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Original Article

# The Effects of Curcumin on Inflammatory and Oxidative Stress Biomarkers in Pediatric Patients on Regular Hemodialysis: A Randomized Placebo-controlled Trial

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**ABSTRACT**

**Aim:** Curcumin is a Chinese plant known for its anti-inflammatory, antioxidant, and anti-tumour activity. Its efficacy and safety in children with end-stage renal disease (ESRD) have not yet been established. This study aimed to evaluate curcumin's effects on inflammatory and oxidative stress biomarkers in children on regular hemodialysis (HD), and to investigate the effects of curcumin supplementation in children with ESRD undergoing regular HD.

**Materials and Methods:** This randomized, placebo-controlled, double-blind, pilot study was conducted on 28 children with ESRD on regular HD. This study was conducted between March 2022 and December 2022 at a pediatric HD unit. The patients were randomly assigned to either one gram of curcumin (the active group) or a starch-based placebo once a day (the placebo group), with both groups having 14 patients. Patient history, organ function assessment, tumor necrosis factor (TNF) as an inflammatory biomarker, malondialdehyde (MDA) as an oxidative stress factor, and coagulation biomarkers such as prothrombin time, partial thromboplastin time, and international normalized ratio were assessed and followed for 6 months.

**Results:** At 3 months, the curcumin group showed a significant reduction in MDA levels when compared to the placebo group (median 4.97 vs. 13.60 nmoL/mL, p=0.001). TNF-α levels had declined significantly within the curcumin group at 6 months (p=0.030). A significant decrease in uric acid levels was also observed at 3 months in the curcumin group (p=0.008). Hemoglobin levels showed a modest but statistically significant increase at 6 months (p=0.0232). No significant changes were noted in high sensitivity C-reactive protein, estimating glomerular filtration rate, creatinine, alanine transaminase, or coagulation parameters when compared to the placebo.

**Conclusion:** Curcumin may have potential benefits in pediatric patients on HD due to its considerable effects in decreasing inflammatory as well as oxidative stress biomarkers.

**Keywords:** Curcumin, chronic kidney diseases, hemodialysis, inflammatory biomarkers, pediatrics

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## Introduction

Curcumin or Turmeric is a natural Chinese plant known for its anti-inflammatory, antioxidant, and anti-tumour activity. The chemical structure of curcumin is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione and it has shown substantial biological activity in treating several diseases (1). The root tuber of Curcuma Aromatica Salisb and the rhizome of Curcuma longa L. (Zingiberaceae) have proven efficacy in improving blood circulation and eradicating blood stasis (2,3). The anti-inflammatory activity of curcumin occurs by inhibiting the differentiation of myeloid protein 2-Toll-like receptor 4 co-receptor pathways, proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-alpha), nuclear factor kappa-B, and interleukin (IL)-1beta, or by the activation of peroxisome proliferator-activated receptor-gamma (4).

Pediatric chronic kidney disease (CKD) is an irreversible decline in renal function which progressively moves towards end-stage renal disease (ESRD) (5). Some European countries recommend hemodialysis (HD) for children older than 3 years (6). The global prevalence of CKD in children and adolescents has been increasing between 1990 to 2019. Furthermore, the age-standardized prevalence rate of CKD in children and adolescents increased globally, with an average annual percentage change of 0.46% (7). The prevalence of pediatric CKD ranges from 55-60 to 70-75 pmarp in some European countries (8). The global burden of CKD disease in Egyptian children under 18 years of age on HD increased by 2% in 2017 (9).

The efficacy and safety of curcumin in adult patients with renal diseases have been demonstrated and a significant impact on reducing the inflammatory and antioxidant biomarkers has been noted (10-14). However, there was a lack of literature on assessing its efficacy or safety in pediatric populations (12,15). Accordingly, this study aimed to evaluate the effects of curcumin supplements on inflammatory and oxidative stress biomarkers in pediatric ESRD patients who were being treated with regular HD.

