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Original Article

Curcumin supplementation prevents cisplatin-induced nephrotoxicity: a randomized, double-blinded, and placebo-controlled trial

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Abstract

Background and purpose: Cisplatin-induced nephrotoxicity (CIN) remains the most prevailing unfavorable influence and may affect its clinical usage. This study sought to explore the possible impacts of curcumin on preventing CIN in human subjects.
Clinical design: The investigation was a placebo-controlled, double-blinded, randomized clinical trial conducted on 82 patients receiving nano-curcumin (80 mg twice daily for five days) or an identical placebo with standard nephroprotective modalities against CIN. Data was gathered on patients' demographics, blood, urinary nitrogen, creatinine (Cr) levels, urinary electrolytes, and urine neutrophil gelatinase-associated lipocalin (NGAL) levels in treatment and placebo groups, 24 h and five days after initiating the administration of cisplatin.
Findings/Results: Both investigation groups were alike considering the demographic characteristics and clinical baseline data. Curcumin administration led to a significant improvement in blood-urine nitrogen (BUN). BUN, Cr, glomerular filtration rate (GFR), and the ratio of NGAL-to-Cr considerably altered during the follow-up periods. However, the further alterations in other indices, including urinary sodium, potassium, magnesium, NGAL values, and potassium-to-Cr ratio were not statistically noteworthy. The significant differences in the NGAL-to-Cr ratio between the two groups may indicate the potential protective impact of curcumin supplementation against tubular toxicity. Curcumin management was safe and well-accepted; only insignificant gastrointestinal side effects were reported.
Conclusion and implications: Curcumin supplementation may have the potential to alleviate CIN and urinary electrolyte wasting in cancer patients. Future research investigating the effects of a longer duration of follow-up, a larger participant pool, and a higher dosage of curcumin are recommended.

Keywords: Clinical trial; Cisplatin; Curcumin; Electrolyte; Nephrotoxicity.

INTRODUCTION

Cisplatin, the most efficient and advantageous chemotherapy drug, is utilized for various types of malignancies such as breast, ovary, lung, bladder, and testicle. It yields cytotoxic characteristics by attaching to the purine bases on DNA, meddling with DNA repair strategies, generating DNA deterioration, and causing programmed cell death in cancer cells (1).

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In the cytoplasm, the chloride atoms of cisplatin are replaced by water molecules, creating a powerful electrophile that can respond to any nucleophile, consisting of nitrogen donor atoms on nucleic acids, and sulfhydryl groups on proteins. Attaching cisplatin with purine nucleic acids leads to DNA damage in cancer cells, cellular division block, and apoptosis (1).

Cisplatin administration involves numerous intricacies, like ototoxicity, gastrointestinal complexities, and myelosuppression. Further, the nephrotoxicity displayed in tubular dysfunction restrains cisplatin dosage and management in chemotherapy treatment regimens (1).

There have been numerous suggested strategies to address cisplatin-induced nephrotoxicity (CIN). These strategies include toxicity of tubular epithelial cells especially in the S3 segment of the proximal tubule as well as the renal vascular system's contraction by activating oxidative stress, destroying mitochondrial function, and increasing inflammatory cytokines response (2).

CIN is generally exemplified by acute kidney injury (AKI), glomerular filtration rate (GFR) decline, and salt-wasting, which can increase the risk of hypocalcemia and hypomagnesemia. Moreover, an incidence of AKI exacerbates the situation of chronic kidney disease leading to terminal renal disease (3). Despite immense hydration and electrolyte administration during cisplatin administration, preventing cisplatin-induced AKI remains a significant clinical dilemma (3). Numerous kinds of research have been performed to assess the defensive impact of natural and chemical substances like flavonoids (4), ascorbic acid (5), theophylline (6), N-acetyl-cysteine (7), silymarin (8), vitamin E (9), cimetidine (10), carvedilol (11), selenium (12), harmine (13), and some herbal extracts such as *Morus alba L*. leaf extracts (14), *etc* in preventing CIN. Due to insufficient safety and efficient data from clinical studies, these examinations were unable to identify any effective and clinically approved compound for the prevention or treatment of CIN. Curcumin is the primary functional component of turmeric with the scientific term *Curcuma longa L*. Turmeric has been extensively utilized as a seasoning, food additive, and also a portion of conventional medicine in equatorial regions, particularly in South and Southeast Asia (15). Multiple animal examinations have been performed to evaluate the probable defensive impacts of curcumin on CIN (16-18). The suggested strategies in the animal investigation were antioxidant and anti-inflammatory impacts. Curcumin is a dual-functioning antioxidant that can instantly assuage free radicals or increase the expression of various cytoprotective and antioxidant proteins (19).

Curcumin can defend against oxidative stress *via* its antioxidant action and invert cisplatin-induced attenuation of antioxidant proteins, including glutathione, superoxide dismutase, and catalase. It also decreases inflammatory markers such as monocyte chemoattractant protein (MCP)-1 and tumor necrosis factor-alfa (TNF-α) (16-18).

Curcumin causes the expression of cytoprotective proteins by activating nuclear factor erythroid-derived 2 (Nrf2) as a superior regulator of the antioxidant response against oxidative stress (20,21).

Furthermore, there is proof indicating that curcumin can regulate the inflammatory response by reducing the action of cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase enzymes, as well as mitogen-activated and Janus kinases. Curcumin has also been discovered to hinder the expression of inflammatory cytokines like TNF-α, interleukins (IL) 1, 2, 6, 8, and 12, MCP, and migration inhibitory proteins (22,23).

