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NEPHROPROTECTION OF CURCUMA LONGA EXTRACT IN RATS WITH ACUTE RENAL FAILURE

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Abstract:
Background: Acute renal failure (ARF) is a severe clinical problem associated with a quickly renal functions decline. Curcuma longa, a medicinal plant with antioxidant and anti-inflammatory features, a lot of previous studies confirm the correlation between used this medical plant and enhance the vital body functions. Therefore, the current study designed to assessment the protection role of Curcuma longa extract against toxic effect of cisplatin to induced ARF in rats by assessing renal function biomarkers, apoptosis markers, and histopathological changes.
Methods: 36 male Wistar rats were selected to achieve the current study by divided them into six groups. first group was control, the second cisplatin-only (5 mg per kg), the third cisplatin with low-dose Curcuma longa (100 mg per kg, orally), the fourth cisplatin and moderate-dose Curcuma longa (150 mg/kg, orally), fifth cisplatin and high-dose Curcuma longa (200 mg/kg, orally), and the last group was with extract-only. Renal functions tests were evaluated by check both of a serum creatinine and blood urea nitrogen (BUN). The CD95L also called Fas Ligand (FasL) was selected as apoptotic markers and Fibroblast Growth Factor-23(FGF-23) biomarkers selected as nephroprotection marker, both of them were assessed using ELISA. Histopathological analysis was performed to examine renal tissue changes.
Results: Cisplatin administration significantly increased creatinine, BUN, FGF-23, and CD95L levels, indicating nephrotoxicity and apoptosis. Curcuma longa extract, particularly at moderate and high doses, significantly reduced these biomarkers compared to group administrated with Cisplatin-only ($p < 0.05$), suggesting renal protection. Histopathological examination further confirmed reduced renal damage in extract-treated groups, with improved tubular integrity and decreased inflammatory cell infiltration.
Conclusion: Curcuma longa extract exhibits dose-dependent nephroprotection role to attenuated the toxic effect of Cisplatin which induced ARF, through antioxidant, anti-inflammatory, and also anti-apoptotic mechanisms. These findings highlight its potential as an adjunct therapy for mitigating cisplatin nephrotoxicity.

Keywords: Cisplatin, ARI, ARF, Curcuma Longa, Medical plant, CD95L, and FGF-23.

Introduction

Acute renal failure (ARF), or acute kidney injury (AKI), is a critical clinical problem correlated with decline renal function tests quickly, there are many causes lead to ARF development such as ischemic, toxic, or septic. Its pathophysiology is complex and included interactions among cellular injury, inflammation, apoptosis, and impaired renal repair mechanisms. (Awdishu & Wu, 2017; Verma & Kellum, 2021) ARF development is result by multiple mechanisms, including renal vasoconstriction, oxidative stress, and tubular and microvascular damage. furthermore, hemodynamic alterations, such as reduced renal blood flow and impaired autoregulation due to drug interference. All there previous factors associated with distribute in renal function tests. (Basile et al., 2012; Scholz et al., 2021)

ARF is a one of growing challenge globally, and considered major causes of hospitalized patients. The incidence was increased in last two decades and this increasing belong to improved recognition, enhanced medical documentation, and more precise diagnostic criteria. In addition the aging of population and increased the incidence of other systematic diseases such as cardiovascular disease, diabetes. (Rewa, & Bagshaw, 2014).

Diagnosing acute renal failure (ARF) is challenging due to the absence of simple diagnostic criteria. The RIFLE classification (Risk, Injury, Failure, Loss, End-stage kidney disease) provides a standardized framework to assess ARF severity, from mild dysfunction to the necessity for dialysis or renal replacement therapy. Therefore, the renal biomarkers are being take attention to improve early detection, diagnosis, and prognosis ARF. (Kellum, 2008; Bellomo et al., 2012)

A lot of markers play a vital role in the diagnosis and prognosis of kidney injuries. (Tejchman et al., 2021; Jana et al., 2022) One of the biomarkers used in the current study is CD95L, which is a member of the tumour necrosis factor receptor family and activates the extrinsic apoptotic pathway upon binding Fas ligand (FasL). In ARF, infiltrating immune cells and damaged renal cells express FasL, engaging CD95L on tubular cells to drive caspase-8-mediated apoptosis. CD95L also amplifies inflammation, creating a vicious cycle of cell death and immune activation. This dual role positions CD95L at the nexus of apoptosis and inflammatory injury in ARF. (Albertine et al., 2002; Linkermann et al., 2011)

