

Research Article

# Protective effects of curcumin against naproxen-induced mitochondrial dysfunction in rat kidney tissue



Zahra Azizaram<sup>1</sup>, Ismael Bilal<sup>2</sup>, Yuan Zhong<sup>3</sup>, Azzadin Kamal Mahmud<sup>2</sup>, Mohammad Reza Roshandel<sup>4\*</sup>



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## ABSTRACT

Naproxen is a common analgesic and antipyretic medication that is widely used around the world. This medicine at high doses leads to liver and kidney necrosis in humans and animals. The mechanism of kidney damage, unlike liver damage, is not well understood and is one of the most common causes of emergency department patients. Therefore, in the present study, the protective effect of curcumin, a compound derived from turmeric, was investigated on renal damage caused by naproxen. For this purpose, 25 male Wistar rats were selected and were randomly divided into five groups. Naproxen was dissolved in a 5% dimethyl sulfoxide (DMSO) solution and was injected intraperitoneally at 1000 mg/kg of animal weight. Also, curcumin was dissolved in 5% DMSO and was injected within peritoneum at a dose of 200 mg/kg of animal weight into the relevant groups. After 24 hours of injection, rats were bled and plasma urea and creatinine levels were measured. The rate of lipid peroxidation, the activity of superoxide dismutase and catalase in the kidney, total plasma antioxidant capacity, and PGC-1 $\alpha$  gene expression were measured. The results showed that naproxen significantly increased the levels of biochemical markers of urea and creatinine in plasma and lipid peroxidation in the kidney; also, it decreased the activity of the antioxidants enzymes. The use of curcumin in naproxen-exposed groups significantly reduced the concentrations of urea, creatinine, and lipid peroxidation. Curcumin increased the activity of catalase, superoxide enzymes, and the total antioxidant capacity of plasma. Also, curcumin increased the expression of the PGC-1 $\alpha$  gene, which reduces the effects of naproxen. Therefore, according to the current study results, curcumin could significantly reduce the harmful effects of naproxen on the kidneys. However, in future studies, the effect of curcumin should be evaluated on the naproxen mechanism in the treatment of those patients who need naproxen.

## 1. Introduction

Naproxen is a medicine used to relieve mild to moderate pain caused by menstrual cramps, inflammatory diseases such as rheumatoid arthritis and fever [1]. It is also used to reduce pain, swelling and stiffness in joints caused by osteoarthritis. It is a non-

steroidal anti-inflammatory drug (NSAID) [2]. Regular naproxen and naproxen sodium are two types of prescription naproxen. Naproxen sodium works faster than regular naproxen [3]. Naproxen works in both fast and delayed forms. Delayed naproxen is a delayed or prolonged form of the effect of naproxen, which lasts longer and is used only to treat

<sup>1</sup> Research and Development Department, Giga Biotics, San Diego, California, USA

<sup>2</sup> Department of Nursing, College of Nursing, Hawler Medical University, Erbil, Iraq

<sup>3</sup> Department of Mathematics, Zhejiang Chinese Medical University, Zhejiang, China

<sup>4</sup> Department of Urology, Icahn School of Medicine, Mount Sinai Hospitals, NY, USA

\*Corresponding Author: Mohammad Reza Roshandel ([reza.roshandel@mountsinai.org](mailto:reza.roshandel@mountsinai.org))

chronic diseases such as osteoarthritis or ankylosing spondylitis [4]. These forms of naproxen will not work fast enough to treat acute pain. Naproxen works by reducing the levels of prostaglandins [5].

Prostaglandins are a group of physiologically active lipid compounds that play a key role in pain, fever, and inflammation [6]. The body produces them at the site of damaged tissue. They cause redness, heat, swelling, and pain. Therefore, if the concentration of prostaglandin decreases, inflammation, pain and fever will decrease [7]. But blocking prostaglandins by naproxen may reduce blood flow to the kidneys, which means lack of oxygen to keep the kidneys alive. This can cause acute kidney damage [8].

