RESEARCH PAPER

Pharmacological Evaluation of Leaves Extract of *Cedrus deodara* on Lead Acetate Induced Nephrotoxicity in Wistar Rats

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Abstract-

Background: The kidneys are highly susceptible to chemical-induced injury due to their substantial blood supply and solute-concentrating role. This study evaluated the protective efficacy of the methanolic leaf extract of *Cedrus deodara* against lead acetate-induced nephrotoxicity in Wistar rats.

Methods: Male Wistar rats were divided into five groups (n=6). Group 1 served as the normal control. Group 2 (disease control) received lead acetate (60 mg/kg p.o.) daily for 4 weeks. Groups 3 and 4 concurrently received lead acetate alongside *C. deodara* extract at 250 mg/kg and 500 mg/kg (p.o.), respectively. Group 5 received standard EDTA (50 mg/kg p.o.). On day 29, serum biomarkers (blood urea, BUN, creatinine, and inorganic phosphorus) were quantified, and renal tissues underwent histopathological examination.

Results: Lead acetate administration caused severe renal impairment, significantly increasing blood urea (24.33± 2.160 mg/dl, serum creatinine (1.840±0.03742 mg/dl, and inorganic phosphorus (15.68±0.3189 mg/dl compared to normal controls ($p < 0.001$). Histopathology confirmed severe tubular necrosis, hemorrhage, and marked lymphoplasmacytic infiltration. Co-treatment with *C. deodara* significantly reversed these biochemical changes ($p < 0.001$). While both plant doses normalized creatinine and urea comparably ($p > 0.999$), the 500 mg/kg dose showed superior efficacy in reducing inorganic phosphorus (8.520±0.4105 mg/dl over the 250mg/kg dose ($p < 0.001$). Histopathologically, the treated groups showed an "almost recovered" pyelonephritis profile with minimal tubular lesions.

Conclusion: The methanolic leaf extract of *Cedrus deodara* exhibits potent nephroprotective activity against lead-induced toxicity. It effectively normalizes key renal clearance biomarkers and preserves microstructural tissue integrity, supporting its potential as a natural therapeutic option.

Key Words: *Cedrus deodara*, Lead acetate, Nephrotoxicity, Serum creatinine

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INTRODUCTION

The kidneys are vital paired organs essential for maintaining systemic homeostasis, regulating fluid and electrolyte balance, managing blood pressure, and excreting metabolic waste products and foreign xenobiotics [1]. Due to their high blood supply—receiving approximately 20–25% of the total cardiac output—and their innate physiological role in concentrating filtered solutes within the renal tubular lumen, the kidneys are uniquely vulnerable to cellular injury and drug- or chemical-induced toxicity [2]. Among the various segments of the nephron, the proximal convoluted tubule epithelial cells are particularly susceptible to metabolic insult because they are highly active in the transport and reabsorption of foreign compounds [2]. Nephrotoxicity is defined as the functional or structural impairment of the kidneys caused by direct or indirect exposure to heavy metals, therapeutic medications, industrial chemicals, or environmental contaminants [1]. Chemically induced renal damage typically presents clinically as an abrupt or progressive decline in the glomerular filtration rate (GFR), marked by abnormal elevations of systemic nitrogenous waste biomarkers such as serum creatinine and blood urea nitrogen (BUN) [2]. On a cellular level, xenobiotics disrupt normal renal biochemistry through interconnected pathways involving mitochondrial dysfunction, endoplasmic reticulum (ER) stress, the depletion of endogenous antioxidant defense systems, and the subsequent activation of pro-apoptotic cascades like caspase-3 [3]. This molecular damage often cascades into profound tissue-level changes, including acute tubular necrosis, glomerular congestion, interstitial edema, and chronic interstitial nephritis [4].