## Materials and Methods

### Study Design and Participants

This randomized, placebo-controlled, double-blind, pilot study was conducted on 28 children with ESRD on regular HD. This study was conducted between March 2022 and December 2022 in a single Pediatric Hemodialysis Unit. Ethical approval for this study was obtained from the Research Ethics Committee of the Ain Shams University Faculty of Medicine (approval number: FMASU MD 181/2021, date: 15.09.2021). Written informed consent was obtained from the parents or caregivers of the participants after explaining the study aim and procedures, with their right to withdraw from this study at any time agreed upon in advance. Furthermore, the confidentiality of the patients' information obtained during this study was guaranteed.

The patients were randomly assigned to either a curcumin group (the active group) or a starch-based placebo group, each consisting of 15 patients, using a simple randomization technique performed by a free online random sample allocator available at GraphPad. Those patients with the following criteria were included: aged between 10 and 18 years of both genders, patients weighing at least 30 kilograms (as accepted for the dosing of available capsules of the supplement), patients with ESRD receiving regular HD for at least 6 months before enrollment, and patients whose parents or legal guardians agreed to sign a written informed consent for study participation. Patients were excluded if they had bleeding disorders, chronic liver disease, diabetes mellitus, or any autoimmune diseases. In addition, patients were excluded if they had been receiving corticosteroids, immunosuppressants, antioxidant supplements, including vitamin E, ascorbic acid, omega-3 fatty acids, or L-carnitine within a 3-month period before study enrollment. Those patients who demonstrated bleeding signs or symptoms as a side effect during the curcumin administration course were immediately excluded from this study and were followed up until full recovery.

### Procedures and Assessment of Variables

The patients enrolled in this study had three HD sessions weekly, where each session lasted for 3-4 hours. Hemodiafiltration mode was used at least once a week when available. High-flux filters were used during the dialysis sessions. Regarding dialysis access, the majority of the enrolled patients either had fistulas in their arms or Mahurkar catheters. The patients in the curcumin group received a one-gram capsule of curcumin one time per day for 3 consecutive months. The curcumin was in the form of hard gelatin capsules manufactured by Puritan's Pride, Inc., Ronkonkoma, NY 11779 USA. The patients in the placebo group received hard gelatin capsules containing starch with the exact colour of the curcumin capsules provided by Jedco International Pharmaceuticals Company, Cairo, Egypt, once daily for 3 consecutive months. The patients were instructed not to include any curcumin in their food throughout the study period. The selected dose of 1 g/day was chosen as a conservative, well-tolerated regimen based

on previous adult studies on curcumin effectiveness and safety. Our patients were enrolled only if weighing ≥30 kg in order to ensure an appropriate mg/kg exposure range, while maintaining a once-daily schedule in order to support adherence and reduce pill burden (16).

Clinical and laboratory assessments were conducted at baseline, after three months of supplementation, and after six months (three months after supplementation ended) in order to evaluate the relatively longer effects of curcumin. Detailed history regarding previous and/or concurrent medications was collected so as to exclude any interactions with curcumin. Demographic data, presenting symptoms, age of onset, duration of the disease, the etiology of CKD, symptoms of volume overload, symptoms of uremia, heart failure, and any history of bleeding were also recorded. Clinical examination included general examination and blood pressure measurement. Signs of anemia, such as pallor, and tachycardia, and bleeding tendency, such as ecchymotic patches or bleeding from orifices, were recorded.

Laboratory investigations were performed by withdrawing 3-5 mL of venous blood samples once from all patients before the first HD session of the first week at baseline, at 3 months, and at 6 months in order to measure the following: complete blood picture, prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT). Urea, creatinine, uric acid, serum alanine transaminase (ALT), and albumin were all tested. The anti-oxidant malondialdehyde level (MDA-SunRed® Biotechnology Catalog No. 201-12-1372) was measured using ELISA. Levels of anti-inflammatory markers, including (TNF-alpha-SunRed® Biotechnology-Catalog No. 201-12-0083) and high sensitivity C-reactive protein (hs-CRP-SunRed® Biotechnology catalog no. 201-121-1806) were also measured by the ELISA technique. The estimated Glomerular Filtration Rate (eGFR) was calculated using the creatinine-based equation (17). All anti-inflammatory and anti-oxidant biomarkers were analyzed via the ELISA technique using a Thermo Scientific Multiscan FC photometer. Study progress and patient compliance were reviewed regularly during medication dispensing every two weeks. Blood samples were collected only when the patients were clinically stable and had been free of any signs or symptoms of acute infection in the week before sampling. The number of capsules was reviewed, and a supply for another two weeks was provided to the patients.

