or moderate stages of CdCl2 induced kidney injury (Prozialeck and Edwards, 2012). Therefore it can be hypothesized that increased creatinine may be due to the destructive effects of Cd on glomerular and renal tubular cell function. In line with our findings, the destructive effects of CdCl2 on kidneys have been reported in various animal models (Chen et al., 2013, 2018 and Kim et al., 2018). Such results may be due to improvements in tubular reabsorption levels, glomerular filtration rate, glomerular ultrafiltration coefficient, and renal blood flow.

Histological examinations of rats' kidney for all groups also revealed the improvement in damaged tissues with the type of *T.chebula* administration of (200, 300, and 400 mg/kg/day orally) due to elevating the level of its antioxidants and phenolic contents.

CONCLUSION

Based on these observations, one can conclude that antioxidant activity and medicinal properties of *T. chebula* may be responsible for protecting against renal damage caused by CdCl2. Therefore, it is proposed that *T.chebula* fruit extract help to alleviate CdCl2-induced nephrotoxicity in rats. Thus, further analysis for its possible pharmacological effects in nephropathy and screening out potential phytoconstituents is worthwhile.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

SHN designed and performleed the experiments and also wrote the manuscript. SHN and SS performed animal treatments, flow cytometry experiments, tissue collection, and data analysis. SHN and SS reviewed the manuscript. All authors read and approved the final version.

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