In preclinical research, environmental heavy metals serve as dependable experimental agents for exploring the underlying mechanisms of kidney injury [4]. Lead acetate ($Pb(CH3COO)_2$) is a water-soluble inorganic compound widely utilized as a standard nephrotoxicant in laboratory rat models because its pathological manifestations closely mimic human heavy metal-induced nephropathy [5]. Upon systemic absorption, lead ions ($Pb2^+$) exhibit a strong affinity for biological membranes and selectively accumulate within the proximal renal tubular cells [6]. The principal mechanism behind lead acetate-induced nephrotoxicity is the excessive generation of reactive oxygen species (ROS), which overpowers the kidney's endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT) [7]. This induced state of intense oxidative stress precipitates lipid peroxidation of the tubular epithelial membrane—evidenced by elevated

malondialdehyde (MDA) levels—which alters membrane permeability, causes cellular vacuolation, triggers nuclear factor-kappa B (NF-κB) mediated inflammatory cytokine release (TNF-alpha, IL-1beta), and ultimately causes structural disintegration of the nephron [8, 3].

Given the limitations, clinical side effects, and high cost of conventional therapeutic regimens like synthetic chelation therapy (e.g., EDTA), there is growing scientific interest in discovering natural, plant-derived phytoconstituents as safer alternative nephroprotective strategies [1]. *Cedrus deodara* (Roxb.) Loud., a large evergreen coniferous tree indigenous to the Himalayan regions, holds a prominent position in traditional Ayurvedic medicine for treating urinary diseases and chronic inflammatory disorders [9]. The medicinal properties of *Cedrus deodara* leaf and heartwood extracts are fundamentally attributed to an abundance of bioactive secondary metabolites, including essential sesquiterpenes (such as himachalol, alpha-himachalene, and beta-himachalene), flavonoids, lignans, and phenolic derivatives [10]. These specific phytoconstituents exhibit potent, multi-targeted pharmacological properties, including free radical scavenging, membrane stabilization, and anti-apoptotic actions [11]. Modern experimental investigations suggest that *Cedrus deodara* mitigates toxic kidney damage by augmenting intracellular reduced glutathione (GSH) reserves, suppressing lipid peroxidation, and decreasing inflammatory cell infiltration [12,13]. Consequently, evaluating this plant's therapeutic potential offers a promising avenue for alleviating oxidative stress and preserving structural renal architecture against heavy metal exposure [14].

Materials and Methods

Collection of plant materials:

The plant material *Cedrus deodara* investigated in the present study was collected from Berinag, Distt- Pithoragarh, Uttarakhand. The plant was identified and authenticated by Botanical survey of India, Dehradun, Uttarakhand, India. Plant identification number- BSI/NRC 2055 / 2026-27/198.

Preparation of the plant extract:

The collected plant material was washed thoroughly in water, dried under shade and ground to coarse powder in electric grinder. Powdered material was then extracted successively in Soxhlet apparatus, using methanol respectively. The extracts were further concentrated to semisolid mass and stored in airtight container in a refrigerator till further use. **[15]**

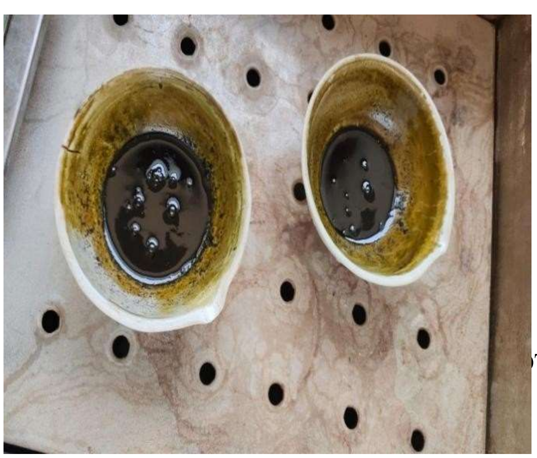


Figure 1. Methanolic Extraction of *Cedrus deodara* leaves using a Soxhlet apparatusExperimental Animals

Healthy adult male Wistar rats (150–200 g) which have been obtained from Shri Guru Ram Rai University and acclimatized under standard laboratory conditions (25 ± 2°C; 12 h light/dark). Animals received standard diet and water ad libitum. All animal procedures were performed according with regulations specified by the institutional animal ethics committee IAEC.

Experimental Design

Rats were divided into five groups (n = 6):

Group 1: (Normal control group): Rats administrated with normal saline water and food.