Different examinations have proved the anticancer impact of curcumin and its potentiating influence in raising the sensitivity of various tumor cells to antineoplastic drugs. In addition, the co-administration of curcumin with different chemotherapy substances reduces worry about meddling with the anticancer process of drugs and functions as an additional treatment in decreasing side effects and raising the radiosensitivity of cancer cells in radiation therapy (24,25).

Furthermore, in-vitro and animal studies' findings have substantiated curcumin's potential to mitigate CIN. However, it is important to gather future information through human trials to evaluate the efficacy of

curcumin in managing CIN especially in patients at risk of developing CIN.

MATERIALS AND METHODS

Study protocol

From March 2020 to December 2021, the clinical experiment was performed at Omid Hematology-Oncology Hospital associated with Isfahan University of Medical Sciences in Isfahan, Iran. The investigation was randomized, double-blinded, and placebo-controlled. Omid Hospital is a tertiary referral hospital specializing in treating cancer patients. The study protocol was supported by the universities' ethics committee (Ethical ID: IR.MUI.RESEARCH.REC.1400.331), and all patients autographed the permission form. Also, the investigation was recorded on the Iranian Registry of Clinical Trials website (IRCT20180722040556N8).

Our inclusion criteria were adult patients suffering from solid tumors while receiving a 2-h cisplatin injection with an unfractionated dosage of 50 mg/m^2 or more. Simultaneously, they fulfilled the inclusion criteria comprising Karnofsky's performance status of more than 70 % (26) and GFR of more than 50 mL/min/1.73 m^2 (according to the chronic kidney disease epidemiology collaboration equation) (27).

For patients presenting with a persistent disease or any signs of sepsis, a record of nephrotoxic agent usage, including nephrotoxic antibiotics (aminoglycosides, amphotericin B, vancomycin, colistimethate sodium), contrast media, calcineurin inhibitors, or non-steroidal anti-inflammatory drugs (NSAIDs) in the past 72 h were encompassed within the exclusion criteria.

We also excluded patients who had suffered from probable side effects like gastrointestinal disorders or headaches, or allergic reactions to curcumin administration during treatment, patients with a record of AKI before registration, and patients who underwent bilirubin levels above 2 mg/dL or liver enzyme 2.5 times above the typical range during the examination. Under the CIN prevention protocol in our hospital, one day before cisplatin administration, all patients received 1 L of intravenous normal saline serum holding 10 mL of potassium chloride 15% w/v and 2 mL of magnesium sulfate 50% w/v inside, which was injected merely before cisplatin injection. Further, 500 mL of normal saline was injected after receiving cisplatin-based regimes.

Randomization and blindness

A computerized random-allocation list generator was used for the block randomization procedure employing the www.randomization.com website. We evaluated four patients in each block to equalize the placebo and treatment groups.

Researchers randomly considered qualified patients into two groups (A or B) based on the generated list. They received either curcumin (group A: 160 mg/day, orally, two soft gelatin capsules twice daily) generated by Exir Nano Sina Pharmaceutical Company, Tehran, Iran, or identical placebo soft gelatin capsules containing polysorbate 80 (group B: two soft gelatin capsules twice daily). To double-blind our trial, researchers and participants were kept unaware of assigned treatment groups by presenting curcumin and placebo in identical-looking packages. Each package was randomly named by a unique number which was allocated to each continuously enrolled participant.

We requested patients to swallow curcumin or identical placebo soft gelatin capsules for 24 h before acquiring cisplatin-based regimes in a regarded cycle of chemotherapy and considered to persist for the next five days as a study protocol. Patients were checked for drug compliance and any probable unfavorable drug reactions during the investigation. We utilized common terminology criteria for adverse events (CTCAE) version 5.0 to evaluate the probable unfavorable events during the study (28). In addition, we regarded patients as non-adherent if they skipped consuming more than five doses of curcumin soft gelatin capsules (analogous to 20% of the total drug).

The Naranjo scale assessed the causality examination of unfavorable effects, and they were presented as possible (score 5-8) (28). We eliminated non-compliant patients and those who had experienced any probable unfavorable drug reactions during follow-ups.

Lab data collection

Blood samples were gathered just before cisplatin-based regimes and 24 h and five days after the curcumin management protocol to examine the complete blood cell test, serum creatinine (SCr), and serum electrolytes, such as sodium, potassium, and magnesium. Sample for the concurrent analysis of urinary electrolytes, Cr, and urinary nitrogen content was conducted with blood evaluation. Urine samples were spun down at 10,000 rpm for 5 min by the researcher instantly after sample collection and subsequently stored in a -70 °C freezer up to laboratory examination for specified metabolites, electrolytes as well as urine neutrophil gelatinase-associated lipocalin (NGAL) marker at the end of the investigation.

