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Protective Effects of Nano-Curcumin Against Cadmium Chloride-Induced Liver and Kidney Damage in Male Rats: Role of Oxidative Stress, Inflammation, and Reproductive Hormones

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KEYWORDS
Nano-curcumin is used to induce toxicity to the liver, kidneys, oxidative stress, inflammation cytokines, and reproductive hormones, and in Wistar rats

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ABSTRACT
Background: Cadmium (Cd) is a heavy metal that is toxic and accumulates mainly in the liver and kidney, resulting in plants being severely damaged due to oxidative stress, inflammation and hormonal imbalance. Cadmium toxicity, though efforts are being put to control human exposures, is one of the biggest health problems in majority of the regions in the world like Iraq. Purpose: The aim of the study was to evaluate the ability of nano-curcumin (NC) to prevent the liver and kidney damages caused by cadmium chloride (CdCl 2) in male Wistar rats with a focus on the oxidative stresses, inflammatory cytokines and hormones. Procedures: The forty adult males (n = 40) were divided into four equal groups (n = 10) to take the number of Wistar rats. Normal saline was used to spray group I (control). Eight weeks later group II was administered CdCl 2 (5 mg/kg body weight, orally, daily). The group III was administered with nano-curcumin (orally, 50mg/kg body weight, every day) within a period of eight weeks. Group IV- an intervention that was done on them to have CdCl 2 and nano-curcumin simultaneous in the same doses over eight weeks. At the conclusion of the experiment, blood and tissue samples were analyzed and examined using the markers of liver (ALT, AST, ALP, total bilirubin, total protein, albumin), kidney (creatinine, urea, BUN, uric acid, total cholesterol, triglycerides) functioning and oxidative stress (MDA, SOD, CAT, GPx, GSH, TAC. Results: The liver enzymes, kidney functioning markers, MDA, inflammatory cytokines and cortisol levels significantly increased in Group II and significantly decreased when compared to control group ($p < 0.05$). All these parameters were also significantly ($p < 0.05$) increased by Group IV treated with the co-treatment with nano-curcumin compared to Group II however not returning to the normal values. Conclusion: Nano-curcumin was discovered to possess immense protective effects against cadmium-induced liver and kidney damage in male rats because it was able to alleviate oxidative stress, decrease the levels of inflammatory cytokines and help in normalization of hormone levels. These results suggest that nano-curcumin can be a natural compound potentially exhibiting good outcomes in alleviating the negative effects of heavy metal toxicity.

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1. INTRODUCTION

Among the most hazardous heavy metals in the environment is Cadmium (Cd) which has spread throughout the soil, water and food is found everywhere, making it a major health problem in the world. Human exposure to Cd mainly occurs by way of food and smoking cigarettes and occupational exposure in battery manufacturing

companies, electroplating and in battery production of phosphate fertilizers [1, 2]. Unlike most other compounds that cause poisoning, Cd is a compound that accumulates in the body over a long time span as the kidneys cannot effectively eliminate the compound thus over time, there is increasing damage on the organs due to low levels of exposure [2]. Compared to other chemicals, Cd among the top-ten of chemicals of great concern to human health put forward by the World Health Organization [1]. The topicality of the given issue in the region also [26] is proven by the toxicity of Cd that in Iraq is reported to have an impact on the hepatic biochemical parameters of the experimental animals. Kidneys and liver are the most affected organs since they are the major organ storage and processing locations of Cd in the body [2, 3].