Group 2 (Disease control): Rats administered lead acetate 60mg/kg orally once a day for 4 weeks.

Group 3 (Treatment): Rats will be treated with leaves extract of *Cedrus deodara* (250 mg/kg) orally once a day for 4 weeks. **[19]**

Group 4 (Treatment with higher dose): Rats will be treated with leaves extract of *Cedrus deodara* (500 mg/kg) orally once a day for 4 weeks. **[19]**

Group 5 (Standard group): EDTA (50 mg/kg, orally) for 4 weeks.

After 4 weeks of *Cedrus deodara* administration various biochemical studies will be performed which are as follows:

RESULT

Statistical analysis

Results were expressed as mean ± SEM, (n=6). Statistical analysis was performed with one-way analysis of variance (ANOVA) followed by Tukey test. P value of $p < 0.05$ was considered statistically significant ($p < 0.01$, $p < 0.001$).

Biochemical Effects

Blood Urea, Blood Urea Nitrogen, Serum Creatinine and Inorganic Phosphorus were estimated as per the lab's standard validated protocols and internal quality controls.

Histological Observations

The Lead Acetate control group exhibited widespread Renal cell degeneration, necrosis, and inflammatory infiltration. Extract-treated groups, particularly at 500 mg/kg, showed improved preservation of renal cords, reduced necrotic zones, and restoration of sinusoidal structure. The EDTA group revealed near-normal

Biochemical Markers

On Day 29, Animals were anaesthetized and sacrificed. Blood and Kidney samples were collected for estimation of Blood Urea, Blood Urea Nitrogen, Serum Creatinine and Inorganic Phosphorus.

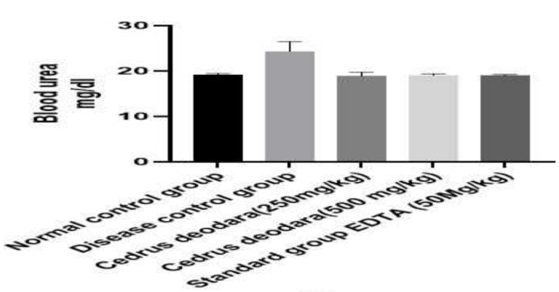
Histopathology

Kidney tissues were fixed in 10% formalin for histopathological evaluation

renal architecture with signs of regeneration.

S. No	Group Name	Blood Urea	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	19.20 ± 0.2280	1	Normal vs. Disease	-5.133	-6.919 to -3.347	Yes	<0.001
2	Disease Control (Lead Acetate)	24.33 ± 2.160	2	Disease vs. Treatment (*Cedrus deodara*) 250mg/kg	5.413	3.627 to 7.199	Yes	<0.001
3	Treatment group (*Cedrus deodara*) 250mg/kg+ (Lead Acetate)	18.92 ± 0.8104	3	Disease vs. Treatment (*Cedrus deodara*) 500mg/kg	5.283	3.497 to 7.069	Yes	<0.001
4	Treatment group (*Cedrus deodara*)500mg/kg+ (Lead Acetate)	19.0 5± 0.3450	4	Disease vs. Standard (EDTA 50mg/kg)	5.333	3.547 to 7.119	Yes	<0.001
5	Standard Group (EDTA) 50mg/kg	19.00 ± 0.2280	5	Treatment 250 mg/kg vs Treatment 500mg/kg	-0.1300	-1.916 to 1.656	No	>.999
			6	Treatment 500mg/kg vs EDTA 50mg/kg	0.05000	-1.736 to 1.836	No	>.999

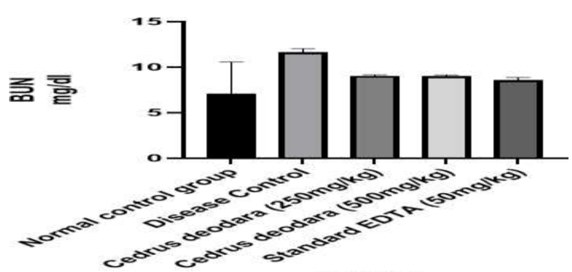
Table 1. Shows Effect of various pharmacological interventions on level of Blood Urea (mg/dl)