We likewise computed the urinary fractional excretion of magnesium (FEMg; equation 1), the urinary fractional excretion of sodium (FENa; equation 2) as well as the urinary potassium/Cr ratio (KCR; equation 3) for every sample at baseline, 24 h, and five days after curcumin and placebo management utilizing the following equations:

$$\mathrm{FENa} = \frac{\text{Urine Na} \times \text{serum Cr}}{\text{Serum Na} \times \text{urine Cr}} \times 100 \quad (1)$$

$$\mathrm{FEMg} = \frac{\text{Urine Mg} \times \text{serum Cr}}{\text{Serum Mg} \times \text{urine Cr}} \times 0.7 \times 100 \quad (2)$$

$$\mathrm{KCR} = \frac{\text{Urine K}}{\text{Urine Cr}} \quad (3)$$

Furthermore, urinary NGAL levels were calculated as a specified marker of AKI incidence employing enzyme-linked immunosorbent assay (ELISA) in a 96-well NGAL human kit (fabricated by ZellBio GmbH, Germany). Indeed, to exclude the effect of hydration or cisplatin-associated polyuria, the computed NGAL levels were modified by urine Cr. We determined to examine the urinary NGAL rather than serum NGAL because of more credible information and a straightforward measurement method. After liquefying the urine samples, the samples were spun down for the second time at 2000 rpm for 20 min. Afterward, five typical solutions (640, 320, 160, 80, 40, 20, and 0 ng/mL) were produced from the urine samples according to the manufacturer's guidelines and transferred to a urinary NGAL kit to detect protein utilizing a plate reader.

Acute kidney injury network (AKIN) criteria were used for detecting AKI occurrence in our investigation (26,29-30), expressed as an > 0.3 mg/dL or 50% rise in SCr compared to baseline or a 25% reduction in GFR compared to the baseline within 48 h.

In practice, determining SCr, urinary NGAL level, and serum/urine electrolytes after curcumin administration was regarded as our study's preliminary results and probable unfavorable impacts as a secondary result.

Sample size calculation

The number of trial samples in this examination was computed using the equation below (equation 4):

$$\mathrm{n} = \frac{(z1 + z2)\, 2\, [p1\,(1 - p1) + p2\,(1 - p2)]}{d2} \quad (4)$$

Based on Ghorbani *et al.*'s research that assessed the defensive impacts of selenium on CIN (30), in this equation, N signifies the number of patients, $z1$ represents the reliability coefficient (95%), $z2$ denotes the power factor (80%), $p1$ and $p2$ show the beta power probability in the first and second groups (50%), and d indicates the study error. According to the equation of each group, the evaluated sample size was 44 (Fig. 1).

Statistical analyses

An independent samples T-test was used to compare baseline parameters across the two treatment groups for continuous variables and the Chi-square test was used to compare categorical variables. To evaluate the outcome measures, a repeated-measures analysis of variance (ANOVA) was used to compare within-group changes over time (baseline, 24 h after, and 5 days after) and groups (curcumin versus placebo) × time interaction effects. The Shapiro-Wilk normality test was conducted to examine the normality of group data. In the case of non-normality, the generalized estimating equations, which account for correlated data due to non-normal continuous repeated measures, were used to assess the effects of treatment. Analyses were adjusted a priori probable confounders.

All data were analyzed using SPSS (version 26; IBM, Armonk, NY). All statistical tests were performed at the two-tailed 5% level of significance, therefore, *P*-values ≤ 0.05 were considered significant.

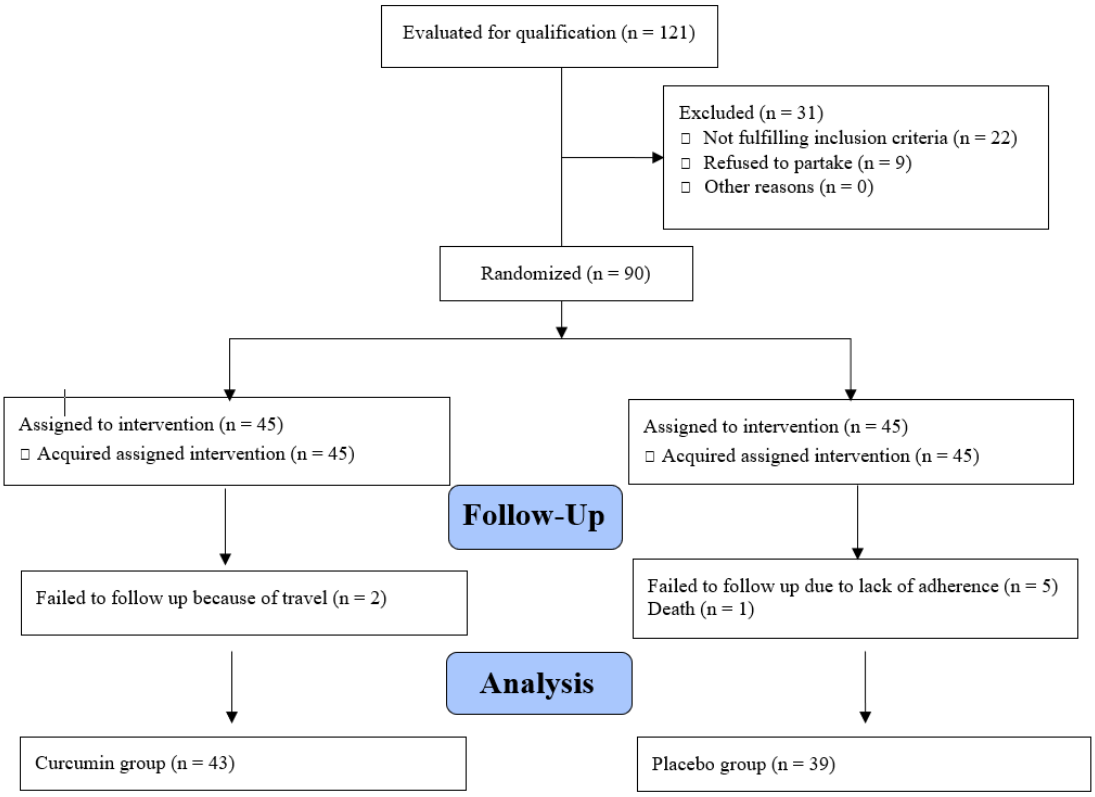

Fig. 1. CONSORT flow chart of study.