Many studies have shown that kidney dysfunction is highly related to metabolic changes in the kidney [9]. For example, changes in PGC-1 $\alpha$  gene expression through genetic or pharmacological intervention can impair renal function [10]. Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1 $\alpha$ ) is a transcriptional coactivator, and it regulates glucose and lipid metabolism, mitochondrial biogenesis, and peroxisomal biogenesis [11]. Naproxen reduces PGC-1 $\alpha$  gene expression by reducing oxygen delivery to the kidneys [12].

Due to the detrimental effects of naproxen on kidney tissue, the use of new drugs or protective compounds, especially natural antioxidants derived from plants, is really important [13]. Several studies showed that various compounds such as vitamins E, C, and melatonin have prevented liver and kidney damage caused by naproxen [13-15]. Curcumin, which is one of the active ingredients of the turmeric plant, is a member of the ginger family (Zingiberaceae) which protective effects on the liver have been identified [16]. In addition to its antioxidant properties, curcumin also has anti-inflammatory properties [17]. Therefore, it seems that this substance can have a better effect than other antioxidants against naproxen. Hence, in this study, the protective effects of curcumin were considered against naproxen-induced mitochondrial dysfunction in rat kidney tissue.

## 2. Materials and methods

### 2.1 Rat treatment

This study was performed on 25 male Wistar rats with a weight range of 200 $\pm$ 25 g and an age of 8 weeks. The animals were exposed to 12 hours of light and 12 hours of darkness, food, and water. Naproxen (Sigma-Aldrich, USA) was dissolved in 5% dimethyl sulfoxide solution (DMSO) and was injected through the peritoneum at a dose of 1000 mg/kg of animal weight. Also, curcumin (Sigma-Aldrich, USA) was dissolved in 5% dimethyl sulfoxide solution (DMSO) and was injected within peritoneum at a dose of 200 mg/kg of animal weight into the relevant groups. The dose selection of naproxen and curcumin was performed based on previous studies [18].

The animals were randomly divided into 5 groups. There were 5 rats in each group. The first group was the control group. The second group was the naproxen injection group. The third group was first injected with naproxen, and then 30 minutes after naproxen injection, they were injected with curcumin. The fourth group received only curcumin injection. The fifth group was the vehicle group injected with DMSO.

After 24 hours of injecting the animals, blood was collected from the inferior vena cava with the help of a heparin syringe and transferred to a test tube. The samples were centrifuged at 3500 rpm for 10 minutes at 4°C and the plasma was separated and transferred to -70°C. The kidneys were immediately rinsed with 0.9% cold saline solution after surgery. They were then cut into pieces, placed on a strainer to dry, and finally weighed.

### 2.2 Assessment of lipid peroxidation products

Four mg of homogenized tissue was used in a ratio of 1: 4 of 0.01 M phosphate buffer (pH = 7), then, 0.2 ml of sodium dodecyl sulfate 8.1% was added. 1.5 ml of 20% acetic acid (pH = 3.5) and 1.5 ml of 0.8% thiobarbituric acid were added. Finally, the mixture was diluted with 1 ml of distilled water and heated at 95°C for 2 h and then centrifuged. The adsorption of the top layer

after centrifugation was then read at 532 nm. The amount of malondialdehyde was determined using a molar extinction coefficient ( $1.56 \times 10^5 \text{ mmol/cm}$ ) [19].

### 2.3 Superoxide dismutase activity

The activity of the superoxide dismutase (SOD) enzyme was measured according to McCord & Fridovich method [20]. First, to measure activity, a sufficient amount of xanthine oxidase (without the presence of homogeneity containing S enzyme) was poured into the well containing the reaction mixture of 0.001 mM ferricytochrome c 0.005 mM xanthine. Enzyme activity was measured for 2 minutes at a wavelength of 550 nm (an absorption range of 0 to 0.1) to obtain the amount of xanthine oxidase enzyme required to produce  $\Delta OD = 25 \text{ mAbs / min}$ . After calculating the unit in each sample, by dividing it by the amount of protein in 50  $\mu\text{l}$  homogeneity, the specific activity of SOD was calculated in terms of U/mgr pro.