### Statistical Analysis

Data were managed and analyzed using SPSS V.28 (IBM Corp., Armonk, NY, USA). Data were either summarized using means and standard deviations in quantitative data or using frequencies and percentages for categorical data. Comparisons between groups were carried out using the Student's t-test for normally distributed variables, while the Mann-Whitney U test was used for non-parametric variables. For comparisons of serial measurements within each group, repeated measures ANOVA was used in normally distributed quantitative variables, while non-parametric Friedman and Wilcoxon signed-rank tests were used for non-normally distributed quantitative variables. In order to compare categorical data, a chi-square ($X_2$) test was performed. The exact test was used instead when the expected frequency was less than 5. A p value of less than 0.05 was considered statistically significant.

## Results

### Demographics and Clinical Characteristics

The curcumin group had an equal gender distribution, whereas the placebo group consisted of 28.6% females (p=0.246). The average age was slightly lower in the curcumin group (p=0.070). At baseline, there were no significant differences in weight (p=0.131) or height (p=0.256). After three months of treatment, there there was a slight but statistically insignificant reduction in SBP among both groups (p=0.233). Diastolic blood pressure remained unchanged between the groups (p=1.0). Hemoglobin levels in the curcumin group exhibited a non-significant rise compared to a decrease in the placebo group (p=0.223). Atrophic kidneys and familial/metabolic nephritis were the most common etiologies of ESRD in the study population (Table I).

### Anti-inflammatory and Anti-oxidant Biomarkers

TNF levels were comparable in both groups after three months (p=0.462). However, there was a drop in the median TNF levels in the placebo group from 114.90 ng/L to 61.30 ng/L. Similarly, hs-CRP levels were also comparable after three months (p=0.061). A significant decrease in MDA median in the curcumin group [4.97; interquartile range (IQR): 2.21-6.47] was observed, and was significantly less compared to the placebo group (13.60; IQR: 9.87-18.10) after 3 months (p=0.001). Uric acid levels were also comparable after three months (p=0.644 and 0.093, respectively) (Table II and Figure 1).

### Kidney, Liver Functions, and Coagulation Profile

At baseline, kidney functions, determined by eGFR, creatinine, and urea, were comparable between the two groups (p>0.05). After 3 months of therapy, the difference

**Table I.** Demographic and clinical data at baseline and three months in the curcumin and placebo groups

| | | Curcumin n (%)/Mean (SD) | Placebo n (%)/Mean (SD) | p value |
|---|---|---|---|---|
| **Sex** | **Female** | 7 (50.0) | 4 (28.6) | 0.246 |
| | **Male** | 7 (50.0) | 10 (71.4) | |
| **Age (years)** | | 13.07±1.54 | 14.14±1.46 | 0.070 |
| **Weight (kg)** | | 34.00±7.69 | 30.32±4.34 | 0.131 |
| **Height (cm)** | | 136.43±9.01 | 132.29±9.86 | 0.256 |
| **SBP at baseline (mmHg)** | | 125.71±21.38 | 129.64±12.78 | 0.560 |
| **SBP at 3 months (mmHg)** | | 120.71±10.72 | 125.00±7.60 | 0.233 |
| **DBP at baseline (mmHg)** | | 77.14±16.84 | 80.00±7.84 | 0.572 |
| **DBP at 3 months (mmHg)** | | 75.71±10.16 | 75.71±8.52 | 1 |
| **Hb at baseline (gm/dL)** | | 8.89±1.49 | 8.97±1.80 | 0.892 |
| **Hb at 3 months (gm/dL)** | | 9.29±1.35 | 8.57±1.69 | 0.223 |
| **Etiology** | | | | |
| **Focal segmental glomerulosclerosis** | | 1 (3.6) | 1 (3.6) | |
| **Rapidly progressive glomerulonephritis** | | 1 (3.6) | 0 (0.0) | |
| **Lupus nephritis** | | 0 (0.0) | 1 (3.6) | |
| **Familial/metabolic nephritis** | | 3 (10.7) | 4 (14.3) | |
| **Obstructive uropathy** | | 1 (3.6) | 0 (0.0) | |
| **Reflux nephropathy** | | 0 (0.0) | 1 (3.6) | |
| **Hemolytic uremic syndrome** | | 0 (0.0) | 1 (3.6) | |
| **Interstitial nephritis** | | 0 (0.0) | 2 (7.1) | |
| **Atrophic kidney** | | 7 (25.0) | 4 (14.3) | |
| **Unknown** | | 1 (3.6) | 0 (0.0) | |