Another biomarker used is Fibroblast Growth Factor (FGF) which promotes renal repair through mitogenic, anti-apoptotic, and metabolic regulatory effects. FGF signalling enhances tubular cell proliferation, modulates oxidative stress, and may counteract apoptotic pathways by stabilizing mitochondrial integrity or suppressing caspase activity. (Hindricks et al., 2014; Neyra et al., 2015)

Acute Renal Failure (ARF) has received growing attention in clinical practice and public health due to its significant effect on morbidity and mortality. In addition to the rapidly increasing worldwide incidence, ARF has emerged as a significant predictor of chronic kidney disease and end-stage renal disease. (Hoste et al., 2018)

However, any efforts that may contribute to enhancing diagnosis or improving the prognosis are valuable. Therefore, the current study is designed to evaluate the healing effect of Curcuma longa extract in Cisplatin-induced Acute Renal Failure in rats.

2. Materials and Methods

2.1. Animals and Ethical Approval

The first, the scientific and ethical committee in the Medical Laboratory Department, College of Medical and Health Techniques, University of Bilad Alrafidain has approved the current study which achieved in a period between July 2024 to January 2025. 36 Male Wistar rats (200-250 g) were used in the current study and the animals were maintained under standardized laboratory conditions, including a 12-hour light/dark cycle, controlled ambient temperature, and unrestricted access to food and water.

2.2. Experimental Groups

The rats were randomly divided to six experimental groups, with each group consisting of six animals. Control group, administrated with normal saline without cisplatin or Curcuma longa extract. In the cisplatin group, cisplatin with a single dose (5 mg/kg, intraperitoneal) utilized to induce ARF. While in Cis-low dose Curcuma longa Group cisplatin (5 mg/kg, IP) and Curcuma longa extract (100 mg/kg, orally, daily for 7 days). Cis-Moderate dose Curcuma longa Group including administration of cisplatin (5 mg/kg, IP) with Curcuma longa extract (150 mg/kg, orally, daily for 7 days). In Cis-high dose Curcuma longa group included administration of Cisplatin (5 mg/kg, IP) with Curcuma longa extract (200 mg/kg, orally, daily for 7 days). In the last group and to prevent the predicted toxic effect of the extract itself, this group administered with extract only.

2.3. Induction of Acute Renal Failure

To induce the nephrotoxicity, Cisplatin (5 mg/kg, IP) was administered as a single then monitored the Rats via creatinine level assessment to confirm the acute renal failure statement (>2.0 mg/dl).

2.4. Plant extract

Curcuma Longa was purchased from a local market in Muqdadiyah, Diyala, Iraq. The method of bioactive extract was mentioned in a previous study (Sahne et al., 2016) which summarized as, Turmeric rhizomes were oven-dried at 105 °C for 3 hours, then ground using a mortar and sieved (mesh 80) to obtain a uniform powder (0.18 mm particle size). The powdered turmeric was stored in a refrigerator to prevent moisture absorption and maintain its stability. For the extraction process, 15 g of turmeric powder was subjected to Soxhlet extraction using acetone as the solvent to ensure efficient isolation of bioactive compounds. The process was conducted at 60 °C for 8 hours. After extraction, acetone was removed using a rotary evaporator with suitable pressure at 35 °C. The remaining oleoresin was dried, weighed, and dissolved in 10 ml of methanol for curcumin content analysis via HPLC. To dissolve the powder, Acetone utilized because it has high capacity to solubilization. The HPLC technique was used as described in the same previous study.

2.4.1. Dose administration

Curcuma longa extract (curcumin) is administered via oral gavage daily for 7 days post-cisplatin injection.

2.5. Animals sacrificing

To animals sacrificing rats, an anaesthetizing mixture of 0.1 ml of xylazine mixed with 0.5 ml ketamine used as mentioned in Kavakli et al., (2011).

2.5.1. Sample collection

After sacrificing the animals, approximately 5 ml of blood was collected via direct heart puncture. The kidneys were then placed in a formalin-filled container. To improve fixation, the organs were washed with normal saline and punctured with a needle to facilitate fixative infiltration into the tissues.

