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Nephron-protective effects of curcuma on oxidative damage and oxidative stress in rat under sub-chronic poisoning of chromium

Malika Saidi[1], Ouassila Aouacheri[1,2], Saad Saka[1,2*], Imene Tebboub[2], Leila Ailane[3]

[1]*Department of Biology, Laboratory of Animal Ecophysiology, University of Badji Mokhtar, Annaba, Algeria*

[2]*Department of Biochemistry, Laboratory of Applied Biochemistry and Microbiology, University of Badji Mokhtar, Annaba, Algeria*

[3]*Department of Biochemistry, Laboratory of Biochemistry and Environmental Toxicology, University of Badji Mokhtar, Annaba, Algeria*

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Abstract

The aim of this study is to evaluate the nephroprotective role of *Curcuma longa*, against acute toxicity effects of hexavalent chromium induced oxidative renal injury. Therefore, different antioxidant and serum biochemical parameters were measured. Male W*istar* rats were divided into four groups and were treated daily for 30 consecutive days. Group I (o-o): control rats received mineral water through oral gavage (*per os*) and were nursed on normal diet. Group II (o-Cur): rats received mineral water and were fed on an experimental diet containing 2 % of curcuma powder. Group III (Cr-o): rats were treated *per os* with potassium dichromate at a dose of 15 mg/kg of body weight and were fed on normal diet. Group IV (Cr-Cur): rats received an oral dose of potassium dichromate at a dose of 15 mg/kg of body weight and an experimental diet containing 2 % of curcuma powder. Renal protein concentration, glutathione content, glutathione peroxidase, glutathione S-transferase and catalase activities were estimated. Exposure of rats to chromium caused significant perturbation in the renal biomarkers (creatinine, urea, uric acid, albumin, and total proteins), while there was a significant decrease in the oxidative stress parameters (GSH, GPx, GST, and CAT). These disruptions were accompanied by histopathological changes in the kidney sections of rats intoxicated with chromium, whereas treatment with *Curcuma longa* restored all the parameters mentioned above to near normal. In conclusion, results revealed the potent antioxidants activity of curcuma that were demonstrated by its ameliorative effects on chromium intoxication. Thus, this plant has a protective effect against nephron-damages induced by the hexavalent chromium.

* **Corresponding Author:** Saad Saka ✉ sakasadz@yahoo.fr

Introduction

Pollution with heavy metals is one of the serious problems threatening our ecosystem; they present a significant worldwide concern due to their biological damaging effects on human health as they can be absorbed through skin, inhalation or orally (Venter *et al.,* 2015; Zhong *et al.,* 2018**)**. Although they are naturally found in the earth's crust, as rocks and soils are their principal natural sources; heavy metals can also be found within the environment in excess due to various anthropogenic actions such as industrial production, agriculture domestic and other technological applications (Bradl, 2005).

Among several heavy metals, chromium (Cr) was identified to be the most powerful toxic metal that induces oxidative stress, and was classified as a human carcinogen (Bagchi *et al.,* 2002). Chromium can be found in the environment under different states, ranging from hexavalent (VI) to trivalent (III) forms. Cr (III) is estimated to be the less toxic form, while the highest toxic form was attributed to the Cr (VI) (De Flora *et al.,* 2016). The latter is a strong oxidizing and corrosive agent known to cause various health conditions including ulcers, nasal mucosa damage, asthma, allergies, skin irritation and may also cause adverse effects in the liver and the kidney (Coetzee *et al.,* 2018). Furthermore, exposure to Cr (VI) could result in severe systemic toxicity in which kidney is the main targeted organ, thus acute renal failure manifestation (Lin *et al.,* 2009). Besides, after penetrating cells, Cr (VI) can generate free radicals causing tissue injuries that provokes several diseases (Sun *et al.,* 2015).