Graph 1. Effect of *Cedrus deodara* with lead acetate on blood urea

S. No	Group Name	Blood Urea Nitrogen	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant ?	Adjusted P Value
1	Normal Control	7.117 ± 3.447	1	Normal vs. Disease	-4.517	-7.161 to -1.873	Yes	<0.001
2	Disease Control (Lead Acetate)	11.63 ± 0.3983	2	Disease vs. Treatment (*Cedrus deodara*) 250mg/kg	2.583	0.06072 to 5.227	No	.058
3	Treatment group (*Cedrus deodara*) 250mg/kg+ (Lead Acetate)	9.050 ± 0.1049	3	Disease vs. Treatment (*Cedrus deodara*) 500mg/kg	2.633	0.01072 to 5.277	No	.051
4	Treatment group (*Cedrus deodara*)500mg/kg+ (Lead Acetate)	9.000± 0.1414	4	Disease vs. Standard (EDTA 50mg/kg)	3.067	0.4226 to 5.711	Yes	.017
5	Standard Group (EDTA) 50mg/kg	8.567 ± 0.2944	5	Treatment 250 mg/kg vs Treatment 500mg/kg	0.05000	-2.594 to 2.694	No	>.999
			6	Treatment 500mg/kg vs EDTA 50mg/kg	0.4333	-2.211 to 3.077	No	>.988

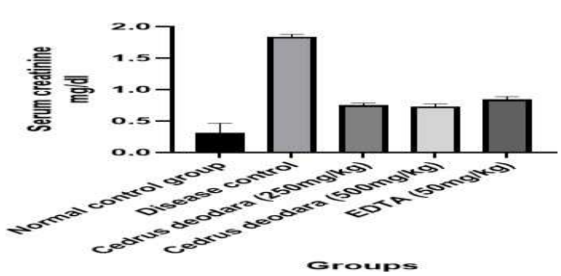
Table 2. Shows Effect of various pharmacological interventions on level of Blood Urea Nitrogen (mg/dl)



Graph 2. Effect of *Cedrus deodara* with lead acetate on blood urea nitrogen

S. No	Group Name	Serum Creatinine	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	0.3167± 0.1472	1	Normal vs. Disease	-1.523	-1.649 to -1.397	Yes	<0.001
2	Disease Control (Lead Acetate)	1.840 ± 0.03742	2	Disease vs. Treatment (*Cedrus deodara*) 250mg/kg	1.088	0.9624 to 1.214	Yes	<0.001
3	Treatment group (*Cedrus deodara*) 250mg/kg+ (Lead Acetate)	0.7517 ± 0.03189	3	Disease vs. Treatment (*Cedrus deodara*) 500mg/kg	1.108	0.9824 to 1.234	Yes	<0.001
4	Treatment group (*Cedrus deodara*)500mg/kg + (Lead Acetate)	0.7317± 0.03869	4	Disease vs. Standard (EDTA 50mg/kg)	0.9967	0.8708 to 1.123	Yes	<0.001
5	Standard Group (EDTA) 50mg/kg	0.8433± 0.04457	5	Treatment 250 mg/kg vs Treatment 500mg/kg	0.02000	-0.1059 to 0.1459	No	.990
			6	Treatment 500mg/kg vs EDTA 50mg/kg	-0.1117	-0.2376 to 0.01423	No	.100

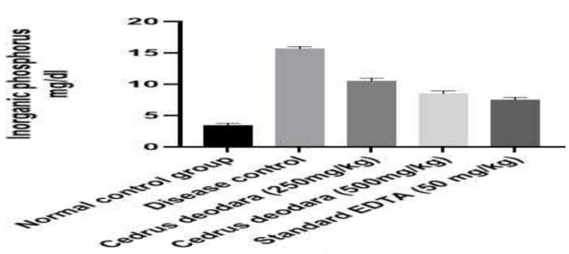
Table 3. Shows Effect of various pharmacological interventions on level of Serum Creatinine (mg/dl)