2.6. Laboratory Tests.

2.6.1. Serological Analysis

Blood samples were collected on days 0, 3, and 7. A serum creatinine test was done to monitor the ARF (>2.0 mg/dl) development in rats and compare among study groups. Then by ELIZA technique, CD95L (fasL), and Fibroblast growth factor 23 assessment were done.

2.6.2. Histopathological Examination

The kidney organ collected for histological assessment via hematoxylin and eosin (H&E) staining by procedure as mentioned in the previous study. (Al-Tameemi et al., 2024) Tissue damage scored based on tubular degeneration, inflammation, and necrosis.

2.7. Statistical Analysis

The data obtained in this study were analyzed using GraphPad Prism (version 8.0). A one-way ANOVA was conducted, followed by Tukey's multiple comparisons test to evaluate differences between groups. A p-value of less than 0.05 was considered statistically significant.

3. Results

The mean serum creatinine concentrations across study groups are shown in Table 1. Tukey’s post hoc analysis revealed no significant differences between the control and extract-only groups (mean difference [MD] = 0.0702 mmol/L, 95% CI: -0.5534 to 0.6938, p-value = 0.9993). However, cisplatin-only (Cis-only) treatment significantly increased creatinine levels compared to groups receiving cisplatin combined with moderate or high doses of the extract. Specifically, the Cis-only vs. Cis-Moderate dose showed a marked elevation (MD = 0.95 mmol/L, 95% CI: 0.3264–1.574, p value = 0.0009), while the Cis-only vs. Cis-High dose exhibited the largest difference (MD = 1.467 mmol/L, 95% CI: 0.8431–2.090, p value < 0.0001). The Extract-only group demonstrated the lowest creatinine levels compared to Cis-only (MD = 1.933 mmol/L, 95% CI: 1.310–2.557, p-value < 0.0001), as shown in Figure No.1.

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Table 1: shows the Conc. of creatinine expressed as means mmol/l of study groups

Tukey's multiple comparisons test	Mean 1	Mean 2	Mean Diff.	95.00% CI of diff.	P Value
Control vs. Extract only	0.8702	0.8	0.0702	-0.5534 to 0.6938	0.9993
Cis-only vs. Cis-Low dose of an extract	2.733	2.217	0.5167	-0.1069 to 1.140	0.1503
Cis-only vs. Cis-Moderate dose of extract	2.733	1.783	0.95	0.3264 to 1.574	0.0009
Cis-only vs. Cis-High dose of an extract	2.733	1.267	1.467	0.8431 to 2.090	<0.0001
Cis-only vs. Extract only	2.733	0.8	1.933	1.310 to 2.557	<0.0001

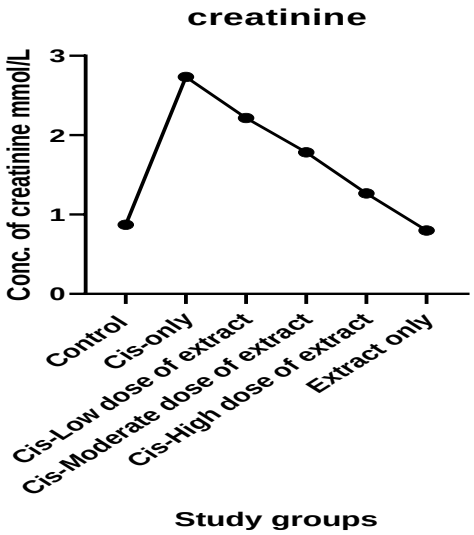

Figure 1: shows the concentrations of creatinine mmol/l expressed as the mean among the study groups.

BUN concentrations are presented in Table 2. According to the table, no significant differences were observed between the control and extract-only groups (MD = -1.733 mg/dL, 95% CI: -6.009 to 2.542, p-value = 0.821). Cis-only treatment resulted in substantially higher BUN levels compared to all extract co-treatment groups. The most pronounced reductions occurred with Cis-High dose (MD = 22.05 mg/dL, 95% CI: 17.77–26.33, p-value < 0.0001) and Extract-only (MD = 23.45 mg/dL, 95% CI: 19.17–27.73, p-value < 0.0001), as shown in figure No. 2.