Directly correlated to the ability to alter the oxidative balance of the cells are the Cd toxic effects on the body. Cd interferes with the activities of key antioxidant enzymes by replacing key metals (e.g. Zn and Se) in their active sites as well as it enhances the production of reactive oxygen species (ROS), which overwhelm the normal defenses of the cell [3]. Such oxidative damage triggers NF-KB protein complex to release pro-inflammatory cytokines like TNF-a, IL-6 and IL-1b leading to a synergistic oxidative and inflammatory damage which can be fatal in cell death and dysfunction of organs [3, 4]. This mechanistic evidence of Cd is similar to the results of the experimental studies carried out in Iraq and which have shown the Cd exposure has significant effect on the hepatic antioxidant and inflammatory markers of the rats [26]. Cd is now in the list of endocrine disruptors, in addition to its liver- and kidney-damaging actions. It interferes with the hypothalamic-pituitary-gonadal axis resulting in low levels of testosterone, LH and FSH and a rise in the level of cortisol in response to stress [5, 6].

In the recent years, there has been an increased interest in compounds with natural occurrence and could be utilised to prevent heavy metal toxicity and in particular those that have anti-oxidative effects and effects on inflammation. Among these polyphenols, one of the most research works was carried out with curcumin one of the polyphenols extracted by the roots of Curcuma longa possessing a variety of biological reactions. It works by inhibiting free radicals, increasing the antioxidant capability of antioxidant enzymes through the Nrf2 pathway and lowering the synthesis of proinflammatory cytokines by suppressing the NF-KB [7, 8]. Direct conjugation of Cd 2+ with curcumin can also be used and this can help in reducing the amount of metal entering the cells harming them [6, 7]. Iraqi researchers have also demonstrated the anti-inflammatory properties of curcumin in experimental animals but should boost its clinical benefits [28]. Despite all these encouraging effects, the insolubility of curcumin in water, rapid degradation in the liver and low absorption in the intestine prevent the practical application of this compound as a nutritional supplement since the concentrations of the compound reaching the target organs are very low with its oral administration [8].

To overcome the limitation of conventional curcumin, scientists have been able to think of investors in nanotechnology as one of the ways of improving the delivery and effectiveness of curcumin. The curcumin itself is more stable when loaded into nanoparticles (polymeric nanoparticles, solid lipid carrier, chitosan-based, etc.) and is more readily retained in the bloodstream, and more readily absorbed by the cells resulting in a significantly increased bioavailability of curcumin relative to free curcumin [8, 23]. Several studies have reported that nano-curcumin (NC) is better than traditional curcumin in preventing the poisoning of animals by heavy metals [9, 10, 14]. Majority of all past research has though focused on a singular aspect of Cd toxicity and little research has looked into the effects of Cd on oxidative stress, inflammation and reproductive hormones in a single research. Experimental studies have also revealed that curcumin-based regimens have a nephroprotective effect in the case of organ injury [27] in Iraq. Therefore, this experiment sought to compare the protective effect of NC in preventing Cd-induced liver and kidney damage in male rats with all the three of these mechanisms being taken into consideration.

MATERIALS AND METHODS

Ethical Approval

The approvals of all the experimental procedures involving animals were provided by the University of Samarra animal care and Ethics Committee (Approval No. IACEC-2023/07). The study was carried out as per the National institute of health guidelines of how to handle and utilize the laboratory animals. The minimal numbers of animals used were used and as much as possible, pain and other forms of discomfort was avoided during the experiment.

Animals and Housing

The locals of the Animal House at the College of Medicine, University of Samarra bought the Wistar adult males (Rattus norvegicus) in large numbers (n=40) weighing between 200 to 230 grams. An experiment was initiated by first giving all the

animals a 2 week time to acclimatize at the normal laboratory environment of; temperature 22 +2 C, relative humidity of 55 +5 and a 12:12 light/dark photiodiod. Food and water were also available to all animals any time of the day of the study.

Experimental Design

After acclimatization the rats were then randomly divided into four groups of ten rats. Group I (Control): This group was given the privileges to inhale normal saline on a day to day basis (1 mL/kg body weight) through oral gavage. Group II (Cd group): The group II (Cd group) was administered cadmium chloride solution (5mg/kg body weight orally and daily)eight weeks. In fact, this dose has been extensively used before in experiments to cause liver and kidney damage but not fatalities [3, 4]. Group III (NC group): 50mg/kg body weight of nano-curcumin suspension (orally on day- by day basis) was administered. After eight weeks Group IV (Cd + NC group) was dosed and with equal dosage and route with cadmium chloride and nano-curcumin concomitantly. At the end of every 1 week of the experiment, body weight of each animal was taken note of.