### 2.4 Catalase activity

In the obtained homogeneity, the degradation of  $\text{H}_2\text{O}_2$  and the reduction of adsorption for 15 seconds at 240 nm by the enzyme catalase in a mixture containing 50 mM phosphate buffer with  $\text{pH} = 7$  and 10 mM hydrogen peroxide can be carried out directly by Abei (1983) method [21]. In this study, a constant velocity relative to the amount of tissue weight (K/gr tissue) was used as the specific activity of the catalase enzyme.

$$K = (2.3/\Delta t) (\text{Log}A1/A2)$$

$$K = (2.3/15) (\text{Log}A1/A2)$$

$$K = 0.153(\text{Log}A1/A2)$$

### 2.5 Measurement of plasma antioxidant capacity

Plasma antioxidant capacity was measured by the FRAP method using the TPTZ reagent. This method evaluates the ability of antioxidants in plasma to reduce the complex  $\text{Fe}^{3+}$ -TPTZ (ferric-tripiridyltriazine) to ferrous ions ( $\text{Fe}^{2+}$ ) and to absorb light at 593 nm. In this reaction,  $\text{Fe}^{3+}$  is converted to  $\text{Fe}^{2+}$  -TPTZ by binding to TPTZ in the presence of plasma antioxidant factors. The amount of FRAP is obtained by plotting the standard adsorption

curve versus the concentration of ferrous ions in the standard solution by  $\mu\text{M/l}$  [22].

### 2.6 Measurement of protein amount

Measurement of protein was performed as standard in tissue homogeneity using Bradford reagent and bovine albumin serum (BSA). After preparing solutions of 1000, 800, 600, 400, 200, and 100  $\mu\text{M/ml}$  proteins, the adsorption was read at 595 nm after 20 minutes of adding 2.5 ml of 0.01% Bradford reagent with 5% ethanol and 10% phosphoric acid in a test tube containing 100  $\mu\text{l}$  of BSA. The concentration of proteins in tissue homogeneity was calculated by using a standard curve and comparing the absorption of tissue homogenates [23]. Plasma urea and creatinine levels were also assessed by Creatinine Urinary Detection Kit (Thermo Fisher Scientific, USA).

### 2.7 PGC-1 $\alpha$ gene expression

RNA extraction was performed using the Total RNA kit (Thermo scientific, USA). The steps were performed according to the kit instructions. DNase kit was used to clean the DNA. Finally, a nanodrop device with a wavelength ratio of 260/280 in the range of 1.9-2.1 was used for measuring RNA concentration. Then, cDNA was synthesized using oligo DT primers and a cDNA synthesis kit (Takara Bio Inc., Japan) according to the instructions of the kit. The obtained cDNA was then stored at  $-70^\circ\text{C}$ .

Real-time PCR was done for PGC-1 $\alpha$  and GADPH (as housekeeping gene) by Rotor-Gene™ 6000 Series (Corbett Life Science, UK) and SYBRGreen PCR Master Mix (Amplicon, UK). PCR reaction for these genes was performed according to the following program. The reaction mixture was first heated at  $96^\circ\text{C}$  for 3 minutes for the first denaturation, and then 35 cycles of denaturation were done at  $96^\circ\text{C}$  for 30 seconds. It was then put at  $59^\circ\text{C}$  for 30 seconds for annealing and at  $72^\circ\text{C}$  for 43 seconds. Finally, it was put at  $72^\circ\text{C}$  for 5 minutes. Primer sequences of genes used in Real-Time PCR analysis are listed in table 1.