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Table2: shows the BUN means of study groups

Tukey's multiple comparisons test	Mean 1	Mean 2	Mean Diff.	95.00% CI of diff.	P Value
Control vs. Extract only	12.08	13.82	-1.733	-6.009 to 2.542	0.821
Cis-only vs. Cis-Low dose of an extract	37.27	29.55	7.717	3.441 to 11.99	0.0822
Cis-only vs. Cis-Moderate dose of extract	37.27	19.85	17.42	13.14 to 21.69	<0.0001
Cis-only vs. Cis-High dose of an extract	37.27	15.22	22.05	17.77 to 26.33	<0.0001
Cis-only vs. Extract only	37.27	13.82	23.45	19.17 to 27.73	<0.0001

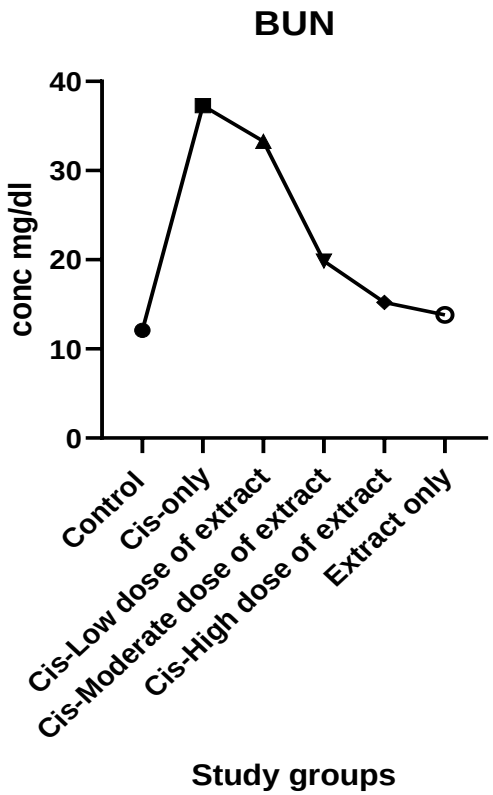

Figure 2: shows the concentrations of BUN mg/ml expressed as the mean among the study groups.

Table and figure No.3 FGF-23 shows mean levels of different study groups. Cis-only administration significantly elevated FGF-23 compared to moderate- and high-dose extract co-treatments. The largest reduction was observed in Cis-High dose (MD = 33.33 pg/mL, 95% CI: 27.96–38.71, p value < 0.0001) and Extract-only (MD = 41.33 pg/mL, 95% CI: 35.96–46.71, p value < 0.0001). No significant differences were detected between Cis-only and Cis-Low dose groups (MD = 3.833 pg/mL, 95% CI: -1.541–9.208, p-value = 0.2812).

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Table 3: shows the FGF-23 mean among the study groups expressed as mean pg/ml.

Tukey's multiple comparisons test	Mean 1	Mean 2	Mean Diff.	95.00% CI of diff.	P Value
Control vs. Extract only	28.17	24.33	3.833	-1.541 to 9.208	0.2812
Cis-only vs. Cis-Low dose of an extract	65.67	61.83	3.833	-1.541 to 9.208	0.2812
Cis-only vs. Cis-Moderate dose of extract	65.67	57.33	8.333	2.959 to 13.71	0.0007
Cis-only vs. Cis-High dose of an extract	65.67	32.33	33.33	27.96 to 38.71	<0.0001
Cis-only vs. Extract only	65.67	24.33	41.33	35.96 to 46.71	<0.0001

