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Original Research Article

The protective effect of curcumin capsules on cisplatin-induced nephrotoxicity: A double-blind randomized controlled trial

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Abstract

Objective: Cisplatin, a widely used chemotherapeutic agent, is widely used in cancer treatment, but its clinical application is limited by nephrotoxicity. Curcumin, a natural polyphenol with antioxidant properties, may mitigate cisplatin-induced kidney damage. This study evaluated the protective effects of curcumin in cancer patients undergoing cisplatin chemotherapy.

Materials and Methods: This study was designed as a randomized controlled trial, and 50 cancer patients were assigned to either an intervention group receiving 500 mg/day standardized turmeric extract capsules for nine weeks or a control group receiving a placebo, alongside standard chemotherapy. Renal markers including serum creatinine (Cr), blood urea nitrogen (BUN), magnesium (Mg), and glomerular filtration rate (GFR) were measured pre- and post-intervention. Data were analyzed using ANCOVA adjusting for baseline values.

Results: Post-intervention analysis showed notable differences between the intervention and control groups in Cr ($p=0.01$), Mg ($p<0.001$), and GFR ($p=0.001$) levels, with improvements observed in the intervention group. However, BUN values showed no considerable difference ($p=0.71$). In the intervention group, intragroup comparisons indicated substantial reductions in Cr ($p=0.001$) and increases in Mg ($p<0.001$) and GFR ($p<0.001$). Conversely, in the control group, Cr ($p=0.001$) and BUN ($p=0.007$) levels showed a significant increase, while Mg ($p=0.001$) increased slightly, and GFR levels decreased markedly ($p<0.001$).

Conclusion: While the findings indicate that curcumin supplementation may offer some protective effects against cisplatin-induced nephrotoxicity, the limited sample size of this trial warrants caution in interpreting these results. Additional studies involving larger and more heterogeneous cohorts are required to confirm these results and determine the clinical relevance of curcumin in this setting.

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Introduction

Globally, an estimated 19.3 million new cancer cases and nearly 10 million cancer-related deaths occurred in 2020 (Sung et al. 2021). Projections indicate that the number of new cases is expected to rise to 28.4 million by 2040, highlighting a significant increase in the global cancer burden (Ghufran et al. 2023). Surgery, chemotherapy, and radiotherapy are commonly used for cancer treatment, and nanotechnology plays a supportive role by enabling the delivery of therapeutic agents. Chemotherapy is one of the most effective and widely used methods for treating all types of cancer (Rezakhani et al. 2022), which uses certain drugs to kill cancer cells or prevent tumor growth and metastasis (Anand et al. 2022; Soerjomataram and Bray 2021). Cisplatin, with the platinum base used as a potent and valuable chemotherapeutic agent, is a turning point in modern chemotherapy (Ghosh 2019). Cisplatin has markedly improved cancer management, as it is widely applied in the treatment of various solid tumors (Romani 2022). Dose-dependent cumulative nephrotoxicity is the major limitation of cisplatin-based chemotherapy and may necessitate dose reduction or treatment discontinuation.(Li et al. 2020). Several mechanisms are involved in the renal toxicity of this drug, the most important of which are the production of Reactive Oxygen Species (ROS) and hydroxyl radicals which cause the peroxidation of fats, the destruction of cell membranes, the oxidation of proteins and nucleic acids, and tissue destruction, which result in the reduction of glomerular filtration and the occurrence of acute kidney toxicity (Dewaeles et al. 2022; Loren et al. 2021).

Numerous natural compounds have been identified for their potential protective effects against nephrotoxicity, particularly in the context of chemotherapy. Among these, silymarin has gained attention due to its hepatoprotective and anti-inflammatory properties (Karimian et al. 2024). Recent studies including a randomized, placebo-controlled trial, have shown that silymarin supplementation can significantly improve liver function in cancer patients undergoing chemotherapy, while demonstrating a favorable safety profile. This highlights the importance of exploring various antioxidant agents, such as curcumin, for their potential roles in mitigating cisplatin-induced nephrotoxicity (Erfanian et al. 2024).

Recent studies have shown that pretreatment with curcumin significantly attenuates cisplatin-induced mitochondrial toxicity in renal tissues and restores both enzymatic and non-enzymatic antioxidant levels. These findings suggest that the reno-protective effects of curcumin may be attributed to its ability to scavenge free radicals and enhance the antioxidant defense mechanisms within kidney mitochondria (Waseem et al. 2013).