Herbs and spices represent an integral part of human nutrition since antiquity. They have been used not only to enhance the flavor, color, and aroma of foods; but also by folk medicine for their conservative, antioxidant, antimicrobial and many other medicinal values (Kehili *et al.,* 2017). Curcuma (*Curcuma longa*), used in this study, is a well-known herbal remedy for centuries (Lim, 2016). This herb provides several therapeutic properties including antioxidant, antimicrobial, anti-inflammatory, antiviral, and anticancer activities (Luthra *et al.,* 2001). In addition, many studies have found that *Curcuma longa* has a potent protective effect in renal diseases (Agarwal *et al.,* 2010; Nabavi *et al.,* 2012; Alvarenga *et al.,* 2018); precisely a study that was carried out recently on a model of chronic kidney disease which has revealed that curcumin, the main biologically active compound in *Curcuma longa*, exerts a healing effect that improves most of physiological, biochemical and histopathological changes (Ali *et al.,* 2018). Moreover, Momeni and Eskandari (2017) reported a nephron-protective effect of curcumin against sodium arsenite poisoning in adult male mice.

In the present study we elucidated the nephron-protective role of *Curcuma longa* against hexavalent chromium induced acute renal injury in rats, by analyzing a few biochemical and antioxidant parameters as well as histopathological observations.

Materials and methods

Animals

Male wistar rats weighing 160±10 g, were obtained from Pasteur Institute of Algiers, Algeria. Rats were housed at constant room temperature (21±2 ◦C) on a 12-h dark/light cycle with free access to food. Rats were fed on specific diet prepared as described by Upreti *et al.* (1989) regime and water *ad libitum*. The animals were acclimatized for 15 days before commencement of the experiments. The research procedures were carried out according to the National Institute of Health Guidelines for Animal Care and approved by the Animal Ethics Committee.

Chromium solution preparation (induction of oxidative stress)

Curcuma longa rhizomes were purchased locally from the market. To obtain turmeric fine powder, rhizomes were milled in the laboratory using mortar and pestle, pulverized with a knife grinder, and then sieved to get uniform size range.

Curcuma powder preparation

Curcuma longa rhizomes were purchased locally from the market and were grinded to fine powder

(turmeric) in the laboratory using a milling instrument (mortar and pestle) then placing in the mixer. Later it was sieved to get uniform size range.

Animal treatment

Animals were divided into four groups and were all treated daily for 30 consecutive days. Group I (0-0): control rats received mineral water through oral gavage (*per os*) and were nursed on normal diet. Group II (0-Cur): rats received mineral water and were fed on an experimental diet containing 2 % of curcuma powder. Group III (Cr-0): rats were treated *per os* with potassium dichromate at a dose of 15 mg/kg body weight and were fed on normal diet. Group IV: (Cr-Cur) rats received an oral dose (15 mg/kg) of potassium dichromate and an experimental diet containing 2 % of curcuma powder.

Experimental procedures

After 30 days of treatment, the animals were sacrificed by cervical decapitation and blood samples were collected in dry centrifuge tubes. The samples were centrifuged at 5000 rpm for 10 minutes to obtain serum which afterwards served for the measurement of creatinine, urea, uric acid, albumin, and total proteins using automatic biochemistry analyzer (ARCHITECT ci4100), and kits that were provided by Spinreact, Spain.

Animals were subsequently dissected. The extracted kidneys were firstly washed with a phosphate buffer (0.1 M, pH=7.4), to remove excess blood and adhering tissues, weighed, then divided into 2 parts. The first part of the kidneys was immediately fixed in 10 % formol solution for histological study, whereas the second part was preserved at -20 °C to stop metabolic activities and served for oxidative stress evaluation.

The reduced glutathione (GSH) content and protein concentration were determined by spectrophotometry methods used by Weckbercker and Cory (1988) and of Bradford (1976), respectively. Catalase activity (CAT) was estimated by the Aebi (1984) method, while glutathione peroxidase (GPx) activity was determined according to Flohé and Günzler (1984) method and glutathione S-transferase (GST) activity was estimated by Habig *et al.* (1974) method.

Statistical analysis

Data were expressed as mean±S.E.M. All values were analyzed through one-way analysis of variance (ANOVA) followed by Tukey's methods. The GraphPad Prism 5.0 software was used to perform the statistics (GraphPad Software, Inc., San Diego, CA). P values of <0.05, <0.01 and <0.001 were considered statistically significant, highly significant and very highly significant, respectively Fisher and Yates (1974).