**Table 1.** Primer sequence of GAPDH and PGC-1 $\alpha$  genes used in Real-Time PCR analysis

Gene	Sequence	Product length (bp)
GAPDH	F(5'-CACCATCCGGTTCCTATAA-3')	44
	R(5'-GAATTTGCCGTGAGTGGAGT-3')	
PGC-1 $\alpha$	F(5'-TGACATGGATGTTGGGATTG-3')	176
	R(5'-TGAGGACCGCTAGCAAGTTT-3')	

## 2.8 Statistical Analysis

The results of quantitative variables were obtained as Mean  $\pm$  SD. After testing the normality of the data by Kolmogorov-Smirnov (KS) test, the test of variance uniformity was used to compare the experimental groups with the control groups by Levene's test. T student test and non-parametric Mann-Whitney U-test were used to evaluate the comparison of means related to the curcumin effect. Spearman correlation coefficient was used to examine the relationship. All tests were performed by SPSS 16 software ( $P < 0.05$ ).

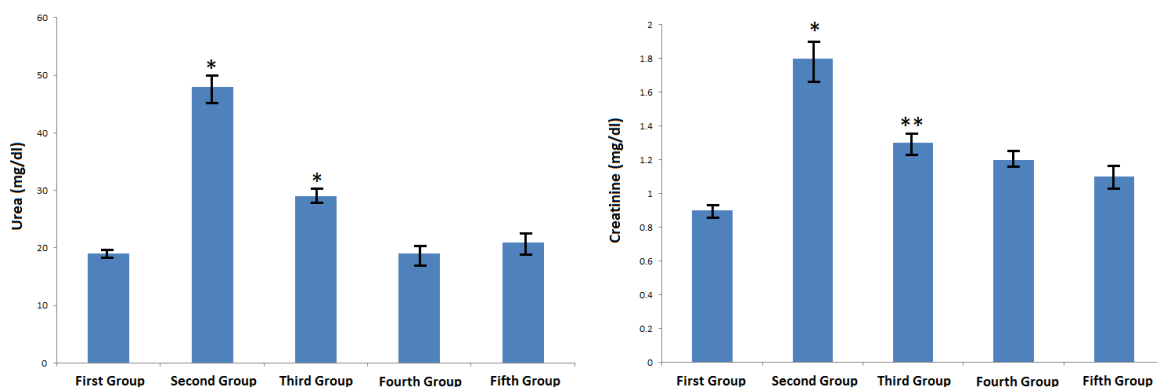
The data obtained from Real-time PCR, which was in the form of ct, were converted to ct $\Delta\Delta$  by Excel software. Formula  $2^{-\Delta\Delta ct}$  was used to quantify the values. The required

statistical data were collected by SPSS 16 software and analyzed with  $P < 0.05$  as a significant level. After making sure that the distribution of research variables was normal, a two-way ANOVA statistical test was used.

## 3. Results

### 3.1 Effect of curcumin on plasma urea and creatinine

Intraperitoneal injection of naproxen resulted in elevated plasma urea and creatinine compared to the control group ( $P < 0.0001$ ). By injecting curcumin 30 minutes after naproxen injection and sampling after 24 hours the amount of urea decreased by 43% and plasma creatinine decreased due to the antioxidant protective effects of this compound ( $P < 0.0001$ ) (Figure 1). The first group was the control. The second group was the naproxen injection group. The third group was first injected with naproxen, and then 30 minutes after naproxen injection, they were injected with curcumin. The fourth group received only curcumin injection. The fifth group was the vehicle group injected with DMSO.



**Fig. 1.** Plasma urea and creatinine concentrations in different experimental groups; \* means  $P < 0.05$ , \*\* means  $P < 0.01$

### 3.2 The effect of curcumin on changes in the activity of antioxidant enzymes and lipid peroxidation in renal tissue

Figure 2 shows that injection of naproxen significantly reduced the activity of superoxide dismutase and catalase enzymes in renal tissue compared to the control group. The use of curcumin can increase the activity of superoxide dismutase by 45% and catalase

by 33% in kidney tissue. The first group is normal control. The second group is the naproxen injection group. The third group is first injected with naproxen, and then 30 minutes after naproxen injection, they were injected with curcumin. The fourth group received only curcumin injection. The fifth group is the vehicle group injected with DMSO.