Graph 3. Effect of *Cedrus deodara* with lead acetate on serum creatinine

S. No	Group Name	Inorganic Phosphorus	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	3.450± 0.3271	1	Normal vs. Disease	-12.23	-12.86 to -11.61	Yes	<0.001
2	Disease Control (Lead Acetate)	15.68 ± 0.3189	2	Disease vs. Treatment (*Cedrus deodara*) 250mg/kg	5.150	4.522 to 5.778	Yes	<0.001
3	Treatment group (*Cedrus deodara*) 250mg/kg+ (Lead Acetate)	10.53 ± 0.4204	3	Disease vs. Treatment (*Cedrus deodara*) 500mg/kg	7.163	6.536 to 7.791	Yes	<0.001
4	Treatment group (*Cedrus deodara*)500mg/kg + (Lead Acetate)	8.520± 0.4105	4	Disease vs. Standard (EDTA 50mg/kg)	8.133	7.506 to 8.761	Yes	<0.001
5	Standard Group (EDTA) 50mg/kg	7.550 ± 0.3619	5	Treatment 250 mg/kg vs Treatment 500mg/kg	2.013	1.386 to 2.641	YES	<0.001
			6	Treatment 500mg/kg vs EDTA 50mg/kg	0.9700	0.3425 to 1.598	YES	.001

Table 4. Shows Effect of various pharmacological interventions on level of Inorganic Phosphorus (mg/dl)