RESULTS

As shown in Fig. 1, out of the 121 patients who were evaluated and fulfilled the inclusion criteria, 90 were deemed eligible for randomization. During the investigation, eight patients gave up the follow-ups owing to the absence of collaboration and an alteration in the chemotherapy regime. Ultimately, 43 patients stayed in the curcumin group and 39 in the placebo group after randomization.

The average age of individuals in the curcumin and placebo groups was 53.60 ± 9.92 and 53.11 ± 10.17 years old for males and 51.95 ± 9.87 and 54.31 ± 10.27 years old for females, respectively. Among all participants, 56% and 41% were men in the curcumin and placebo groups, respectively. According to Table 1, the baseline clinical and lab data of both intervention groups in terms of their kidney function (SCr, GFR, blood urine nitrogen (BUN)), liver and hematologic function, as well as serum electrolytes were not statistically significant before intervention implementation.

Though not significant from a statistical standpoint, the cisplatin-received dosage was higher in the curcumin group 103 mg (85-150 mg), in comparison to the placebo group, 94 mg (75-130 mg) in the first chemotherapy cycle. Baseline demographic features and laboratory information are reported in Table 1. Head and neck cancer was the most prevalent (17.1%) among the enlisted patients. However, the most declared cancers were ovarian and endometrial cancers in the curcumin group and head and neck cancer and lung cancer in the placebo group. As illustrated in Table 2, both investigation groups were alike considering the type of chemotherapy regimes, mainly weekly cisplatin (23.3% and 28.2% in curcumin and placebo groups, respectively).

According to AKIN criteria (31), 2 (4.7%) patients in the curcumin group and 7 (17.9%) patients in the control group faced AKI phase 1 (P = 0.056). Neither of the enlisted patients underwent an oliguria episode. The SCr levels of patients who faced AKI while obtaining cisplatin-based regimes reverted to baseline before the next chemotherapy cycle.

Table 1. Baseline clinical, demographic, and laboratory information in control and treatment groups.

Variables	Curcumin group (n = 43)	Placebo group (n = 39)	*P*-values
Age (years)*	52.58 ± 9.80	55.49 ± 9.54	0.178
Gender, male, n (%)	24 (56%)	16 (41%)	0.185
*Body surface area (m^2)	1.73 ± 0.08	1.73 ± 0.12	0.874
*Cisplatin dose (mg)	103.14 ± 23.95	93.59 ± 21.94	0.064
Serum creatinine(mg/dL)*	0.98 ± 0.16	0.93 ± 0.14	0.136
Glomerular filtration rate (mL/min/1.73 m^2)*	78.80 ± 13.02	78.80 ±14.85	0.999
* Blood urine nitrogen (mg/dL)	14.60 ± 3.59	15.87 ± 5.02	0.190
*Serum sodium (mEq/L)	137.00 ± 2.63	137.02 ± 3.14	0.979
*Serum potassium (mEq/L)	3.84 ± 0.41	3.97 ± 0.31	0.133
*Serum magnesium (mEq/L)	1.88 ± 0.23	1.99 ± 0.21	0.028
*Serum calcium (mg/dL)	9.34 ± 0.40	9.43 ± 0.27	0.195
Serum albumin (g/dL)*	4.42 ± 0.32	4.40 ± 0.33	0.743
*Leukocyte count (10^3/L)	6.30 (5-12.5)	6.40 (4.8-10.2)	0.798
Hemoglobin (g/dL)*	14.32 ± 0.83	14.04 ± 0.87	0.134
Platelet count (109/L)*	219.30 ± 393.89	205.26 ± 427.76	0.126
Serum aspartate aminotransferase (U/L)#	21 (11-29)	18 (14-33)	0.190
# Serum alanine aminotransferase (U/L)	26 (11-41)	25 (16-41)	0.676
#Serum alkaline phosphatase (U/L)	87 (54-136)	84 (43-121)	0.144
Total bilirubin (mg/dL)*	0.76 ± 0.13	0.76 ± 0.15	0.912
Uric acid (mg/dL)*	5.00 ± 1.01	5.17 ± 0.98	0.425

*, Indicates data presented as mean ± SD; #, the data which present median (range).

Table 2. The number of chemotherapies' regimens and type of malignancy in control and treatment groups**.**

Treatment regimes	Curcumin group (n = 43), n (%)	Placebo group (n = 39), n (%)	*P*-value
Cisplatin	10 (23.3)	11 (28.2)	
Cisplatin + gemcitabine	10 (23.3)	10 (25.6)	
Cisplatin + docetaxel+ fluorouracil	2 (4.7)	2 (5.1)	
Cisplatin + fluorouracil	2 (4.7)	4 (10.3)	
Cisplatin + fluorouracil + folinic acid	3 (7)	1 (2.6)	0.79
Cisplatin + cyclophosphamide+ vincristine	3 (7)	1 (2.6)	
Cisplatin + etoposide	6 (14)	3 (7.7)	
Cisplatin + pemetrexed	3 (7)	5 (12.8)	
Cisplatin + fluorouracil+ topotecan	4 (9.3)	2 (5.1)	
Malignancy types			
Lung cancer	1 (2.3)	8 (20.5)	
Gastrointestinal cancer	7 (16.3)	4 (10.3)	
Lymphoma	8 (18.6)	3 (7.7)	
Head and neck cancer	6 (14)	8 (20.5)	
Ovarian and endometrial cancers	9 (20.9)	1 (2.6)	0.009
Renal cell carcinoma	0	2 (5.1)	
Sarcoma	4 (9.3)	2 (5.1)	
Bladder cancer	3 (7)	3 (7.7)	
Breast cancer	0	4 (10.3)	
Melanoma	5 (11.6)	4 (10.3)	