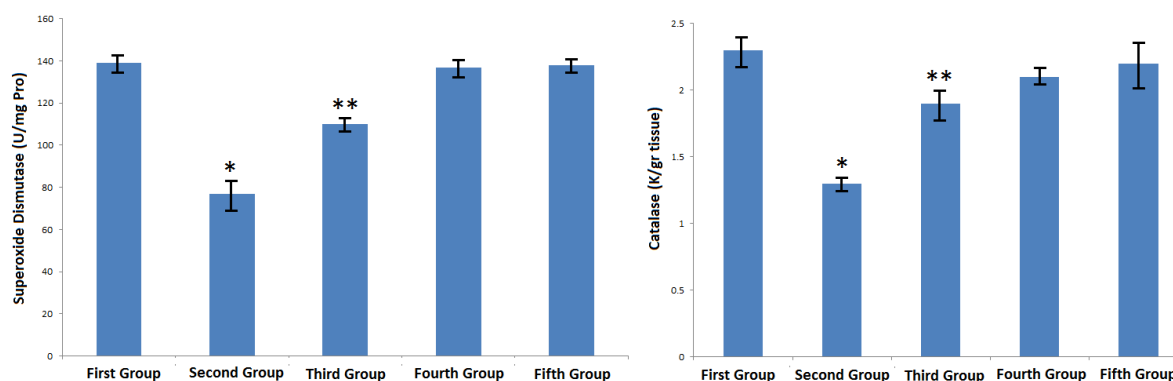


Fig. 2. Renal tissue superoxide dismutase and catalase activity in different experimental groups; \* means  $P < 0.05$ , \*\* means  $P < 0.01$

The results of plasma FRAP measurement showed that the use of curcumin increased the rate of this factor from  $321.82 \pm 27.03$  (in the second group) to  $695.17 \pm 21.12$  (in the third group) (Figure 3).

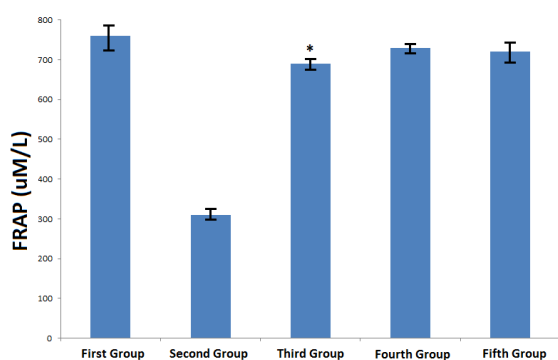


Fig. 3. Plasma FRAP level in different experimental groups; \* means  $P < 0.05$

The intensity of lipid peroxidation was significantly increased in rat kidney tissue when they were exposed to naproxen compared to the control group. Administration of curcumin 30 minutes after naproxen injection was able to reduce the intensity of lipid peroxidation in renal tissue by 45% (Figure 4).

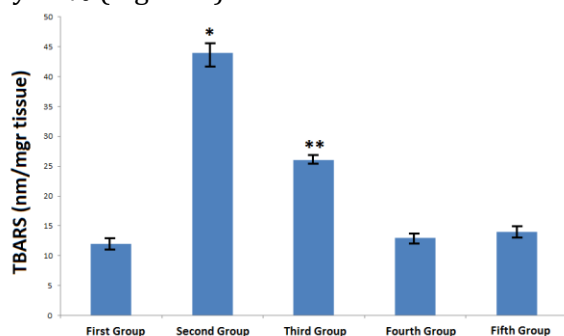


Fig. 4. Renal tissue TBARS in different experimental groups; \* means  $P < 0.05$ , \*\* means  $P < 0.01$

### 3.3 PGC-1 $\alpha$ gene expression

According to the results obtained in this section, naproxen reduced the expression of the PGC-1 $\alpha$  gene. But as expected, curcumin was able to positively affect the expression of the PGC-1 $\alpha$  gene and increase it significantly (Figure 5).