Studies show that immediately after the use of cisplatin, symptoms of nephrotoxicity such as a decrease in Glomerular Filtration Rate (GFR) and an increase in Blood Urea Nitrogen(BUN)and creatinine levels are observed (Liu et al. 2018). Following a single dosage of cisplatin, around 25 to 35 percent of patients show signs of nephrotoxicity. The symptomatic lesion in patients with acute kidney failure is acute necrosis of the proximal tubule (Salman et al. 2014).

In recent years, there has been a great interest in the multiple activities of natural molecules (Badiei et al. 2023; Huang et al. 2021; Rahmati et al. 2023). Curcumin, a natural yellow compound present in turmeric rhizomes (*Curcuma longa* L., Zingiberaceae), has a wide range of pharmacological and biological activities (Lestari and Indrayanto 2014). Curcumin has been claimed to be a potential anti-inflammatory agent. The anti-inflammatory and antioxidant effects of curcumin have been evaluated in different *in vitro* and *ex vivo* models (Grynkiewicz and Ślifirski 2012; Sumanont et al. 2004). Curcumin is a

dual-functional antioxidant that can directly quench free radicals or regulate various cellular protective and antioxidant proteins (Zhang et al. 2022). Also, several studies have reported that curcumin protects the kidneys by preventing mitochondrial damage, modulating inflammatory responses, boosting antioxidant defenses, and lowering oxidative stress levels. Curcumin can act as a protector against cisplatin nephrotoxicity through its anti-inflammatory activity attributed to its direct anti-inflammatory and strong antioxidant properties. Hence, curcumin has a strong potential for adjuvant therapy in cisplatin nephrotoxicity (Soetikno et al. 2013).

Studies show that curcumin reduces cisplatin-induced nephrotoxicity by preventing oxidative stress, inflammation, and apoptosis. Therefore, these results may provide a basis for further research on the effects of curcumin and contribute to the development of preventive strategies against cisplatin-induced nephrotoxicity. However, most of the available evidence has been obtained from cell line and animal studies, and clinical evidence in humans remains limited. Thus, we aimed to investigate the effects of curcumin in reducing the renal complications of cisplatin in humans. This study aimed to investigate the protective effects of curcumin on acute kidney toxicity caused by cisplatin treatment in people with cancer.

Materials and Methods

Study design and population

This double-blind, randomized controlled trial was conducted at the Cancer Research Center of Shahrekord University of Medical Sciences from September 2021 to December 2023.

This trial and its formulation received approval from the Ethics Committee of Shahrekord University of Medical Science (IR.SKUMS.MED.REC.1401.037). A total of 50 newly diagnosed cancer patients with various types of cancer, who met the eligibility criteria were recruited through convenience sampling. Participants were randomly assigned to either the intervention group (n=25) or the control group (n=25) using a block randomization method. Sample size calculation was performed based on the study of Kia et al. (2021), taking into account a mean difference of 0.17 and a standard deviation of 0.14 for the variable of serum creatinine, as well as the type 1 error (α= 0.01) and the type 2 error (β= 0.10), the required sample size was calculated equal to 21 patients in each group, taking into account possible dropouts of 15%, the required sample size was estimated as 25 in each group (Kia et al. 2021). Patients were enrolled before the start of cisplatin chemotherapy, and the initiation of this study coincided with the commencement of their chemotherapy regimen. In addition to standard chemotherapy, the intervention group received 500 mg standardized turmeric extract capsules (Each capsule contained 50 mg turmeric rhizome extract,Curcuma Dineh, manufactured by Dineh Iran Pharmaceutical Company) once daily for 9 weeks, while the control group received standard chemotherapy and placebo. The placebo capsules were prepared by the same company and were visually identical to the curcumin capsules.

Inclusion and exclusion criteria

Inclusion criteria included cancer patients aged 5–60 years who were treated with cisplatin, had no kidney tumors or kidney failure, and were receiving similar medications and supplements. Exclusion criteria included the occurrence of any adverse effects, refusal to continue participation, death, or a diagnosis of kidney stones. All patients received the standard treatment throughout the study, and the intervention did not result in any treatment-related adverse effects.

Data gathering

Demographic baseline characteristics (age, gender, and weight) were recorded for

all participants. Before and after the intervention, key biomarkers were measured, including creatinine (Cr), magnesium (Mg), blood urea nitrogen (BUN), glomerular filtration rate (GFR), white blood cells (WBC), hemoglobin (HGB), and platelets (PLT). The study maintained a double-blind design, ensuring that both patients and researchers were unaware of the group assignments.