Table 3 illustrates blood indices alterations at the baseline, 24 h, and five days time points after implementing the intervention in both placebo and curcumin groups. As demonstrated, both groups' GFR values were non-significantly lowered after administration of cisplatin. However, the reduction in the placebo group was more evident than in the curcumin group, even though the discrepancy was not greatly noteworthy. Further, as the GFR decreased, the serum Cr levels non-significantly increased in both treatment groups compared to the baseline and there were statistically significant discrepancies between the two intervention groups ($P < 0.05$).

Table 3. Comparing blood indices in control and treatment groups at various periods of follow-ups by implementing a repeated-measures ANOVA test. Data are presented as mean ± SD.

Blood indicators	Time	Curcumin group (n = 43)	Placebo group (n = 39)	Within group *P*-value	Between-group *P*-value
Glomerular filtration rate (mL/min/1.73 m^2)	Baseline	78.80 ± 13.02	78.80 ± 14.85	0.48	0.001 >
	24 h later	78.30 ± 14.16	77.70 ±14.72		
	Five days later	75.43 ± 11.43	70.79 ± 11.70		
Blood urea nitrogen (mg/dL)	Baseline	15.87 ± 5.02	15.21 ± 3.59	0.03	0.001 >
	24 h later	17.41 ± 4.17	16.32 ± 3.33		
	Five days later	21.48 ± 4.02	20.73 ± 4.34		
Creatinine (mg/dL)	Baseline	0.93 ± 0.14	0.96 ± 0.16	0.21	0.001 >
	24 h later	0.94 ± 0.14	0.97 ± 0.18		
	Five days later	1.01 ± 0.16	1.02 ± 0.18		
Magnesium (mEq/L)	Baseline	1.99 ± 0.21	1.88 ± 0.23	0.07	0.96
	24 h later	1.96 ± 0.24	1.92 ± 0.11		
	Five days later	1.94 ± 0.29	1.91 ± 0.14		
Sodium (mEq/L)	Baseline	137.01 ±3.14	137.02 ± 2.64	0.07	0.62
	24 h later	137.49 ± 1.88	136.74 ± 2.94		
	Five days later	136.97 ± 4.45	136.93 ± 3.86		
Potassium (mmol/L)	Baseline	3.97 ± 0.31	3.90 ± 0.41	0.02	0.008
	24 h later	4.02 ± 0.29	3.94 ± 0.32		
	Five days later	4.10 ± 0.17	4.02 ± 0.35		
Sodium excretion fraction	Baseline	2.03 ± 1.1	2.23 ± 0.9	0.44	0.60
	24 h later	2.30 ± 0.8	2.42 ± 1.1		
	Five days later	2.56 ± 1.2	2.79 ± 1.4		
Magnesium excretion fraction	Baseline	4.02 ± 3.63	5.99 ± 6.60	0.03	0.12
	24 h later	3.82 ± 2.13	6.53 ± 7.48		
	Five days later	4.49 ± 2.53	7.57 ± 9.75		

After cisplatin administration, there was a substantial increase in BUN levels in both groups. In addition, there were considerable discrepancies in BUN levels between the groups after the treatment was implemented. The average blood magnesium and sodium levels were not considerably altered during follow-up periods in both groups, unlike potassium which showed a significant increase within and between two intervention groups.

Table 3 indicates the outcomes of repeated-measures ANOVA on the percentage of sodium and magnesium fractional excretion in the groups. The outcomes demonstrated that time and group did not extensively influence sodium excretion fraction alterations. In contrast, the quantity of magnesium excretion fraction was higher in the placebo group than in the curcumin group, revealing the probable potential defensive impacts of curcumin in preventing salt wasting.

The changes in outcomes of urinary indices in the treatment groups during three follow-ups have been displayed in Table 4 utilizing the repeated-measures ANOVA model. The results were adjusted by significant variables between the two groups according to baseline investigations.

The outcomes demonstrated that urinary indices, such as BUN, Cr, and the ratio of NGAL-to-Cr considerably altered during the follow-up periods. However, the further alterations in presented indices, including urinary sodium, potassium, magnesium, NGAL values, and potassium-to-Cr ratio were not statistically noteworthy. The levels of urine NGAL were identical at the baseline in the treatment groups and, after receiving cisplatin-based regimes, topped out at 24 h in both relative groups and lowered after that, conceivably indicating the pattern of fulfilling acute kidney injury after cisplatin exposure.

Table 4. Comparing urinary indices in placebo and curcumin groups at various times by utilizing repeated-measures ANOVA modeling. Data are presented as mean ± SD. The results were adjusted by age, sex, GFR measures, and type of malignancy as significant variables between the two groups according to baseline investigation.