Results

Renal parameters study

When compared to the control group, exposure to chromium in Cr-0 group caused a significant increase in creatinine, urea, and uric acid levels as well as a significant decrease in albumin and total proteins levels. Conversely, results have shown an improvement of the same biochemical parameters after curcuma administration in Cr-Cur group when compared to control and Cr-treated groups (Table 1).

Table 1. Serum biochemical parameters in control (0-0) and treated rats (0-Cur, Cr-0, Cr-Cur) after 30 days of treatment (values represent the mean ± SEM of 8 rats).

Parameters	Groups			
	0-0	0-Cur	Cr-0	Cr-Cur
Creatinine (mg/L)	6.681±0.61	6.161±0.68	11.94±1.27**	9.889±0.88**
Urea (g/L)	0.4729±0.05	0.4255±0.04	0.6649±0.04*	0.5128±0.05
Uric acid (mg/dl)	2.883±0.40	2.409±0.36	4.680±0.46*	4.520±0.58*
Albumin (g/L)	32.13±4.15	32.25±2.042	21.88±2.689	25.88±2.482
Total proteins (g/L)	65.75±4.01	79.13±4.60*	41.88±4.62**	59.75±3.81##

* p <0.05, ** p <0.01, 0-Cur; Cr-0; and Cr-Cur treated groups versus the control group.

p <0.01, Cr+Cur; Significantly difference from (Cr-0) group.

Antioxidants profile

Antioxidants biomarkers were significantly decreased in chromium treated rats compared with the control (Figs 1-4), whereas, the curcuma supplementation in (Cr-Cur) group caused an amelioration of these levels compared to (Cr-0) group.

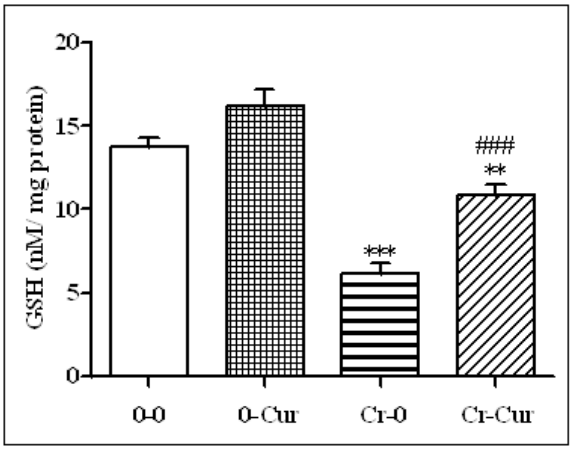

Fig. 1. Glutathione content (nM/mg prt) in the four groups of rat's kidney after 30 days of treatment (values represent the mean ± SEM of 8 rats).

** p <0.01, *** p <0.001; Significantly difference from control (0-0) group.

p <0.001; Cr-Cur; Significantly difference from (Cr-0) group.

Histological finding

The representative photomicrographs in Fig. 5 showing transverse sections of kidney tissue from all experimental groups. In Fig. (5a, 5b) normal structure is evidenced, with normal appearance of glomerulus in control and curcuma-fed rats respectively. Chromium treated rats (Fig. 5c) section shows vascular congestion (asterisks), large Bowman's space (arrowheads), as well as segmental glomerular necrosis (arrows). In contrast, curcuma supplementation in treated rats (Fig. 5d) shows less renal damage by presenting vascular congestion (asterisks) with normal glomerulus.

Discussion

In our study, it was found that treatment with Cr (VI) increases serum urea and creatinine levels, they are the significant parameters of the glomeruli functional status (Dodiya *et al.,* 2011), resulting in renal damage accompanied by nephrotoxicity (Hojo and Satomi, 1991). These results are in agreement with another study in which renal damage was caused in adult rats and their progeny following exposure to Cr (VI) (Soudani *et al.,* 2011).