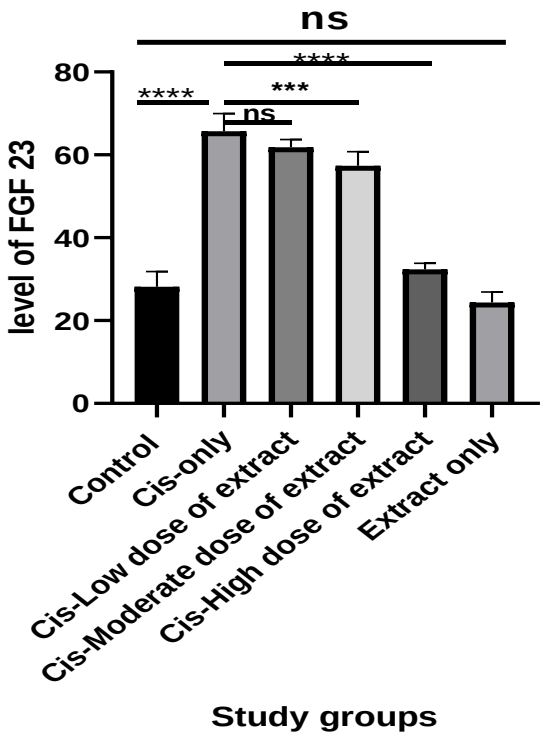

Figure 3: shows the concentrations of FGF-23 pg/ml expressed as mean among the study groups.

CD95L levels are shown in table, and figure No. 4. Cis-only treatment significantly increased CD95L expression relative to all extract co-treatment groups. The most notable suppression occurred with Cis-High dose (MD = 17.78 pg/mL, 95% CI: 13.95–21.61, p-value < 0.0001) and Extract-only (MD = 22.45 pg/mL, 95% CI: 18.62–26.28, p-value < 0.0001). A moderate but significant reduction was observed in the Cis-Low dose (MD = 4.417 pg/mL, 95% CI: 0.5883–8.245, p value= 0.0164). Finally, figure No.5 shows the normal and pathological changes among different study groups.

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Table 4: shows the conc. Of CD 9% expressed as means pg/ml among the study groups.

Tukey's multiple comparisons test	Mean 1	Mean 2	Mean Diff.	95.00% CI of diff.	P Value
Control vs. Extract only	10.9	12.17	-1.267	-5.095 to 2.562	0.9122
Cis-only vs. Cis-Low dose of an extract	34.62	30.2	4.417	0.5883 to 8.245	0.0164
Cis-only vs. Cis-Moderate dose of extract	34.62	27.02	7.6	3.772 to 11.43	<0.0001
Cis-only vs. Cis-High dose of an extract	34.62	16.83	17.78	13.95 to 21.61	<0.0001
Cis-only vs. Extract only	34.62	12.17	22.45	18.62 to 26.28	<0.0001

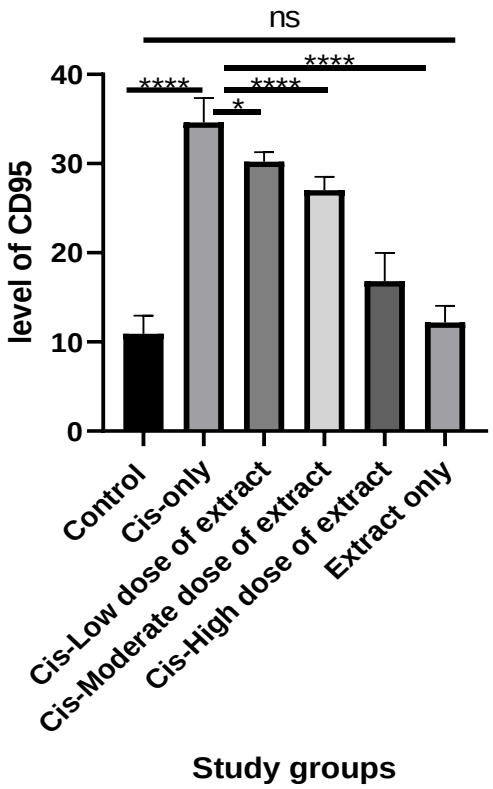

Figure 4: shows the concentrations of CD 95L pg/ml expressed as the mean among the study groups.