p value of <0.05 was considered statistically significant
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: Hemoglobin, kg: Kilograms, cm: Centimetres

**Table II.** Comparison of anti-inflammatory, anti-oxidant biomarkers, and kidney functions between the curcumin and placebo groups

| Anti-inflammatory and anti-oxidant biomarkers | | Curcumin Median (IQR)/Mean ± SD | Placebo Median (IQR)/Mean ± SD | p value |
|---|---|---|---|---|
| **TNF (ng/L)** | **At baseline** | 59.20 (52.00-69.50) | 114.90 (61.50-133.50) | 0.280 |
| | **At 3 months** | 59.01 (47.70-74.90) | 61.30 (54.81-166.05) | 0.462 |
| **hs-CRP (mg/L)** | **At baseline** | 2.13 (1.24-2.60) | 4.00 (2.28-4.74) | 0.076 |
| | **At 3 months** | 1.77 (0.92-3.74) | 2.95 (1.78-18.00) | 0.061 |
| **MDA (nmoL/mL)** | **At baseline** | 10.58 (9.26-14.47) | 9.90 (7.18-13.40) | 0.603 |
| | **At 3 months** | 4.97 (2.21-6.47) | 13.60 (9.87-18.10) | 0.001* |
| **Uric acid (mg/dL)** | **At baseline** | 10.23±2.50 | 9.86±1.61 | 0.644 |
| | **At 3 months** | 8.17±2.47 | 9.50±1.43 | 0.093 |

*p value of <0.05 was considered statistically significant
TNF: Tumour necrotizing factor, hs-CRP: High sensitivity C-reactive protein, MDA: Malondialdehyde, IQR: Interquartile range

in kidney function remained insignificant. There was an insignificant difference in liver functions (ALT and albumin) at baseline (p=0.224 and 0.874, respectively) and after three months (p=0.064 and 0.937, respectively). Coagulation profiles, represented by PT, PTT, and INR, were within normal ranges and comparable in both groups at baselines and after three months of therapy (Table III).

**Anti-inflammatory and Anti-oxidants in The Curcumin Group Over Time**

There were no significant changes in TNF levels from baseline to 3 months (p=0.683); however, a significant decrease in median TNF levels was observed after 6 months, compared to the baseline levels (p=0.030). There was a significant decrease in the median MDA levels detected after 3 months (p=0.004) and 6 months (p=0.026). In contrast, no significant changes in hs-CRP levels were observed over the study period in the curcumin group (p=0.778 and 0.638, respectively). Mean uric acid at baseline was 10.23 (±2.50) compared to 8.17 (±2.47) after 3 months in the curcumin group (p=0.008) (Table IV).

**Kidney, Liver Functions, and Coagulation Profile in The Curcumin Group Over Time**

In those patients receiving curcumin, Hb levels significantly improved from baseline to 3 months (p=0.063) and at 6 months (p=0.0232). Regarding kidney functions, eGFR, urea, and creatinine levels were comparable across all timepoints. There were no significant changes in liver function tests at 3 months and at 6 months, including ALT (p=0.932 and 1.000, respectively) and albumin (p=0.420 and 0.724, respectively). Coagulation parameters (PT, PTT, and INR) also remained within normal ranges with no significant changes (Table V).