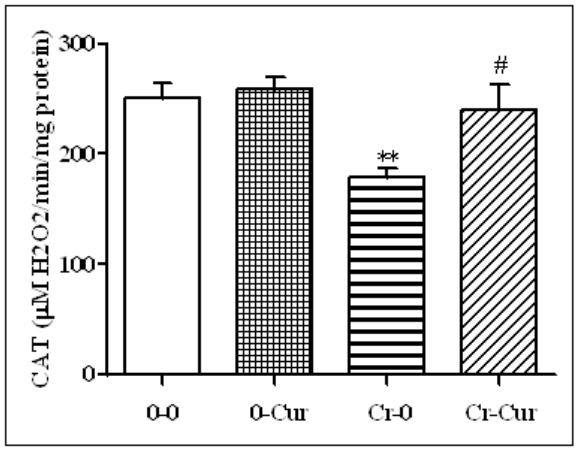

Fig. 2. Catalase activity (µM H_2O_2/min/mg prt) in the four groups of rat's kidney after 30 days of treatment (values represent the mean ± SEM of 8 rats).

** p <0.01; Significantly difference from control (0-0) group

# p <0.05, ## p <0.01, ### p <0.001; Significantly difference from (Cr-0) group

Uric acid, the final product of purine catabolism (Grassi *et al.,* 2013), is known to be a potent antioxidant that scavenges singlet oxygen, oxygen radicals, and peroxynitrite transition metals. However, it is also considered to be a pro-oxidant factor by its pathogenicity (So and Thorens, 2010), hence an association between hyperuricemia and renal damage has been reported by Vargas-Santos and Neogi (2017).

In our study we perceived an increase is the levels of serum uric acid which can be explained by the extreme catabolism of the genome, or probably related to the presence of free radicals generated by Cr (VI).

The present study has also revealed histological changes. According to Shil and Pal (2018), hyperuricemia can impair the histology of renal tissue. In addition, urate can also induce renal damage resulting in endothelial dysfunction (Khosla, 2005) and glomerular morphological changes (Nakagawa *et al.,* 2003). Furthermore, Kelley and Weiner (1978) have reported that the presence of

interstitial nephritis was evident due to the precipitation of uric acid and urates in the interstitial tissue. Thus, we conclude that, all these damages are the result of Cr (VI) accumulation and its toxicity.

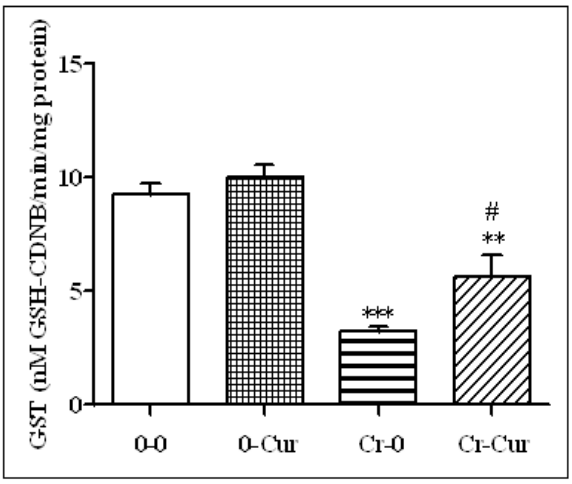

Fig. 3. Glutathione S-transferase activity (nM GSH-CDNB/min/mg prt) in the four groups of rat's kidney after 30 days of treatment (values represent the mean ± SEM of 8 rats).

** p <0.01, *** p <0.001; Significantly difference from control (0-0) group.

# p <0.05; Significantly difference from (Cr-0) group.

Curcuma longa is an important perennial herb, traditionally known for its culinary and medical utility. It appears that curcuma administration causes a significant decrease in uremia and serum creatinine; additionally, it provides nephron-protective effect against free radicals through the induction of antioxidant enzymes (Aggarwal, 2007). Indeed, as stated by Trujillo *et al.* (2013), curcumin possesses a protective effect against nephrotoxicity induced by Cr (VI); this property was related to the prevention of mitochondrial oxidative stress.