Urinary indicators	Time	Curcumin group (n = 43)	Placebo group (n = 39)	Within-group *P*-value	Between-group *P*-value
Blood urea nitrogen (mg/dL)	Baseline 24 h later Five days later	473.33± 231.50 482.98 ±192.35 481.21 ± 189.11	448.46 ± 320.98 528.59 ± 351.01 607.15 ± 304.50	0.015	0.037
Creatinine (mg/dL)	Baseline 24 h later Five days later	117.12 ± 95.17 83.73 ± 46.18 70.57 ± 44.33	90.79 ± 64.68 88.57 ± 63.37 86.56 ± 68.42	0.048	0.040
Magnesium (mEq/L)	Baseline 24 h later Five days later	3.41 ± 0.81 3.35 ± 1.01 3.33 ± 1.16	3.39 ± 0.75 3.36 ± 0.76 3.51± 0.92	0.721	0.163
Sodium (mEq/L)	Baseline 24 h later Five days later	152.77 ± 64.82 150.20 ± 55.65 145.77 ± 56.23	128.15± 43.64 134.16 ± 37.66 134.98 ± 37.31	0.487	0.383
Potassium (mEq/L)	Baseline 24 h later Five days later	20.47 ± 10.20 17.65 ± 7.01 15.60 ± 6.81	18.46 ± 12.89 19.09 ± 13.17 21.93 ± 16.06	0.526	0.052
Potassium to creatinine ratio (mEq/g creatinine)	Baseline 24 h later Five days later	23 ± 9 23 ± 8 24 ± 10	23 ± 6 27 ± 9 34 ± 26	0.284	0.343
Urine neutrophil gelatinase-associated lipocalin (ng/mg)	Baseline 24 h later Five days later	103.86 ± 12.64 105.07 ± 9.36 104.04 ± 18.76	103.36 ± 16.09 108.17 ± 11.46 108.03 ± 10.08	0.202	0.183
Urine neutrophil gelatinase-associated lipocalin to creatinine (ng/mg)	Baseline 24 h later Five days later	2.07 ± 2.94 1.76 ± 1.31 1.95 ± 1.09	2.92 ± 3.44 3.12 ± 3.51 3.14 ± 3.81	0.875	0.002

The urine potassium-to-Cr ratio of a spot urine sample above 1.5 mmol/mmol (13 mmol/g) was presented to exhibit renal potassium loss. The spot urine potassium-to-Cr ratio is a diagnostic test that indicates an increase in 24-h urinary potassium excretion. It is beneficial when a dependable 24-h urine sample is not accessible. An over 20 mmol of potassium to mmol Cr ratio is suitable for the renal reaction to hyperkalemia as our data in Table 3 were shown (31). However, the protective effects of curcumin were not demonstrated in this item, cisplatin administration led to kidney salt wasting in both intervention groups.

Conversely, Table 3 demonstrates substantial alterations in the groups' urinary indices of the NGAL-to-Cr ratio. This suggests that curcumin has probable defensive impacts on renal injury compared to the placebo group. In the placebo group, the urine NGAL-to-Cr ratio trend increased, while in the curcumin group, it decreased in reverse. (Table 4). Curcumin management has been regarded for adverse event assessment during five-day follow-ups. According to Table 5and CTCAE Version 5.0 (31), curcumin supplementation had insignificant unfavorable effects compared to the placebo and was well-accepted. The two relative groups reported mild gastrointestinal disorders and recurrent headaches, which were not statistically influential.

Table 5. Unfavorable drug reactions in enlisted patients according to common terminology criteria for adverse events, version 5.0. During the investigation, grades 4 and 5 responses were not presented.

Adverse drug reactions	Curcumin group (n = 39), n (%)	Control group (n = 43), n (%)	*P*-value
Nausea	17 (43.6%)	19 (44.2%)	
Grade 1	12	11	0.409
Grade 2	4	8	
Grade 3	1	1	
Vomiting	10 (25.6%)	12 (27.9%)	
Grade 1	7	6	0.449
Grade 2	2	4	
Grade 3	1	1	
Headache	4 (10.3%)	3 (7%)	
Grade 1	2	1	0.797
Grade 2	2	2	
Grade 3	0	0	
Fatigue	6 (15.4%)	4 (9.3%)	
Grade 1	3	3	0.615
Grade 2	3	1	
Grade 3	0	0	
Prickling in legs and arms	2 (5.1%)	4 (9.3%)	
Grade 1	1	3	0.336
Grade 2	1	1	
Grade 3	0	0	

DISCUSSION

In our investigation, for the first time, it was uncovered in a randomized and placebo-controlled clinical experiment that curcumin supplementation has the potential for probable defensive impacts on CIN. Our study found that cisplatin-based chemotherapy regimens raise renal electrolyte wasting and GFR decline in cancer patients. Curcumin administration (160 mg/day) may have the potential to alleviate CIN especially by preventing tubular impairment and alleviating BUN and SCr during supplementation. There were no noteworthy adverse effects associated with curcumin administration.

It is not uncommon for patients undergoing cisplatin-based chemotherapy to experience cisplatin nephrotoxicity. Kidney injury presents itself a few days after cisplatin administration and its symptoms comprise lower GFR, higher SCr levels, and decreased serum magnesium and potassium levels (32). Conversely, it is essential to comprehend the lasting impact of cisplatin nephrotoxicity fully. However, it is supposed that cisplatin administration may result in a lasting, unnoticed decline in GFR.

During the investigation, it was observed that there were 9 incidents (11%) of AKI. This adverse reaction had a significant impact on the decline of GFR. Our report aligns with earlier research that highlighted the occurrence rate of AKI episodes ranging from 8-40%. It was reported that one-third of patients experiencing cisplatin therapy encountered a GFR decline (8,32,33). The differences in the cisplatin-induced AKI occurrence can be influenced by multiple elements, including various definitions of AKI, the patients' hydration levels during therapy, the baseline renal function, and the clinical features of patients acquiring cisplatin (34).