Preparation of Nano-Curcumin

To make nano-curcumin the solvent-injection process was followed as described by Moballegh Nasery et al. [23] with slight modifications. The solution was made by dissolving the curcumin (99 percent purity Sigma-Aldrich, St. Louis, MO, the USA) in ethanol to 5mg/mL. The solution was subsequently gradually drop wise added to an aqueous solution of polyvinyl alcohol (1% w/v) and mixed with continual rotation (1, 000 rpm) in 30 minutes, at room temperature. The mixture was subjected to ultrasound at 100 W using a Branson Sonifier (USA) and then centrifuged at 15,000 1 g in 20 min to be able to retrieve the nanoparticles. The net particles were washed out in distilled water thrice and finally dissolved in normal saline that was to be administered orally. The measurements of size, and surface charge of the nanoparticles were made by scheme dynamic light scattering with Malvern Zetasizer Nano ZS (UK). Nanoparticles had a mean size of 148.6124.4 nm, polydispersity index of 0.21 0.03 and zeta potential of - 24.81.7 mV indicating a stable and uniform suspension of the nanoparticle. This was measured by UV- Vis spectrophotometry at 425 nm which gave its encapsulation efficiency at 87.3 +2.6%.

Nondestructive and Destructive sampling.

All the animals were starved during the night after the eight weeks experimentation and samples of the animals were collected. The xylazine and ketamine (80/10mg/kg body weight) were injected intraperitoneally and anesthetized all the rats. Cardiac puncture of the blood samples in plain tubes was performed and left to clot at room temperature then centrifugation at 3000 rpm was done over a period of 15 minutes. This serum was split up and aliquots collected and kept at -80 C until the analysis. A liver tissue and kidney tissue were taken out and weighed within this period without delay and frozen in liquid nitrogen followed by homogenates of tissues made by homogenizing each sample tissue ice with glass homogenizer in 10% w/v phosphate- buffered saline (pH 7.4). The up upin case of enzymatic measurements the homogenate was centrifuged at a setting of 10,000 x g and the quick suspension was removed and placed on the enzymatic measurements and set at 4o C over a period of 20 minutes.

Biochemical Analyses

The alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, total protein and albumin, creatinine, urea and blood urea nitrogen (BUN) levels, and uric acid, total cholesterol, triglyceride levels in the tissue homogenates were measured using color A commercial kit of Cayman chemical (Ann Arbor, MI, USA) was used to determine the levels of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The amount of glutathione (GSH) was ascertained using the DTNB and that of the total antioxidant capacity (TAC) by the ferric reducing antioxidant power (FRAP). The TNF- alpha, IL-6 and IL-1 beta serum levels were hingeed on enzyme-linked immunosorbent assays (ELISA) on specific rat kit (R&D Systems, Minneapolis, MN, USA) as per the manufacturer directions. Serum testosterone, LH, FSH and cortisol electrochemiluminescense immunoassay (ECLIA) was done on a Cobas e 411 analyzer (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

All the results are in mean + SD. Normality of the data was checked using Shapiro-Wilk and Levene test and actions were done to test the equality of the variances of the groups. These differences were analyzed to compare the group differences using one way analysis of variance (ANOVA) and in case there was significant difference found; it would be followed by a post-hoc test (Tukey) which would do multiple comparisons. The p-value that was considered significant was deemed to be less than 0.05. The SPSS software version 26.0 (IBM corp, Armonk, NY, USA) aided in statistical analysis.

RESULTS

Eight weeks of oral cadmium chloride therapy revealed great variation in all the biochemical parameters measured in Group II than in the control group. The addition of nano-curcumin along with cadmium chloride (Group IV) to animals indeed resulted in an apparent improvement of these parameters with values, between those of the control and cadmium-only groups. Animals in Group III with nano-curcumin only exhibited no significant change compared to the control group in all of the parameters measured suggesting that nano-curcumin at the dose of this study is not a toxicant all by itself.