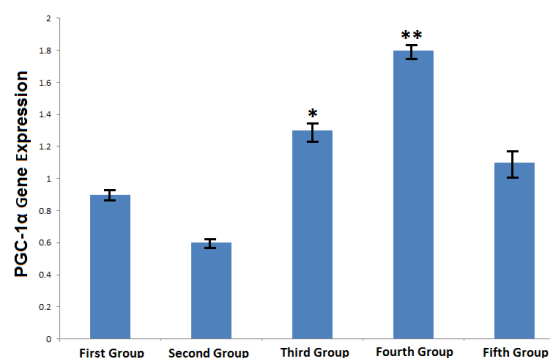


Fig. 5. Changes in PGC-1 $\alpha$  gene expression between study groups; \* means  $P < 0.05$ , \*\* means  $P < 0.01$

### 4. Discussion

Naproxen overdose poisoning is one of the most well-known causes of liver and kidney damage, and toxic metabolites produced in the liver and other organs are known to be the main mechanism of this toxicity [24]. As noted in the results part, in order to investigate the protective effects of curcumin on nephrotoxicity caused by naproxen administration, urea and creatinine were evaluated as functional markers. Figure 1 shows a significant increase in these two markers in experimental animals after naproxen administration. This indicates impaired renal function and improvement following curcumin injection. In kidney



disease, urea accumulation is due to decreased clearance. This happens when the plasma produces urea, but the kidneys cannot get rid of it. Elevated plasma creatinine also occurs when nephrons are damaged. Numerous studies have shown that the use of naproxen in therapeutic doses reduces renal blood flow, glomerular filtration rate, sodium secretion, and prostaglandin E2 in rats and humans [25-27]. Administration of high doses of naproxen (10-15 g/day) is associated with acute toxicity, necrosis, and proximal tubular damage [27].

Due to the antioxidant properties of curcumin, it collects, neutralizes, and scavenges free radicals, thereby inhibiting oxidative enzymes such as cytochrome P450 [28]. This compound also prevents oxidative reactions from occurring by chelating metal ions (such as iron) and prevents their oxidative properties from occurring [17]. There are reports of inhibition of the production of superoxide anion and hydroxyl radicals by curcumin through  $\text{Fe}^{2+}$  oxidation in the Fenton reaction [29]. It is believed that the antioxidant properties of curcumin are due to its beta-ketone domain and the formation of relatively stable radicals due to the structure of its double-conjugated bonds [30]. The role of hydroxyl radicals in the onset and progression of nephrotoxicity has been demonstrated.  $\text{H}_2\text{O}_2$  and superoxide anion are involved in the metabolic activation of naproxen. This causes a decrease in glutathione and subsequent cell damage [31]. The products of these reactants are enhanced by cellular macromolecules such as DNA, proteins, and lipids [32]. As shown in the results part of the study, TBARS significantly increased in rats exposed to naproxen compared to the control group and decreased significantly when using curcumin. Increasing the amount of TBARS as an indicator of lipid peroxidation indicates the severity of damage caused by naproxen [33].