Various renal protective methods and substances have been investigated for controlling CIN (3,6,8). However, the only suggested effective methods involve replenishing electrolytes and ensuring sufficient hydration (2).

In this investigation, we pioneered a human investigation to assess the probable renal protective impact of curcumin's simultaneous supplementation with cisplatin-based chemotherapy regimes on CIN and corresponding salt wasting. Earlier research on animals (35-38) has examined curcumin management in the dosage range of 100-200 mg/kg and nano curcumin in the dosage of 50-100 mg/kg at various planned times for controlling CIN. Investigators of *in vivo* examinations presented curcumin as an

unexplored medicinal nominee for the clinical significance of CIN administration after exhibiting favorable outcomes. As stated, curcumin holds a wide variety of pharmacological and biological actions, among which its antioxidant and anti-inflammatory actions are nearly crucial (35-38).

The proposed strategy of CIN especially in animal studies involves an increase in reactive oxygen species caused by a decrease in defensive enzymes like superoxide dismutase, glutathione, and catalase. Additionally, cisplatin controls oxidative stress by disrupting the Nrf2 and NF-κB expression and activator protein one expression, which is noticeable in creating inflammatory cytokines like TNFs and ILs (35-38).

Our outcomes demonstrated the significant usage of curcumin in alleviating the nephrotoxic impact of cisplatin and indicated its discerning clinical significance. It can be supposed that curcumin demonstrates a defensive impact due to its anti-inflammatory activity. However, the occasions exhibited that it wields a distinct impact relying on the disposal time.

Kuhad *et al*. in their examination of rats showed that curcumin administration dose-dependently maintained kidney function, decreased lipid peroxidation, and reinstated lowered levels of glutathione, superoxide dismutase, and catalase. Thus, curcumin holds defensive influences on cisplatin nephrotoxicity, associated with its direct antioxidant and anti-inflammatory impacts (16).

In another investigation, Topcu-Tarladacalisir *et al.* uncovered that besides antioxidant and anti-inflammatory impacts, curcumin enhances the laboratory information status in animals, such as histopathological alterations, inflammatory reaction (myeloperoxidase and TNF-α, IL-1β, IL-6, IL-10 levels), malondialdehyde lipid peroxidation, renal tubular cell apoptosis (active caspase-3), the expression of corresponding proteins (p53, Fas, and Fas ligand) and kidney function (urea and Cr) biomarkers (36).

The curcumin renal protective impacts on further nephrotoxic substances like doxorubicin (39), gentamycin (40), and cyclosporine (41) were likewise illustrated. In 2018, Benzer *et al*. studied the management of 100-200 mg/kg curcumin in rats treated with doxorubicin for one week. They discovered that the renal protective impacts of curcumin resulted in reducing serum toxicity markers and rising antioxidant enzyme actions. Curcumin supplementation was related to diminishing the quantities of inflammatory and oxidative DNA impairment markers. These results revealed that curcumin defends against doxorubicin-induced nephrotoxicity (39).

More information available from clinical experiments concerning the effects of curcumin on nephrotoxic substances is required. However, in a newly issued meta-analysis, curcumin underwent clinical impacts in improving cancer therapy. In this respect, outcomes underlined that curcumin co-management with medicinal methods, including radiotherapy or chemotherapy, enhanced patients' survival duration, increased anti-metastatic protein expression, and decreased their adverse effects (42). Furthermore, there are some records about the influence of curcumin on ameliorating chemotherapy's unfavorable impacts, like dermatitis (43) or mucositis (44).

Kia et al. examined the influences of nano micelle curcumin on oral mucositis caused by radiotherapy in patients with head and neck cancer. The patients received curcumin nano micelle capsules at 80 mg twice daily for seven weeks. They demonstrated that the curcumin-treated group experienced lower levels of pain and mucositis severity. Eventually, they deduced that curcumin capsules effectively prevent and treat mucositis caused by chemotherapy (45). Based on all records, curcumin is an efficacious and secure substance for the co-management treatment of chemotherapy drugs to relieve unfavorable effects and cancer cells' increasing sensitivity to chemotherapy.

In addition, there are many potential documents for preventing renal toxicity during the management of nephrotoxic chemotherapy substances reviewed by Chiruvella *et al*. (46).

In 2021, a study to evaluate the feasibility and potential efficacy of nano-curcumin supplementation in patients with localized

muscle-invasive bladder cancer was conducted. In this double-blind, placebo-controlled trial, 26 patients were randomized to receive either nano-curcumin (180 mg/day) or placebo during chemotherapy and followed up for four weeks after the end of treatment to assess the complete clinical response to the chemotherapy as a primary endpoint. In addition, in this study, the nephrotoxicity incidence of cisplatin in patients receiving curcumin was checked. The limited sample size of the study is considered a noticeable hindrance to reaching a certain conclusion, despite the findings indicating the potential nephroprotective benefits of curcumin supplementation (47).