The impact of cadmium chloride and nano-curcumin treatment on liver hepatic functions,, are demonstrated in Table 1. Rats in Group II showed a significant increase in serum ALT (67.8 vs. 28.4 U/L), AST (89.4 vs. 32.6 U/L), ALP (178.6 vs. 84.2 U/L), and total bilirubin (1.18 vs. 0.42 mg/dL) compared to the control group ($p < 0.05$). Concurrently, total protein (5.14 vs. 7.82 g/dL) and albumin (2.87 vs. 4.21 g/dL) were greatly lower in Group II indicating that it implies a deterioration of the employment of the liver to synthesize proteins. Group IV Co-treatment with nano-curcumin brought about a significant decrease of these abnormalities relative to Group II ($p < 0.05$) and these values were not fully restored to normal, meaning that nano-curcumin partially had protectivity to the liver.

Table 1. The effect of cadmium chloride on serum liver function parameters, after exposure and co-treatment of the male Wistar rats using nano-curcumin (Mean ± SD, n = 10 each group).

Parameter	Group I (Control)	Group II ($CdCl_2$)	Group III (Nano-Cur)	Group IV ($CdCl_2$ + NC)
ALT (U/L)	28.4 ± 2.1	67.8 ± 4.3*	27.1 ± 1.9	38.2 ± 2.7*†
AST (U/L)	32.6 ± 2.8	89.4 ± 5.7*	31.4 ± 2.3	47.3 ± 3.1*†
ALP (U/L)	84.2 ± 6.1	178.6 ± 9.4*	81.7 ± 5.8	112.4 ± 7.2*†
Total Bilirubin (mg/dL)	0.42 ± 0.04	1.18 ± 0.09*	0.40 ± 0.03	0.71 ± 0.06*†
Total Protein (g/dL)	7.82 ± 0.34	5.14 ± 0.28*	7.91 ± 0.31	6.73 ± 0.29*†
Albumin (g/dL)	4.21 ± 0.18	2.87 ± 0.14*	4.18 ± 0.16	3.56 ± 0.17*†

Note. * $p < 0.05$ vs. Group I (Control). † $p < 0.05$ vs. Group II ($CdCl_2$). ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; NC = nano-curcumin.

The level of markers of kidney functions and lipid profile is presented in table 2. The group II rats had significantly higher concentration of serum creatinine (1.84 vs. 0.68mg/dL), urea (78.6 vs. 32.4 mg/dL), BUN (36.7 vs. 15.1mg/dL) and uric acid (6.47 vs. 2. Exposed to nano-curcumin Group IV rats, and to cadmium, all these markers were significantly lower than Group II ($p < 0.05$) suggesting that nano-curcumin would be able to protect the kidneys, as well as to improve lipid metabolism. These findings are in line with the researches that were conducted by Iraqis; which also revealed similar curcumin protection effects of kidney damage in test animals [27].

The results of the oxidative stress in liver and kidney tissues expressed in form of oxidative stress markers are presented in table 3. The exposure to cadmium in Group II induced a significant elevation in the MDA level (4.87 vs. 1.24 nmol/mg protein; $p < 0.05$) which was almost four times more than the level in the control group. In parallel, the SOD, CAT and GPx activities together with GSH and TAC measured quantities were significantly decreased in Group II, which demonstrates that cadmium was a severe damage to the enzyme and non-enzyme antioxidants of the tissues. Group IV: There was a significant decrease in all these parameters in Group IV when nano-curcumin was used with cadmium ($p < 0.05$) relative to Group II (2.61 nmol/mg protein and 34.8 U/mg protein). These findings indicate that nano-curcumin was effective in preventing oxidative damage, which was probably via neutralizing free radicals or by stimulating antioxidant defenses processes in the tissues exposed.