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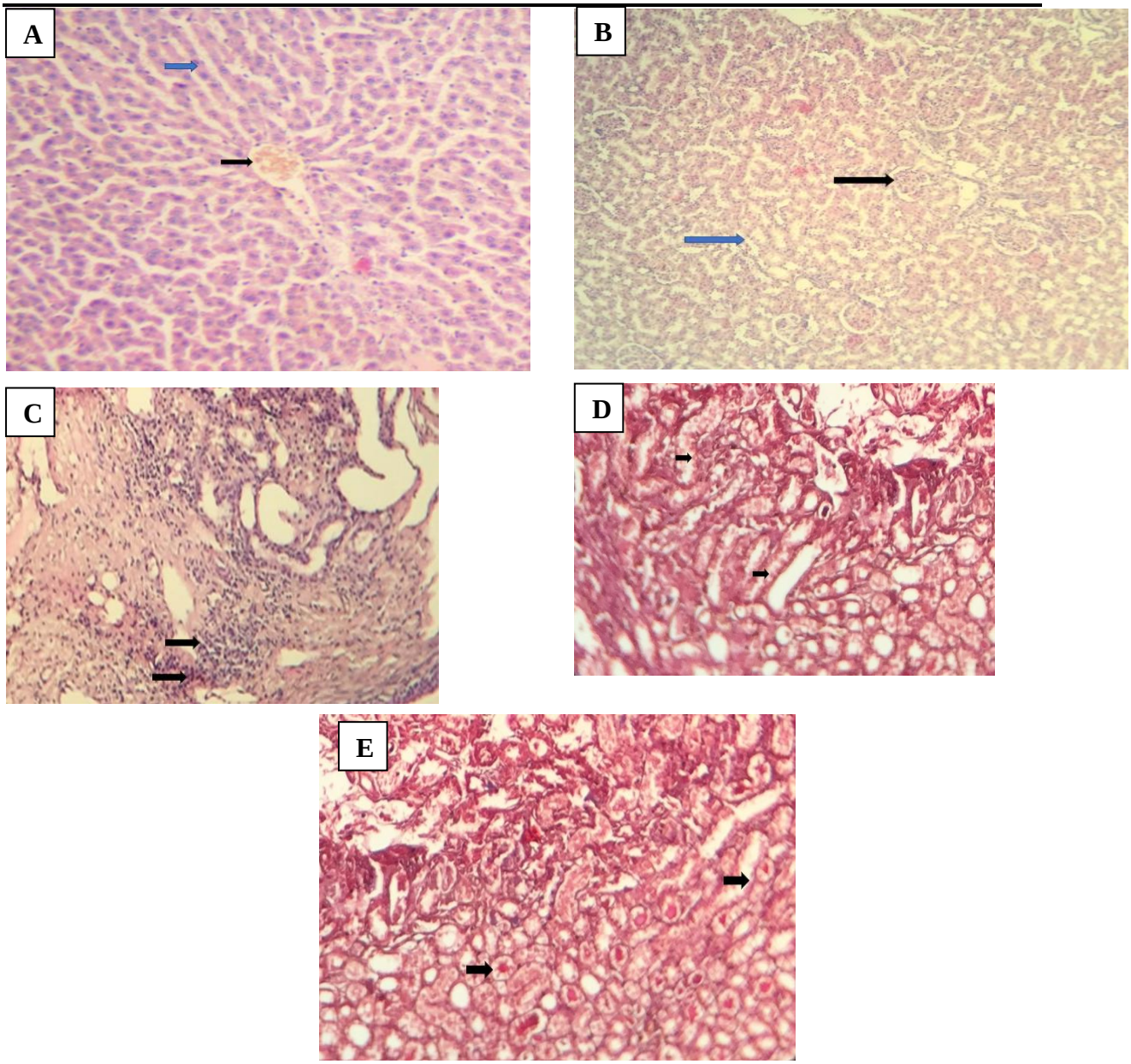

Figure 5A-C: Shown the normal and histological changes in renal tissues among different study groups. A & B refer to normal tissue in the control group black pointer refer to normal healthy glomerulus, and blue pointer refers to normal healthy kidney tubules. C-represents the tissue of the kidney in a group with cis-platin treatment (ARF) the black pointers refer to inflammatory cell infiltration. D-refer to the tissue of Cis-Moderate extract dose, the black pointers refer to healing of epithelial layers which line the kidney tubules. E section refers to renal tissue of the group with Cis-High dose of extract, black pointers refer to regeneration healing of the epithelial lining of the kidney tubules.

4. Discussion

Acute Renal Failure (ARF) is a clinical condition characterized by a significant reduction in daily urine output and extracellular fluid overload due to fluid retention. It is defined by (i) the glomerular filtration rate (GFR) decline within a short time frame and (ii) serum creatinine, and BUN increased, in addition to disturbances in electrolyte and acid-base balance. (Corona et al., 2022) A lot of medicinal plants were documented previously their role in enhancing renal functions. (Sujana et al., 2022) The interactions between FGF-mediated survival signals and pro-apoptotic mechanisms (CD95L) may aid in understanding the mechanism of ARF development and then good treatment and management protocol. Therefore, the current study is designed to evaluate the role of Curcuma longa in nephroprotection against cisplatin nephrotoxic by indicating these biomarkers.