In rats, the excessive urinary secretion of proteins is the most sensitive biomarker of renal damage induced by either Cr (VI) intoxication or inhalation of soluble hexavalent chromium trioxide [CrO_3 (VI)]; which results in serum proteins reduction (Gad, 1989; Kumar and Barthwal, 1991; Kim *et al.,* 2004). Likewise, the present study has shown a decrease of total proteins and serum albumin in rats exposed to Cr (VI). According to Julian *et al.* (2009) because of renal damage, some proteins escape into the urine resulting in their serum reduction. On the contrary, a significant increase of total proteins and serum albumin was detected in rats exposed to Cr (VI) and treated with curcuma at the same time. These results are in consonance with other studies that have reported potent effects of curcuma in raising serum proteins and albumin levels, including the study of Attia *et al.* (2017) which revealed significant increases in the total protein levels after administration of different dietary concentrations of curcuma, as well as the study Salama *et al.* (2013) made on *Curcuma longa* rhizome ethanolic extract that ameliorated the total protein and albumin levels. Furthermore, curcumin was found to enhance the levels of albumin and total protein levels under the effect of bioactive phytoconstituents (Sreepriya and Bali, 2005).

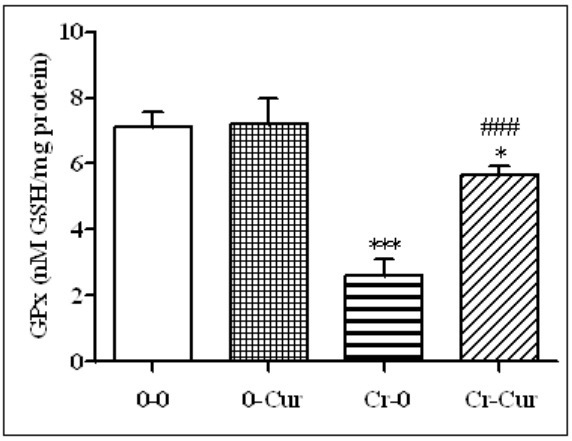

Fig. 4. Glutathione peroxidase activity (nM GSH/mg prt) in the four groups of rat's kidney after 30 days of treatment (values represent the mean ± SEM of 8 rats). * p <0.05, *** p <0.001; Significantly difference from control (0-0) group.

p <0.001; Significantly difference from (Cr-0) group.

Previous studies have demonstrated that the administrated Cr (VI) is rapidly reduced in order to generate free radicals such as superoxide, nitrogen species like peroxynitrite, nitric oxide and hydroxyl, causing an imbalance in oxidative stress system (Silbergeld *et al.,* 2000).

The protection of the cells against the damage induced by oxidative stress can be achieved through non-enzymatic and enzymatic antioxidant (Saka and Aouacheri, 2017). In the present study,

administration of Cr (VI) decreased renal glutathione levels which can be explained by the intense defense of the cell against the toxic actions of free radicals (Aouacheri *et al.,* 2015), or to the consumption of GSH in the Cr (VI) reduction process into Cr (III) that presents lower toxicity. This reduction is mediated by non-enzymatic antioxidants such as ascorbate, one of the most effective biological reductant of Cr (VI), as wells as the reactions with cysteine and GSH (Venter *et al.,* 2017).

Enzymatic antioxidants are essential for protection against damage caused by free radicals (Gutteridge, 1995). Catalase and glutathione peroxidase are the major enzymatic antioxidants that contribute in the reduction of hydrogen peroxide (H_2O_2).