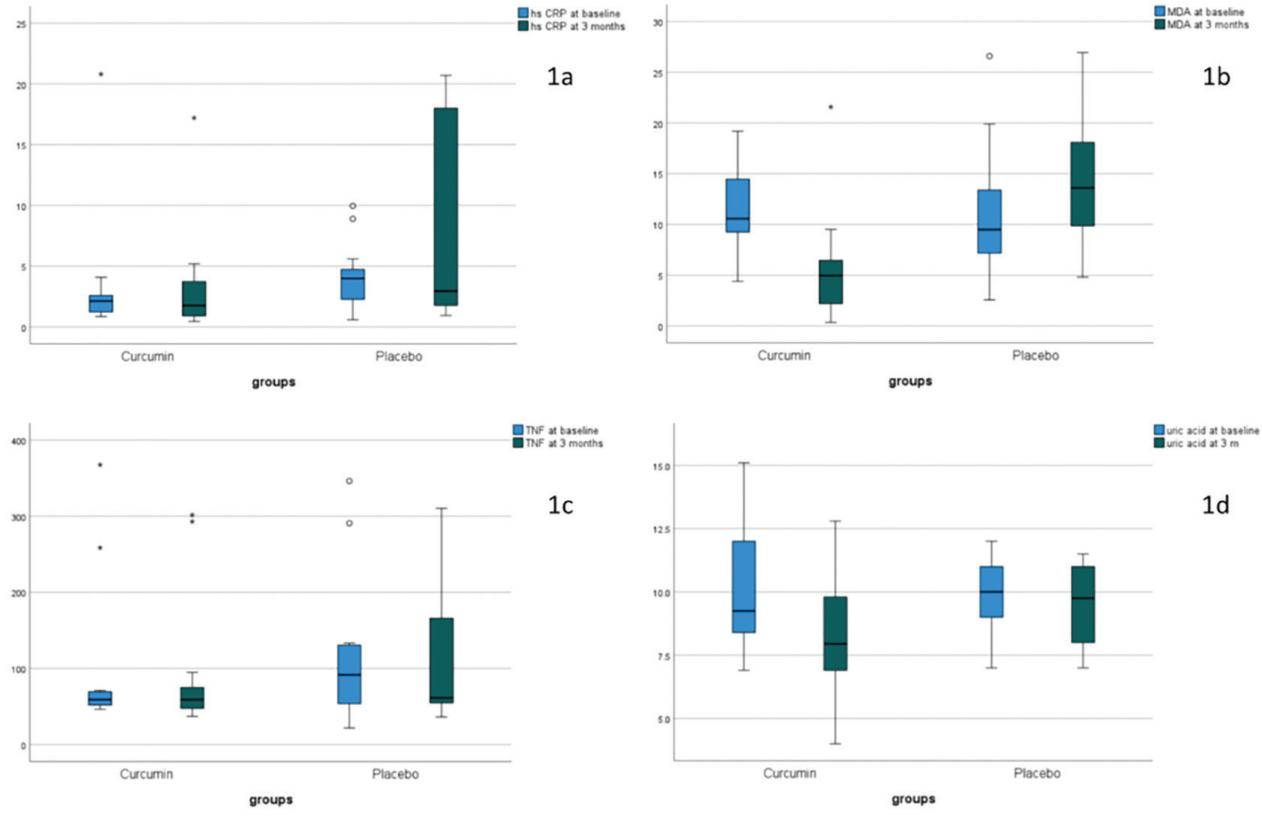


**Figure 1.** Box plot of anti-oxidant and anti-inflammatory biomarkers in the curcumin versus placebo groups at baseline and after 3 months. **1a)** Box plot of hs-CRP in the curcumin group versus the placebo group at baseline and after 3 months of supplementation (p=0.061), **1b)** Box plot of MDA in the curcumin group versus placebo group at baseline and after 3 months of supplementation (p=0.001), **1c)** Box plot of TNF-alpha in the curcumin group versus placebo group at baseline and after 3 months of supplementation (p=0.462), **1d)** Box plot of uric acid in the curcumin group versus the placebo group at baseline and after 3 months of supplementation (p=0.093)
*hs-CRP: High sensitivity C-reactive protein, MDA: Malondialdehyde, TNF: Tumour necrotizing factor*