Data analysis

After data collection, their analysis was done using SPSS version 20 software. A total of 50 patients (25 in the intervention and 25 in the control group) were included in this study. The principal investigator and the data analyst were blinded to the content of the medication assigned to the participants. Data were analyzed using descriptive statistics and inferential statistics using the Chi-square test, Mann-Whitney and ANCOVA test for intergroup comparisons, and the Wilcoxon test for intragroup comparisons.

Ethical considerations

Prior to enrollment, all participants provided written informed consent to take part in the study. This study was conducted following the principles of the Declaration of Helsinki and was approved by the ethics committee of Shahrekord University of Medical Sciences (IR.SKUMS.MED.REC.1401.037).

Results

Patient characteristics

In this double-blind clinical trial study, the effect of curcumin capsules on preventing kidney damage caused by chemotherapy with cisplatin was investigated. A total of 50 cancer patients treated with cisplatin were initially recruited, with 49 individuals meeting the eligibility criteria. In the intervention group, 1 participant died and was subsequently excluded from the study, resulting in data analysis based on 24 individuals in this group. Some of the demographic information of the study subjects, including the age, weight, and gender of the participants, is shown in (Table 1).

As presented in Table 1, the mean age of the patients was 58.04 years in the intervention group and 58.28 years in the control group, indicating no significant difference between the two groups. Additionally, there was no significant difference in the weight of the participants between the intervention and control groups ($p = 0.13$). The results also showed no statistically significant difference in the gender distribution of the participants between the two groups ($p = 0.24$), with the control group consisting of 9 females and 6 males, and the intervention group consisting of 5 females and 19 males.

Table 1. Baseline demographic and clinical characteristics of the study participants

Variable		Control group	Intervention group	p-value
age (years)		58.28± 14.9	58.04± 9.8	0.95
weight (kg)		60.92± 13.0	66.04± 10.2	0.13
Gender	Female	9 (36.0)	5 (20.8)	0.24
	Male	16 (64.0)	19 (79.2)	
Cancer type	Bladder	9 (36.0)	9 (37.5)	0.850
	Testicular	2 (8.0)	3 (12.5)	
	Ovarian	3 (12.0)	4 (16.7)	
	Lung	11 (44.0)	8 (33.3)	
Cisplatin dose (mg/m²), mean ± SD		85.96 ± 9.06	85.58 ± 9.09	0.885

Data are presented as mean ± standard deviation (SD) for continuous variables and number (%) for categorical variables.

Clinical outcomes of curcumin supplementation

The average values of Mg, BUN, Cr, and GFR during the study in the intervention and control groups are presented in Table 2. The Wilcoxon analysis for intra-group comparison showed a significant difference in Mg, BUN, Cr, and GFR values in both groups after the intervention. The results of the statistical tests indicated a substantial increase in Mg ($p<0.001$) and GFR values ($p = 0.001$) following the intervention. Additionally, Cr values decreased significantly ($p<0.001$). Moreover, the BUN level decreased after the intervention, and this decrease was statistically significant ($p = 0.02$).

The results of the statistical tests showed no significant differences in WBC ($p = 0.60$), HGB ($p = 0.86$), or PLT ($p = 0.06$) values between the intervention and control groups after the intervention (Table 3).

Table 2. Comparison of Mg, Cr, BUN, and GFR levels before and after the intervention in the groups of study.

Variable	Control group	Intervention group	p-value
Mg(mg/dL) before the intervention	2.00 (1.90, 2.80)	1.80 (1.63, 1.90)	0.04
Mg(mg/dL) after intervention	1.70 (1.60, 1.80)	1.90 (1.80, 2.00)	<0.001*
P-value Within-group	<0.001	<0.001	-
Creatinine (mg/dL) before intervention	1.00 (0.80, 1.20)	0.98 (0.82, 1.18)	0.49
Creatinine (mg/dL) after intervention	1.10 (0.93, 1.30)	0.88 (0.75, 1.00)	<0.001*
P-value Within-group	0.001	0.001	-
BUN (mg/dL)before intervention	20.00 (12.50, 29.50)	25.00 (20.00, 30.00)	0.08
BUN (mg/dL)after intervention	21.00 (17.00, 28.00)	21.00 (18.00, 27.00)	0.02*
P-value Within-group	0.007	0.001	-
GFR(mL/min/1.73 m²) before intervention	74.57 (59.63, 79.81)	80.43 (65.70, 96.37)	0.16
GFR(mL/min/1.73 m²) after intervention	64.91 (57.63, 74.48)	86.63 (72.58, 113.81)	<0.001*
p-value Within-group	<0.001	<0.001	-

* ANCOVA test, considering the baseline values as covariate.
Values are presented as median (Q1, Q3); numbers in parentheses indicate the first (Q1) and third (Q3) quartiles.