Our results indicated that the group treated with curcumin experienced considerable positive alterations in their renal function. This was indicated by amelioration in their GFR, Cr, BUN, and urine NGAL-to-Cr levels. However, the BUN index can indicate azotemia and the increase in its levels may be due to kidney injury that is pre-renal, renal, or post-renal. Blood urine nitrogen should not be solely relied upon as an indicator of kidney function. It should be analyzed alongside other indicators; however, when it was reported by significant alleviation in Cr and NGAL-to-Cr ratio, the BUN changes are justifiable (42,46-48). Also, there was a notable discrepancy in the pattern of GFR recovery between the curcumin and placebo groups. However, regarding the BUN levels in the curcumin group, it can be deduced that the overall influence of curcumin supplementation was pursuing kidney function enhancement.

Owing to the prolonged increase of serum creatinine as a biomarker of CIN, additional new biomarkers, like kidney injury molecule 1, NGAL, and cystatin-C, have been proposed for primarily identifying CIN (49). A rise in the concentration of SCr cannot indicate all features of kidney injury, while tubular impairment is the primary outcome of CIN. Moreover, we used urinary NGAL, a new, greatly sensitive, and particular marker for identifying CIN. Our outcomes exhibited, though negligible, that the urine NGAL level of the curcumin group was lower in both 24 h and five days after cisplatin administration compared to the placebo. Likewise, the urine NGAL-to-Cr ratio displayed a considerable reduction compared to the placebo group in both periods, affirming the probable defensive effect of curcumin supplementation in CIN.

Further, we investigated the influence of curcumin supplementation on CIN and salt wasting caused by cisplatin. Consequently, the urine excretion ratio of electrolytes, such as sodium, potassium, and magnesium, was calculated. Cisplatin-induced urinary magnesium wasting is a frequent unfavorable impact during cisplatin-based regimes in as many as 90% of patients (7). Additionally, routine observation of serum magnesium and management of supplementary magnesium has been suggested in patients receiving cisplatin-based chemotherapy regimens. In our investigation, curcumin could not indicate a substantial positive effect on CIN because cisplatin induces salt-wasting, particularly sodium, and magnesium. However, the possible protective impact of curcumin on cisplatin-induced salt wasting should be assessed in comprehensive and well-designed clinical studies.

Despite the confirmed effects of curcumin on biology and medicine, there is a concern that it may not be effective in human patients due to its low uptake rate and bioavailability when taken orally. The oral availability of curcumin is evaluated to be approximately 1% (50), resulting in executing different pharmaceutical mechanisms like solid dispersions, nano/microparticles, polymeric micelles, and nanosuspensions to enhance its value (51). During the examination, we employed a curcumin nanoparticle named Sinacurcumin®, which was found to ensure more acceptable security and bioavailability in earlier published investigations (52,53).

To indicate the proper dose of curcumin plasma level in phase II, an open-labeled randomized controlled trial in colorectal cancer patients by Howells *et al*. examined the influence of adding the curcumin supplement to the FOLFOX regime. They discovered that curcumin is a secure and tolerable complement to the FOLFOX chemotherapy regimen. The levels of curcumin and its metabolite, curcumin glucuronide, were assessed in this experiment. They deduced that a significant level of

curcumin glucuronide (> 1.00 pmol/mL) in plasma specimens of patients acquiring curcumin additions was calculated (54).

There are several limitations to our examination. Our investigation held a restricted sample size because we faced challenges recruiting cancer patients. Further, the treatment protocol only involved one cycle of cisplatin administration. Thus, we could not evaluate the impact of curcumin supplementation on the accumulative nephrotoxicity of cisplatin treatment during successive rounds of chemotherapy. In this respect, patient adherence was inevitable for the first planned clinical experiments.

Conversely, the significant unfavorable impacts, like AKI and hypomagnesemia, may appear 4 or 5 days after cisplatin administration and in some way after release from the hospital. In comparison, our follow-up period was restricted to 5 days. All restrictions did not identify statistically substantial results in probable defensive impacts of curcumin on AKI incidence or salt wasting. However, other methods, like raising the curcumin dosage to overcome its low bioavailability and follow-up period, could be beneficial.

However, regular saline hydration in cisplatin dose protocols can considerably affect the absolute level of urinary markers. Although it has benefits, correcting urine markers to creatinine should not be optimal for cancer patients as their nutrition and catabolic condition can remarkably impact creatinine excretion (55).

Overall, performing additional investigations with more substantial sample sizes, different curcumin dosages, and a more extended follow-up period are recommended. In addition, future clinical experiments should investigate the impact of administering curcumin as a pretreatment for a duration exceeding 24 h.

CONCLUSION

This investigation detected a reduction in AKI incidents in the curcumin group in comparison to placebo, though it was not statistically influential. Pretreatment with curcumin may have the potential to alleviate BUN and demonstrate some helpful influence on GFR as a marker of kidney function. Likewise, it could considerably decrease the urinary NGAL-to-Cr ratio as a marker of tubular kidney injury. Curcumin could not indicate a substantial positive effect on CIN remarkably because cisplatin induces salt-wasting, particularly sodium and magnesium. Hence, considering the security and tolerability of curcumin and the paucity of data, it can be recommended as a secure and potentially advantageous supplement for further clinical studies in this era.

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Conflict of interest statement

The authors declared no conflicts of interest in this study.

Authors' contributions

A. Moghaddas, H. Mehrab, MH. Aarabi and M. Sharifi assisted with the literature review, study design, acquiring the data, writing and revising the manuscript; A. Akhavan, M. Sharifi, A. Moghaddas, E. Mosavi, and H. Mehrab were responsible for enrolling the patients; H. Mehrab and M. Mansourian were responsible for data collecting and analysis; A. Moghaddas supervised the entire investigation. The finalized article was approved by all authors.

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