**Table III.** Comparison of kidney, liver functions, and coagulation parameters between both groups

| | | Curcumin Mean ± SD | Placebo Mean ± SD | p value |
|---|---|---|---|---|
| **eGFR (mL/min/1.73 m²)** | **At baseline** | 5.46±0.83 | 5.29±1.06 | 0.623 |
| | **At 3 months** | 5.60±0.96 | 5.49±1.34 | 0.798 |
| **Creatinine (mg/dL)** | **At baseline** | 10.07±1.39 | 9.89±1.83 | 0.765 |
| | **At 3 months** | 9.59±1.33 | 9.28±2.01 | 0.630 |
| **Urea (mg/dL)** | **At baseline** | 157.43±38.14 | 133.64±34.57 | 0.096 |
| | **At 3 months** | 142.71±33.24 | 139.07±34.43 | 0.778 |
| **ALT** | **At baseline** | 31.50±1.95 | 30.57±1.99 | 0.224 |
| | **At 3 months** | 32.07±1.86 | 30.71±1.86 | 0.064 |
| **Albumin (gm/dL)** | **At baseline** | 4.23±0.39 | 4.25±0.31 | 0.874 |
| | **At 3 months** | 4.31±0.53 | 4.29±0.41 | 0.937 |
| **PT (sec)** | **At baseline** | 12.94±0.95 | 12.71±0.81 | 0.486 |
| | **At 3 months** | 12.41±0.71 | 12.83±0.81 | 0.155 |
| **PTT (sec)** | **At baseline** | 34.35±2.70 | 33.30±3.43 | 0.376 |
| | **At 3 months** | 34.31±2.18 | 33.13±2.89 | 0.231 |
| **INR** | **At baseline** | 1.05±0.07 | 1.04±0.05 | 0.520 |
| | **At 3 months** | 1.04±0.05 | 1.05±0.07 | 0.520 |

eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; PT: Prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; p value of <0.05 was considered statistically significant

**Table IV.** Anti-inflammatory and anti-oxidant biomarkers throughout study duration in the curcumin group

| | Baseline Median (IQR)/Mean ± SD | 3 months Median (IQR)/Mean ± SD | 6 months Median (IQR) | p1 | p2 |
|---|---|---|---|---|---|
| **TNF (ng/L)** | 59.20 (52.0-69.5) | 59.01 (47.7-74.90) | 53.17 (41.2-67.1) | 0.683 | 0.030* |
| **hs-CRP (mg/L)** | 2.13 (1.24-2.60) | 1.77 (0.92-3.74) | 2.08 (0.72-2.34) | 0.778 | 0.638 |
| **MDA (nmol/mL)** | 10.58 (9.26-14.47) | 4.97 (2.21-6.47) | 5.97 (3.60-6.90) | 0.004* | 0.026* |
| **Uric acid (mg/dL)** | 10.23±2.50 | 8.17±2.47 | - | 0.008* | - |

P1 value between baseline and 3 months, P2 value between baseline and 6 months. *A p value less than 0.05 was considered statistically significant
TNF: Tumour necrotizing factor, hs-CRP: High sensitivity C-reactive protein, MDA: Malondialdehyde, Hb: Hemoglobin