Table 3. Comparison of blood WBC, HGB, and PLT levels before and after the intervention in the intervention and control groups.

Variable	Control group	Intervention group	p-value
WBC(×10³/µL) before intervention	5500 (4300, 6600)	5750 (4125, 10500)	0.67
WBC (×10³/µL) after intervention	5250 (4350, 6650)	5450 (4250, 10000)	0.59*
p-value Within-group	0.03	0.01	---
HGB(g/dL) before the intervention	11.80 (10.35, 13.30)	12.00 (11.05, 13.50)	0.60
HGB(g/dL) after the intervention	11.60 (9.90, 12.90)	11.65 (10.03, 13.50)	0.86*
p-value Within-group	0.02	0.003	---
PLT (×10³/µL) count before intervention	180.0 (132.0, 200.0)	200.0 (162.2, 257.2)	0.06
PLT (×10³/µL) count after intervention	165.0 (130.0, 190.0)	180.0 (151.2, 218.0)	0.05*
p-value Within-group	0.001	0.01	---

* ANCOVA test, considering the baseline values as covariate.Values are presented as median (Q1, Q3); numbers in parentheses indicate the first (Q1) and third (Q3) quartiles.

Discussion

Cisplatin is a widely used chemotherapeutic agent in the treatment of solid tumors. However, nephrotoxicity remains its primary dose-limiting adverse effect, and significant efforts have been directed toward mitigating these renal complications (Duffy 2018). Cisplatin has been shown to decrease the levels and activity of natural antioxidant enzymes such as superoxide dismutase (SOD), thereby contributing to oxidative stress and cytotoxicity (Zhou et al. 2022). In light of these issues, curcumin, as a natural product extracted from turmeric with antioxidant capabilities emerged as a promising candidate to mitigate the toxic effects of cisplatin and combat cisplatin-resistant cancer cells (Rezaee et al. 2017). Numerous studies have highlighted curcumin ability to counteract cisplatin-induced toxicity, reinforcing its potential as a powerful tool in enhancing the therapeutic index of cisplatin and improving patient outcomes; hence, the antioxidant effect of curcumin can lessen the cytotoxicity induced by cisplatin, while enhancing its therapeutic benefit (Hussain et al. 2021). This dual benefit arises from curcumin antioxidant and anti-inflammatory properties. Thus, the combination of cisplatin and curcumin may enhance therapeutic efficacy, reduce toxicity, and improve patient outcomes by lowering cisplatin resistance and the required chemotherapy doses.

Evidence from recent randomized controlled trials (RCTs) and meta-analyses indicates that curcumin supplementation may provide systemic benefits beyond nephroprotection. For instance, a randomized controlled trial showed improvements in vascular and cognitive functions in patients with chronic kidney disease (Gimblet et al. 2024) and a recent systematic review and meta-analysis confirmed beneficial effects of curcumin on renal function across multiple clinical trials (Sadeghian et al. 2023). These findings further support the multifunctional therapeutic potential of curcumin in renal pathologies. This study aimed to assess the potential protective role of curcumin in patients undergoing cisplatin-based chemotherapy.

Our findings indicate that daily administration of 500 mg standardized turmeric extract capsules significantly improved glomerular filtration rate (GFR) in the intervention group compared to the control group**.**These results are consistent with previous studies conducted on animal models and cell lines, which reported dose-dependent renoprotective effects of curcumin (El-Gizawy et al. 2020). Curcumin has been discovered to protect against cisplatin nephrotoxicity, which is attributed to its antioxidant and anti-inflammatory properties. In a study by (Louisa et al. 2023) curcumin was found to improve serum Cr and BUN levels**.** The observed improvements in renal function in our study can be attributed to curcumin ability to decrease Cr and BUN levels while increasing serum Mg levels, collectively enhancing GFR. These findings highlight the clinical relevance of curcumin in mitigating cisplatin-induced nephrotoxicity. Similar renal protective effects of curcumin have also been documented for other nephrotoxic agents, including gentamicin (Abdelmoaty and Imam 2018), cyclosporine (Fattah et al. 2010), and polymyxin (Vazin et al. 2020). Moreover, Fan et al. found that curcumin, as a multifunctional agent, exhibits a protective effect against doxorubicin-induced nephrotic syndrome in mice. This finding provides a pharmacological basis for the further development of curcumin and underscores the potential benefits of multi-targeted drugs (Fan et al. 2020).