Table 2. How CdCl 2 exposes male Wistar rats to damage serum kidney functions (markers) and co-treatment with nano-curcumin (Mean ± SD, n = 10 per group) affects lipid profiles.

Parameter	**Group I (Control)**	**Group II ($CdCl_2$)**	**Group III (Nano-Cur)**	**Group IV ($CdCl_2$ + NC)**
Creatinine (mg/dL)	0.68 ± 0.05	1.84 ± 0.12*	0.71 ± 0.04	1.12 ± 0.08*†
Urea (mg/dL)	32.4 ± 2.7	78.6 ± 5.2*	31.8 ± 2.4	51.3 ± 3.6*†
BUN (mg/dL)	15.1 ± 1.3	36.7 ± 2.8*	14.8 ± 1.1	23.9 ± 1.9*†
Uric Acid (mg/dL)	2.84 ± 0.21	6.47 ± 0.43*	2.91 ± 0.18	4.12 ± 0.32*†
Total Cholesterol (mg/dL)	142.6 ± 8.4	198.4 ± 11.2*	139.8 ± 7.9	167.3 ± 9.1*†
Triglycerides (mg/dL)	86.4 ± 5.8	152.7 ± 9.4*	84.1 ± 5.2	118.6 ± 7.3*†

*Note. * $p < 0.05$ vs. Group I (Control). † $p < 0.05$ vs. Group II ($CdCl_2$). BUN = blood urea nitrogen; NC = nano-curcumin.*

Table 3. The biomarkers of oxidative stress in tissues of male Wistar rats exposed to CdCl 2 and co-treated with nano-curcumin (Mean ± SD, n = 10 each).

Parameter	**Group I (Control)**	**Group II ($CdCl_2$)**	**Group III (Nano-Cur)**	**Group IV ($CdCl_2$ + NC)**
MDA (nmol/mg protein)	1.24 ± 0.09	4.87 ± 0.32*	1.18 ± 0.08	2.61 ± 0.19*†
SOD (U/mg protein)	48.7 ± 3.2	18.4 ± 1.6*	51.3 ± 3.6	34.8 ± 2.7*†
CAT (U/mg protein)	32.4 ± 2.4	12.7 ± 1.1*	34.1 ± 2.6	23.8 ± 1.8*†
GPx (U/mg protein)	28.6 ± 2.1	10.2 ± 0.9*	29.8 ± 2.3	19.4 ± 1.6*†
GSH (µmol/g tissue)	8.42 ± 0.61	2.87 ± 0.24*	8.91 ± 0.68	5.64 ± 0.43*†
TAC (mM/L)	1.84 ± 0.13	0.62 ± 0.05*	1.91 ± 0.14	1.18 ± 0.09*†

*Note. * $p < 0.05$ vs. Group I (Control). † $p < 0.05$ vs. Group II ($CdCl_2$). MDA = malondialdehyde; SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GSH = reduced glutathione; TAC = total antioxidant capacity; NC = nano-curcumin.*

The levels of inflammatory cytokines and reproductive hormones are presented in Table 4. Compared to the control group, Group II rats were significantly more than control rats in TNF-alpha (68.7 vs. 18.4 pg/mL), IL-6 (54.3 vs. 12.8 pg/mL) and IL-1 (42.8 vs. 9.74 pg/mL) indicating that the exposure of this range of animals to cadmium induced a On hormonal levels, Group II was characterized by a significant decrease in testosterone (1.47 vs. 4.82 ng/mL), LH (1.18 vs. 3.64 mIU/mL), and FSH (0.94 vs. 2.87 mIU/mL) and the significant increase in cortisol (98.4 vs. 42. Group IV The combination of nano-curcumin and the inflammatory and hormonal parameters were also significantly improved in Group IV compared to Group II ($p < 0.05$), with testosterone reaching 2.94 ng/mL and cortisol decreasing to 68.7 ng/mL, indicating that nano-curcumin was able to reduce the inflammatory and the hormonal parameters and to

Table 4. Male Wistar rats control (CdCl2 exposure) and nano-curcumin co-treated (nano-curcumin) serum samples (Mean ± SD, n = 10 per group) pro-inflammatory cytokines and steroid hormones.