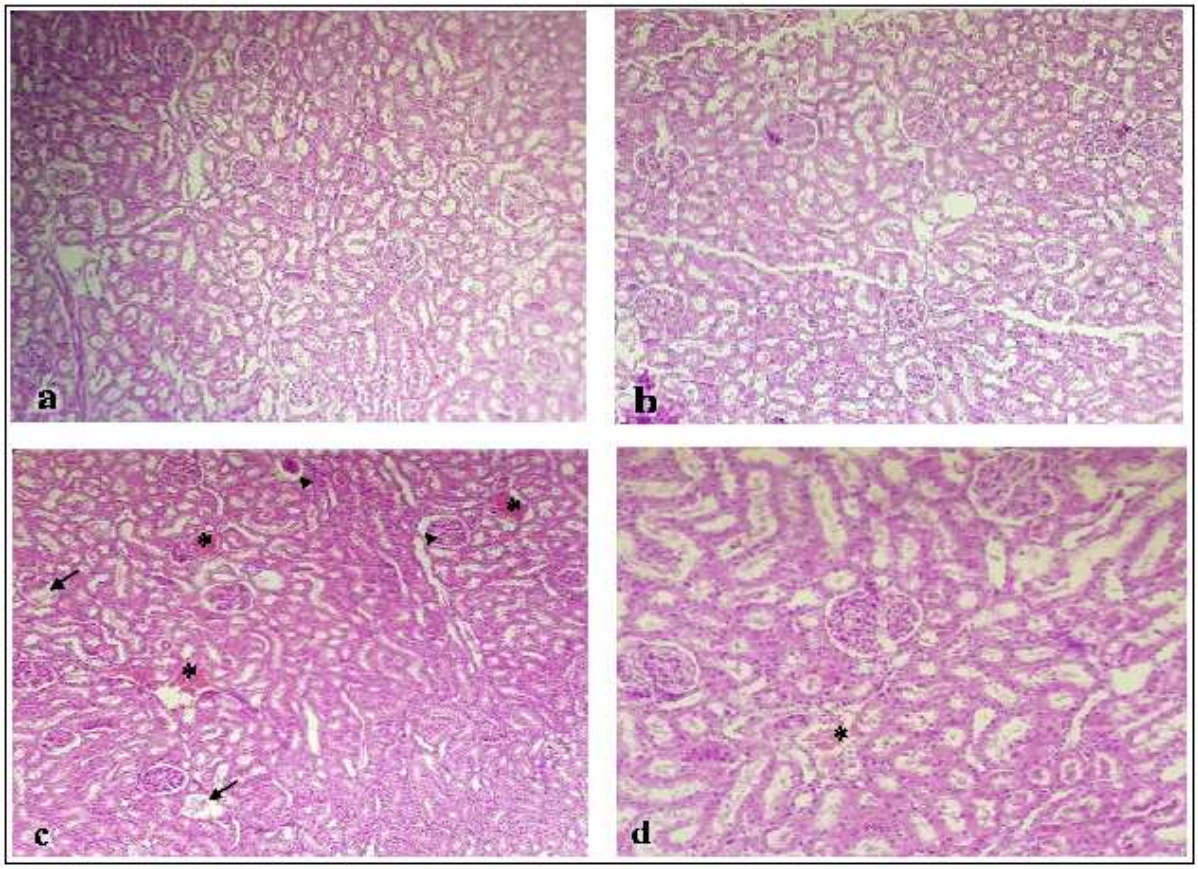

Fig. 5. Histological sections of rat's kidney in control (0-0) and treated rats (0-Cur, Cr-0, Cr-Cur) after 30 days of treatment. Optic microscopy (×200, H&E).

The latter's intracellular accumulation, as well as the one of superoxide anions in renal tissue lead to the decrease of both CAT and GPx activities. Similarly, low levels of GSH causes decline of glutathione S-transferase activity (Sahu *et al.,* 2014). However, another study on rats suggests that the enzymatic activity of CAT was suppressed by Cr (VI) treatment (Boşgelmez and Güvendik, 2004).

It has been clearly demonstrated, in our study, that curcuma treatment improves the renal damage caused by oxidative stress. Pretreatment with curcumin attenuated the structural and functional kidney damage along with preventing mitochondrial oxidative stress, thus curcumin prevents the decrease in the antioxidant enzyme activities. (Trujillo *et al.,* 2013). Besides, other study suggested that treatment with curcumin at doses of 10 and 20 mg/kg restores the activity of antioxidant enzymes, and normalizes the level of GSH and lipid peroxidation in renal tissue of rats (Nabavi *et al.,* 2012). These protective properties of curcumin were assigned to its conjugated structure which includes two methoxylated phenols and one enol form of β-

diketone (Abdel-Moneim *et al.,* 2015) as it gives curcumin the capacity to be a free radical scavenger as well as to enhance the activities of other antioxidant enzymes, such as SOD, CAT and GPx (Agarwal *et al.,* 2010).

Conclusion

In conclusion, the data of the current study demonstrate that rats' supplementation with *Curcuma longa* attenuates the renal dysfunction induced by Cr (VI). Our findings provide evidence that supports the benefits of *Curcuma longa* in improving the biochemical and the histological changes in rats treated with chromium, resulting from its free radicals scavenging properties. Therefore, this medicinal herb can be an alternative natural therapy for the treatment of kidney disease caused by chromium injury.

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Conflict of Interests

The authors report no conflict of interests.

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