**Table V.** Comparison of kidney, liver functions, and coagulation parameters over time in the curcumin group

| | Baseline Mean±SD | 3 months Mean±SD | 6 months Mean±SD | p1 | p2 |
|---|---|---|---|---|---|
| **Hb (g/dL)** | 8.89±1.49 | 9.29±1.35 | 9.17±1.48 | 0.063 | 0.0232* |
| **eGFR (mL/min/1.73m²)** | 5.46±0.83 | 5.60±0.96 | 5.56±0.88 | 1 | 1 |
| **Urea (mg/dL)** | 157.43±38.14 | 142.71±33.24 | 143.21±19.57 | 0.055 | 0.16 |
| **Creatinine (mg/dL)** | 10.07±1.39 | 9.95±1.33 | 9.94±1.67 | 0.189 | 0.763 |
| **Albumin (g/dL)** | 4.23±0.39 | 4.31±0.53 | 4.25±0.40 | 0.420 | 0.724 |
| **ALT (U/L)** | 31.50±1.95 | 32.07±1.86 | 31.57±1.95 | 0.932 | 1 |
| **PT (Sec)** | 12.94±0.95 | 12.41±0.71 | 12.75±0.72 | 0.298 | 0.639 |
| **PTT (Sec)** | 34.35±2.70 | 34.31±2.18 | 34.56±0.40 | 1 | 1 |
| **INR** | 1.05±0.07 | 1.04±0.05 | 1.04±0.05 | 1 | 1 |

Wilcoxon signed rank test. P1 value between baseline and 3 months, P2 value between baseline and 6 months. *A p value of <0.05 was considered statistically significant
eGFR: Estimated glomerular filtration rate, ALT: Alanine transaminase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio

## Discussion

Evidence from *in vitro* and *in vivo* studies, and clinical trials has shown probable beneficial effects of curcumin in various chronic diseases, including arthritis, pancreatitis, inflammatory bowel disease, chronic anterior uveitis, and tumors (18), diabetes mellitus (19), and CKD (10). This study assessed the effects of curcumin on inflammatory, hematological, and oxidative stress factors, as well as organ function. Our study revealed a significant decrease in MDA in the curcumin group when compared to the placebo group after 3 months of supplementation. Moreover, a significant decrease in TNF after 6 months from baseline assessment was detected. Furthermore, there was a significant decrease in MDA detected after 3 months and 6 months from baseline, as well as in uric acid, among those patients who were on one gram of curcumin per day for 3 months.

Among the fundamental biomarkers released during the inflammatory process in CKD are CRP, IL-6, IL-1, and TNF-α, which directly correlate with CKD progression (20). Our study revealed a significant reduction in TNF by the end of the study. Likewise, previous studies have linked curcumin administration with blocking the initiation of TNF, inhibiting the activation of necrotic factor (NF-κB), as well as hindering cell signaling triggered by TNF in various cell types (21,22). In line with this, curcumin significantly decreased TNF levels by 4.69 pg/mL (CI: -7.10, -2.28, $p<0.001$), as revealed by one meta-analysis, which was found to be correlated with the severity of CKD (23).

Furthermore, our study demonstrated a significant decrease in MDA detected after 3 months and after 6 months. Similarly, a meta-analysis revealed a significant decline in MDA levels in various chronic diseases at curcuminoid doses above 600 mg/d (24). One study, a rat model of chronic obstructive pulmonary disease, revealed that curcumin could reduce oxidative stress through a reduction in MDA and increased production of glutathione peroxidase, superoxide dismutase, and catalase in skeletal muscle mitochondria.

Healthy children typically have plasma MDA levels ranging from 1.49 to 5.87 nmoL/mL (25-27). Our study demonstrated substantially higher baseline levels of MDA (median =10.58 and 9.90 nmoL/mL in the curcumin and placebo groups, respectively). Similarly, reported serum TNF-α levels range from 32.81 to 68.27 ng/L in healthy children (28). Our study showed high TNF-α in children on HD (median =59.20 and 114.90 pg/mL in the curcumin and placebo groups, respectively), supporting the presence of oxidative stress and systemic inflammation among children with ESRD on regular hemodialysis. These comparisons support the pathophysiological burden in this population and the rationale for evaluating anti-inflammatory and antioxidant interventions such as curcumin.

Several studies have demonstrated the efficacy of curcumin in reducing serum levels of creatinine and improving renal function as a result of reactive oxygen species (ROS) inhibition (29-31). ROS are released in diabetic kidney diseases (32), renal oxidative stress (33), and ischemic renal perfusion (34) and these were found to be inhibited by curcumin. Similarly, clinical trials showed curcumin inhibiting xanthine oxidase expression, which triggers uric acid induction in CKD patients during oxidative stress flares (35,36). In our study, curcumin did not impact creatinine levels, albumin, or other kidney functions. However, uric acid significantly decreased after 3 months of therapy. Although trials assessing the efficacy of curcumin on uric acid in patients with renal disorders are lacking, curcumin nanoparticles demonstrated a significant reduction in ankle swelling and uric acid concentrations in mice with uric acid nephropathy (37). In patients with non-alcoholic fatty liver disease, curcumin was found to lower uric acid levels after 8 weeks of treatment ($p<0.001$) (38).