Parameter	Group I (Control)	Group II ($CdCl_2$)	Group III (Nano-Cur)	Group IV ($CdCl_2$ + NC)
TNF-α (pg/mL)	18.4 ± 1.4	68.7 ± 4.8*	17.2 ± 1.3	38.4 ± 2.9*†
IL-6 (pg/mL)	12.8 ± 1.1	54.3 ± 3.7*	12.1 ± 0.9	29.6 ± 2.2*†
IL-1β (pg/mL)	9.74 ± 0.82	42.8 ± 3.1*	9.18 ± 0.71	23.4 ± 1.8*†
Testosterone (ng/mL)	4.82 ± 0.34	1.47 ± 0.12*	4.91 ± 0.38	2.94 ± 0.22*†
LH (mIU/mL)	3.64 ± 0.27	1.18 ± 0.09*	3.71 ± 0.29	2.38 ± 0.18*†
FSH (mIU/mL)	2.87 ± 0.21	0.94 ± 0.07*	2.94 ± 0.23	1.82 ± 0.14*†
Cortisol (ng/mL)	42.8 ± 3.1	98.4 ± 6.7*	41.4 ± 3.0	68.7 ± 4.9*†

Note. * $p < 0.05$ vs. Group I (Control). † $p < 0.05$ vs. Group II ($CdCl_2$). TNF-α = tumor necrosis factor-alpha; IL = interleukin; LH = luteinizing hormone; FSH = follicle-stimulating hormone; NC = nano-curcumin.

DISCUSSION

This experiment examined the biochemical changes of cadmium chloride in liver and kidney of male rats, and the capacity of nano-curcumin in alleviating this injury. The animal model of this study, which relies on oral intake CdCl 2, at dosage of 5 mg/kg body weight over a period of eight weeks, is a long-established model in the field of toxicology, which produces reliably liver and kidney damage but not death to allow toxic changes ample time to occur [3, 4]. In this study, the dose of nano-curcumin used (50 mg/kg body weight) was calculated based on effective doses in other studies which employed the same formulation of a nano particle in toxicity models of heavy metals [9, 13, 14].

The marked increase in serum ALT, AST, ALP and total bilirubin in Group II is a classic indicator of liver cell injury and bile obstruction and these results agree with the prior researches that followed the same conditions of cadmium exposure on the rat [4, 7, 10]. The decrease in the total protein and albumin in the same group is indicative of the liver having part of its protein producing cells being replaced by damaged or dead cells due to cadmium toxicity. It is believed that this damage is realized due to the promotion of the formation of reactive oxygen species by cadmium, which in turn attacks the membranes of mitochondria, ultimately causing death of the cells [3]. Similar tendencies of liver enzyme elevation by cadmium exposure have also been found in Iraqi studies under rats, a finding further developed by these studies [26]. Group IV, nano-curcumin treatment resulted in vastly less liver enzyme leakage than Group II, which is not surprising given earlier reports from Elgebaly et al. [10] and Nassar et al. [9] that revealed that nano-curcumin deliver curcumin to liver cells more efficiently.

Such a large rise in serum creatinine, urea, BUN, uric acid in Group II indicates that exposure to cadmium resulted in damage to the filtering units and the tubules in the kidney. The greatest sensitivity of the kidneys would be to cadmium because the kidney cells take up cadmium-metallothionein complexes of the filtered blood actively and as a result; cadmium would accumulate inside these cells at a much higher level compared to levels in the blood [2]. The resultant increase reported in the total cholesterol and triglycerides ofGroup II is also comparable to earlier reports that cadmium disrupts fat regulation of the liver through decreasing activity of lipoprotein lipase and enhancing synthesis of cholesterol via the HMG-CoA reductase pathway [4, 5]. Group IV that treated with nano-curcumin had a significant reduction in all the markers of kidney function, and levels of lipids as compared to Group II. This finding is consistent with the results of Rehman et al. [8] who stated that nano-curcumin inhibited cadmium accumulations in the kidneys by approximately 40, which may be due to the binding of the cadmium ions and aid in their excretion out of the body via the digestive tract. The protective role of curcumin-based treatments has also been substantiated by the protective influence on the kidney damage of experimental models of the drug in Iraqi studies [27], which further support the results.