Various studies have shown that the use of naproxen in rats reduces the activity of the SOD enzyme, which is responsible for collecting superoxide ions and converting them to hydrogen peroxide [33]. The activity of the catalase, which is involved in the removal of hydrogen peroxide, is also

associated with a decrease. These results are similar to ours, emphasizing the production of oxidative stress and reduced activity of these enzymes when taking acetaminophen and naproxen [34]. On the other hand, other studies have shown that despite increasing the amount of malondialdehyde, as a marker of lipid peroxidation in renal tissue homogeneity, the activity of catalase increases and the activity of glutathione peroxidase decreases, but Curcumin decreases catalase activity and increases glutathione peroxidase activity [35]. Since the factors that produce or counteract oxidative stress are interacting with each other, their separate measurement in some cases gives contradictory results that justify these differences in the pattern [36]. Therefore, by measuring all the antioxidants in the plasma with the help of methods such as FRAP, the general condition can be observed and investigated [37].

The FRAP results obtained in this study show positive overall changes and enhancement of effective plasma antioxidant system factors such as total protein, bilirubin, uric acid, etc. By examining these factors in future studies, valuable information can be obtained on the coping mechanisms of this toxicity. On the other hand, these contradictory results in various studies indicate the complexity of metabolic pathways in terms of toxicity in method, time and dose of drug administration, as well as antioxidants used *in vivo* and *in vitro*. Therefore, it is suggested that other supplementary studies be performed in order to achieve a better understanding of these cases [30, 34].

Regarding the expression of the PGC-1 $\alpha$  gene, studies have shown that exposure to a high level of naproxen causes the loss of crystals and mitochondrial defects, and sometimes causes mitochondrial collapse [38]. These indicators indicate that mitochondrial function is impaired by naproxen. Therefore, it may also affect PGC-1 $\alpha$  [12]. Because curcumin increases PGC-1 $\alpha$ , it reduces the effects of naproxen on PGC-1 $\alpha$  gene expression [39]. One of the reasons for this is the accumulation of reactive oxygen species (ROS) in the mitochondria, which causes the formation of several physiological

signaling cascades, resulting in mitochondrial dysfunction and the PGC-1 $\alpha$  gene [40].

In general, according to the results of this study and previous studies, curcumin, in addition to its antioxidant properties, has anti-inflammatory properties, so it seems that this substance can have a better effect on naproxen than other antioxidants. But, further studies need to prove this claim.

## 5. Conclusion

In this study, the protective effects of curcumin were investigated on the severity of the renal impairment due to naproxen overdose in 25 rats. In this regard, plasma urea and creatinine levels were evaluated as renal function markers. TBARS has also been used as an indicator of lipid peroxidation products along with catalase, superoxide dismutase and plasma antioxidant capacity as a factor. Also, PGC-1 $\alpha$  gene expression was evaluated as a mitochondrial health factor.

The results showed that naproxen significantly increased the levels of biochemical markers of urea and creatinine in plasma and lipid peroxidation in the kidney; also it decreased the activity of the enzymatic antioxidants. The use of curcumin in naproxen-exposed groups significantly reduced the concentrations of urea, creatinine and lipid peroxidation. Curcumin also significantly increased the activity of catalase and superoxide enzymes and in particular the total antioxidant capacity of plasma. Also, curcumin increased the expression of the PGC-1 $\alpha$  gene, which this increasing reduces the effects of naproxen.

Therefore, according to the current study results, curcumin could greatly reduce the harmful effects of naproxen on the kidneys. However, in future studies, the effect of curcumin should be evaluated on the naproxen mechanism in the treatment of those patients who need naproxen.

## Conflict of interest

None of the authors have any conflict of interest to declare.

## Consent for publications

All authors approved the final manuscript for publication.

## Availability of data and material

The authors have embedded all data in the manuscript.

## Authors' contributions

**Z.A.** designed the idea, helped for doing, helped in data analysis, and article drafting, **I.B.** helped for doing and helped in sampling and data collection, **Y.Z.** helped in data collection and Writing Manuscript, **A.K.M.** helped in sampling and data collection, and **M.R.R.** helped in study design, sampling, data collection, doing, and article drafting.

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## Ethics approval and consent to participate

This study design was approved by ethical code IRAKMU.AH.REC.1397.3232 in the research unit. Also, consent forms were completed for all participants.

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