Interestingly, recent research has shown that a mixed hydroalcoholic extract of *Nigella sativa* and *Curcuma longa* also provides significant renal protection against (Mohebbati et al. 2017) reported that the combined administration of Nigella sativa and Curcuma longa extracts attenuated adriamycin-induced renal injury in rats by reducing urinary protein excretion and

improving serum albumin levels. These findings suggest that combining curcumin with other natural bioactive compounds may enhance its nephroprotective effects. However, further clinical studies are needed to determine whether such synergistic effects can also be achieved in patients receiving cisplatin-based chemotherapy

Consistent with our results, Mehrab et al. reported that curcumin supplementation may have the potential to reduce cisplatin-induced nephrotoxicity in cancer patients. However, the study also emphasizes the need for more information from clinical trials to better understand the effects of curcumin on nephrotoxic substances (Mehrab et al. 2023).

The results of Cao et al. study, which investigated the combined effect of curcumin and metformin against gentamicin-induced nephrotoxicity, demonstrated that curcumin, when used alongside metformin effectively reduces gentamicin-induced nephrotoxicity (Cao et al. 2019). Additionally, another study investigating the protective effect of curcumin on reducing proteinuria in patients with diabetic nephropathy found that curcumin had a significant effect after two months of intervention, even in patients with a slight decrease in GFR (Vanaie et al. 2019).

However, not all studies align with our findings. For instance, an investigation into the protective effects of curcumin against nephrotoxicity caused by contrast material in patients undergoing selective coronary angiography found that, although curcumin reduced creatinine levels, this difference was not statistically significant. Additionally, no significant difference was observed in GFR changes between the two groups (Sabaghian et al. 2020). These findings are not consistent with the results of the present study, which may be attributed to differences in the research population.

In our study, intra-group comparisons in the control group revealed significant differences in Cr, BUN, Mg, and GFR values before and after the intervention. Specifically, there was an increase in Cr and BUN levels along with reductions in Mg and GFR rate. These changes indicate that cisplatin nephrotoxicity is common, as evidenced by increased Cr and BUN levels, decreased serum Mg levels, and reduced GFR. These findings align with previous studies, including the study by Sutandyo et al. who reported that nephrotoxicity, marked by a decrease in GFR, occurred in 45.2% of patients undergoing cisplatin-based chemotherapy courses (Sutandyo et al. 2023). Similarly, the study by Ghadrdan et al. investigated the effect of melatonin on cisplatin-induced renal toxicity and reported that renal biomarkers, including blood and urine creatinine, increased, while GFR levels decreased following cisplatin administration. This finding further supports the notion that cisplatin induces significant nephrotoxicity, as evidenced by the increase in creatinine levels and the decrease in GFR (Ghadrdan et al. 2020).

This study demonstrated that curcumin supplementation may help reduce cisplatin-induced nephrotoxicity and improve renal function parameters in cancer patients receiving cisplatin chemotherapy. Although curcumin has generally shown a favorable safety profile in clinical studies, further large-scale randomized controlled trials are required to confirm its efficacy and safety before it can be routinely recommended as an adjunct to cisplatin-based chemotherapy.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to this work

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Ethical Considerations

This research was conducted following the guidelines of the Ethics Committee of Shahrekord University of Medical Sciences and was approved with the ethics code IR.SKUMS.MED.REC.1401.037. The study is also registered with the Iranian Registry of Clinical Trials (IRCT) under the code IRCT 20221211056777N3.

Code of Ethics

20221211056777N3.

Authors' Contributions

All authors contributed to the conception and design of the study, as well as to the preparation of materials and the collection of data were performed by K. Fekri, R. masoumi, P Javadian, Y salehi, and M. Haghani. Data analysis was conducted by H. Raeisi Shahraki. The first draft of the manuscript was written by M. Haghani and Sh. Rahmati. All authors reviewed earlier drafts, and gave final approval of the manuscript.

Informed consent

All participants were fully informed about the purpose of the study, the methods involved, and any possible risks and benefits. This information was presented in a clear and accessible manner. It was clearly explained that participation was completely voluntary, and participants were free to withdraw at any point without any impact on their medical treatment.

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