4.1. Creatinine Levels and Renal Function

Creatinine is a widely used biomarker for kidney function, with elevated levels typically indicating renal impairment. The results demonstrate that cisplatin administration (Cis-only group) significantly increased creatinine levels compared to the control group, suggesting nephrotoxicity. And these results completely consistent with a lot of previous studies found the Cisplatin doses can be lead to ARF. (Faubel et al., 2007; Kridis et al., 2023; Abdullah et al., 2025)

However, treatment with moderate and high doses of the extract significantly reduced creatinine levels, indicating a protective or reno-protective effect of the extract. The most profound effect was observed in the group with a high extract dose, suggesting that the extract has potential nephroprotective properties. These findings are in line with Khoursandi, & Ourazizadeh, who found that CURCUMA LONGA extract may have a protective role against induced tubular necrosis in mice. (Khoursandi & Ourazizadeh, 2008) Another study also confirmed this protective role (Mohebbati et al., 2017)

4.2. BUN among the different study groups.

Blood urea nitrogen (BUN) is a key biomarker of renal function, with elevated levels often indicating impaired glomerular filtration (Nosrati et al., 2021). In this study, the Cis-only group shown a significant increase in BUN levels, confirming cisplatin-induced nephrotoxicity (Ghaneialvar et al., 2022; Jana et al., 2023). However, administration of moderate and high doses of Curcuma longa extract resulted in a significant reduction in BUN levels, which another supporting its nephroprotective potential.

The observed decreasing in BUN level suggests enhanced renal clearance and filtration capacity, likely due to the extract's ability to mitigate tubular damage. These findings align with previous research on plant-derived antioxidants, which have been shown to protect against cisplatin-induced nephrotoxicity by reducing oxidative stress and inflammation (Sirait & Djatisoesanto, 2021).

4.3. FGF-23 level among different study groups.

Fibroblast Growth Factor-23 (FGF-23) plays a vital role in phosphate metabolism regulation and is frequently elevated in kidney disease due to impaired phosphate excretion (Portales-Castillo & Simic, 2022).

Findings of the present study indicate that cisplatin administration significantly increased FGF-23 levels, potentially due to disrupted phosphate homeostasis and renal dysfunction. These results consistent with previous studies demonstrating that FGF-23 elevation can be attributed to cisplatin-induced kidney tubule damage (Elseweidy et al., 2018; Münz et al., 2021).

However, treatment with moderate and high doses of Curcuma longa extract led to a significant reduction in FGF-23 levels, suggesting its role in restoring phosphate balance and mitigating the risk of secondary complications, such as mineral bone disorders. These findings are consistent with previous research confirming the protective effects of the extract in preserving and enhancing kidney tubular function (Zhang et al., 2011; Rapa et al., 2019; Sirait & Djatisoesanto, 2021; Khisa et al., 2023).

4.4. CD95L level among different study groups.

CD95L, also known as Fas Ligand (FasL), is a vital apoptotic marker involved in programmed cell death (Lagunas-Rangel, 2023). The findings of this study indicate that cisplatin administration significantly upregulated CD95L expression, suggesting an increase in apoptotic activity and renal cell damage (Zhang et al., 2021; Lee et al., 2024). However, treatment with moderate and high doses of Curcuma longa extract resulted in a significant reduction in CD95L levels, indicating a potential anti-apoptotic effect (Seyrek et al., 2024).

The downregulation of CD95L which result from extract administration suggests a decrease in renal cell apoptosis, potentially through the inhibition of pro-apoptotic signaling pathways. The extract's nephroprotective effects may be attributed to its ability to modulate oxidative stress-induced apoptosis and enhance the expression of anti-apoptotic proteins, such as Bcl-2.

5. Conclusion

The findings of the current study suggest that the extract exerts in a dose-depending manner a nephroprotective effect by reducing cisplatin-induced renal toxicity, as indicated by decreased creatinine, BUN, FGF-23, and CD95L levels. These effects may be attributed to antioxidant, anti-inflammatory, and anti-apoptotic mechanisms.

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