In addition, curcumin upregulated messenger ribonucleic acid (mRNA) and protein expression of the sirtuin family (39), which led to an upsurge in the expression of peroxidase proliferator-activated receptor gamma coactivator 1α randomized clinical trials and lowered the production of ROS (40). Many studies highlighted the anticoagulant effect of curcumin (41,42). One study demonstrated a significant increase in activated partial thromboplastin time and prothrombin time, and inhibition of thrombin and FXa generation (41). Another study revealed an upsurge in protein C levels and partial thromboplastin time levels (42). However, our study did not reveal any significant differences regarding these factors when compared to the placebo.

CRP released during CKD has been associated with erythropoietin resistance, malnutrition, cardiovascular diseases, and mortality (43). Several trials have demonstrated the strong impact of curcumin in inhibiting inflammatory mediators, including hs-CRP (3,15,44-46). One trial revealed that 2.5 grams of curcumin, 3 times a week for 12 weeks, decreased mRNA release of hs-CRP in adult patients undergoing HD (47). In contrast, another study revealed that one gram of curcumin daily for 12 weeks was not enough to achieve an effect on oxidative stress biomarkers such as hs-CRP in HD patients (48), which is in line with our study results where comparing hs-CRP levels in both groups

showed a statistically insignificant decrease after 3 months of therapy. This insignificant finding regarding curcumin in reducing hs-CRP could be due to the low doses of curcumin used in the current study.

Curcumin bioavailability is generally low, and pharmacokinetics could be impacted by interindividual variability, including ethnicity, gender, and the age of patients. Previous multi-ethnic studies in adults showed the impact of age-related disorders on curcumin absorption, distribution, metabolism, and excretion (49,50). Gender has also been suggested to have an influence on curcumin levels, where healthy females were found to have up to 2.1 times higher plasma levels when compared to males (51). However, data related to curcumin bioavailability in pediatric patients with renal disorders or ESRDs remain limited and require future attention and studies. Although no major adverse events were observed in this study, the safety of curcumin in children with ESRD should be further investigated due to its potential interactions with anticoagulants, its effects on platelet function, and its influence on drug metabolism (52). Larger, multicenter studies with extended follow-up durations are needed in order to fully assess its safety before clinical use in this patient population can be recommended.

### Study Limitations

This study had some limitations. The sample size is considered to be relatively small to be able to generalize this study's outcomes and draw definitive conclusions. Additionally, this study could not evaluate different responses associated with dose escalation. Those patients receiving antioxidant supplements were excluded at enrollment, and the participating patients were instructed to avoid taking them during the study period. However, it is difficult to ensure that participants did not consume other dietary or over-the-counter antioxidant products. This study also lacked long-term follow-up to assess post-discharge outcomes and any possible later complications. Future studies should focus on larger, multicenter trials with standardized protocols and longer durations in order to better understand the impact of curcumin in ESRD children receiving hemodialysis.

## Conclusion

Curcumin may have an anti-inflammatory and antioxidant effect in pediatric patients receiving HD. Future large-scale studies are warranted in order to assess the effective dose, possible interactions, as well as any potential variabilities between HD patients which may affect curcumin efficacy.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Research Ethics Committee of the Ain Shams University Faculty of Medicine (approval number: FMASU MD 181/2021, date: 15/09/2021).

**Informed Consent:** A written informed consent was obtained from the parents or caregivers of participants after explaining the study aim and procedures, with their right to withdraw from the study at any time.

### Footnotes

### Authorship Contributions

Concept: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Design: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Data Collection or Processing: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Analysis or Interpretation: A.H.H., I.Z.E., Literature Search: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Writing: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E.

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