This massive increment in the tissue MDA and a substantial decrease in SOD, CAT, GPx, GSH, and TAC in Group II are clear indication that in this

study, oxidative stress was a major factor leading to the liver and kidney damage brought about by cadmium. This process of depletion of antioxidants is because, the cadmium replaces the important metals like zinc and manganese in the active sites of the antioxidants, and at the same time enhances the production of harmful free radicals like hydrogen peroxide and hydroxyl radicals through the Fenton reaction [3, 16]. The initiation of a sign of substantial recovery of the antioxidant markers in Group IV could propose that nano-curcumin assisted in restoring antioxidant defense system, which is agreeable with past research indicating that curcumin can activate the Nrf2 pathway, and augment the expression of principal antioxidant enzymes, comprising SOD, HO-1, and glutathione S-transfer This protective effect was probably increased by the use of nanoparticles which enabled the delivery of higher levels of curcumin to the liver and kidney cells at which the oxidative damage was taking place as reported by Abdel-Daim et al. [14] and Sungur et al. [12].

The dramatic upsurge of TNF- -, IL-6, and IL-1ba levels in Group II indicates that exposure to cadmium triggered inflammatory response in this group of animals, probably via the NF- - -signaling pathway, which is known to suppress production of these inflammatory proteins in response to toxic substances including cadmium [4, 25]. Iraqi scientists have also demonstrated the same anti-inflammatory properties of curcumin on animal-induced cardiovascular disease which further confirms its use as a curb to cadmium induced inflammation in the current research [28]. The decreased levels of testosterone, LH, FSH, along with the increase of cortisol among Group II indicate that the hormone system of these animals was disturbed by cadmium as well. It is believed that the direct effect of cadmium on the cells which produce the testosterone in the testes, and also its presence in the adrenal glands (by causing oxidative damage) contributes to this hormonal imbalance [5, 18, 19, 20]. This result is corroborated by another study conducted by Jahan et al. [18] and Ahmad et al. [20] that also concluded that, in cadmium-exposed rats, antioxidant treatment could partially prevent and/or restore both testosterone and gonadotropin levels. Group IV also showed a great improvement in nano-curcumin therapy of inflammation cytokines as well as hormones than the Group II, which indicates that nano-curcumin could decrease the inflammatory cytokines and restore hormonal balance simultaneously. The combination of this effect on various processes of cadmium toxicity makes nano-curcumin an even more promising protective compound in view of its potential to combat a broader range of treatments that treat a single pathway.

CONCLUSION

This research finds that oral administration of nano-curcumin (50 mg/kg of body weight) offered substantial and beneficial protective measures against liver and kidney damage by cadmium chloride in male Wistar rats. This defense was realized in three key ways: one, by enhancing the antioxidant defense mechanisms in the tissues of interest; second, by suppression of the synthesis of the inflammatory cytokines by inhibition of NF-xB pathway; and finally by preventing the increase in cortisol productions induced by cadmium exposure. The findings also indicate that the nanoparticle of curcumin proved to be more efficient compared to regular curcumin which has been reported in other papers, probably because of better absorption and delivery of curcumin to the target organs once encapsulated in nanoparticles. These results raise the question of believing that nano-curcumin is a promising natural agent in terms of prevention of heavy metals toxicity and it is advisable to conduct further investigations based on molecular and cellular methodology to gain better insights on the exact mechanism at play.

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