Graph 4. Effect of *Cedrus deodara* with lead acetate on Inorganic Phosphorus

Histopathology of Rat Kidney-

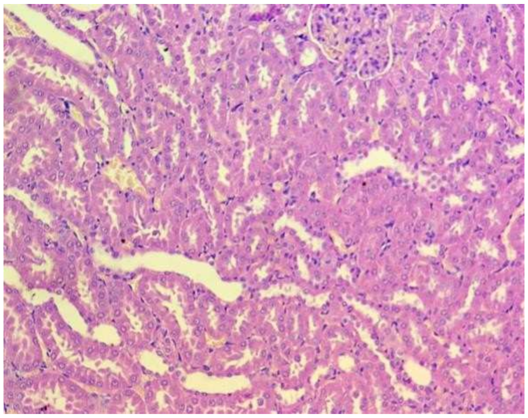


Fig- (a) Normal Control

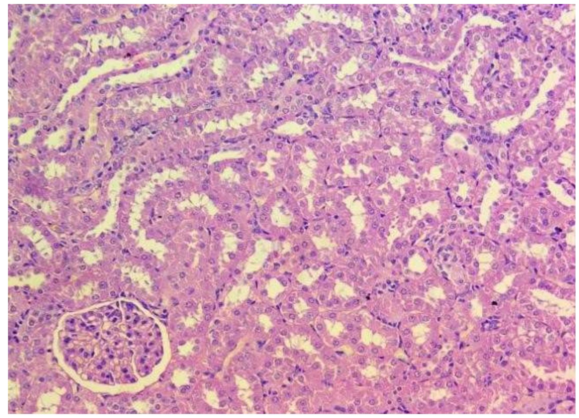


Fig- (b) Disease Control

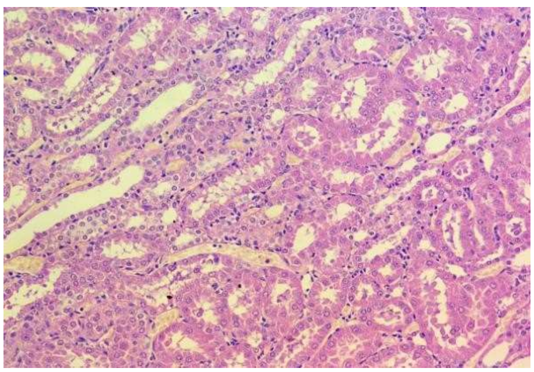


Fig- (c*) C. deodara* 250mg/kg

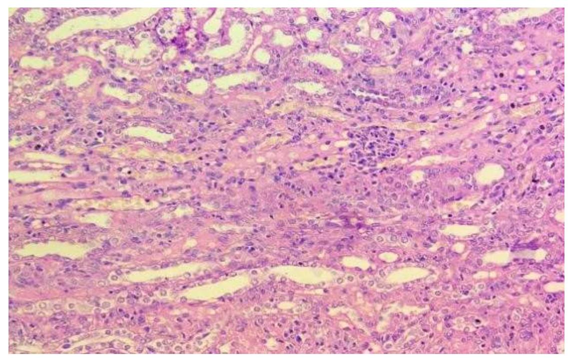


Fig- (d) *C. deodara* 500mg/kg

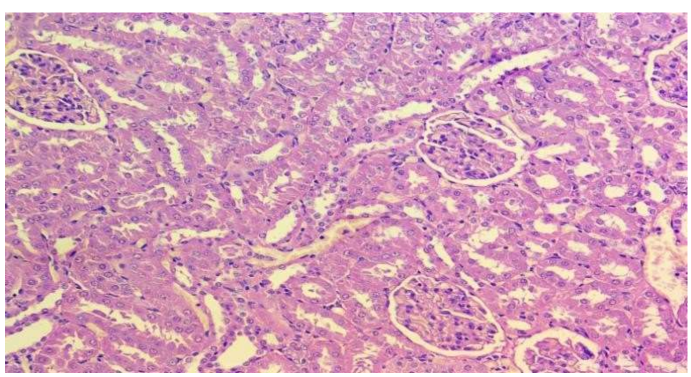


Fig-(e) EDTA 50 mg/kg

(Fig a) shows normal pathology of kidney. Areas around kidney veins appear normal. **(Fig.b)** Section of kidney shows tubular necosis showing moderate thyroidisation. Crystal deposition is noted mostly in tubule along with moderate fibrinous deposition, no fibrosis noted. Interstitium show marked lymphoplasmacytic infiltration. Glomeruli show marked congestion and increase mesengial cellularity noted in many of glomeruli. Marked hemorrhage and vascular congestion noted. No cystic change noted. Features of pyelonephritis, tubular necrosis and some glomerular changes identified. **(Fig.c)** shows focal tubular necrosis, tubules showing moderate focal thyroidisation, Crystal deposition noted occasionally in tubule along with fibrinous deposition, no fibrosis noted. Interstitium show mild lymphoplasmacytic infiltration. Glomeruli show minimal congestion and minimal increase mesengial cellularity noted in occasional glomeruli. Mild hemorrhage and vascular congestion noted. No cystic change noted. Features of almost recoverd pyelonephritis with occasional glomerular changes identified. **(Fig.d)** shows occasional tubular necrosis, tubules showing moderate focal thyroidisation. Crystal deposition noted occasionally in tubule along with fibrinous deposition, no fibrosis noted. Glomeruli show minimal congestion and minimal increase mesengial cellularity noted in occasional glomeruli. Mild hemorrhage and vascular congestion noted. No cystic change noted. Features of almost recoverd pyelonephritis with occasional glomerular changes identified. **(Fig. e)** shows occasional tubular necrosis, tubules showing moderate focal thyroidisation. Crystal deposition noted occasionally in tubule along with fibrinous deposition, no fibrosis noted. Interstitium show mild lymphoplasmacytic infiltration. Glomeruli show minimal congestion and minimal increase mesengial cellularity noted in occasional glomeruli. Mild hemorrhage and vascular congestion noted. No cystic change noted.

Discussion-

The administration of lead acetate (60mg/kg) for 4 weeks induced severe nephrotoxicity in Wistar rats, as evidenced by a profound elevation in systemic nitrogenous waste biomarkers. The accumulation of lead ions (Pb^{2+} in proximal tubular epithelial cells triggers a cascade of reactive oxygen species (ROS), resulting in significant functional impairment. This is demonstrated by an increase in serum creatinine (1.840±0.03742mg/dl, blood urea (24.33± 2.160 mg/dl, and inorganic phosphorus (15.68± 0.3189 mg/dl.

Concurrent treatment with the methanolic leaf extract of *Cedrus deodara* (250 mg/kg) and (500 mg/kg) significantly reversed these elevations ($p < 0.001$). While both doses displayed a comparable capacity to normalize serum creatinine and blood urea ($p>0.999$), the 500 mg/kg high-dose group demonstrated clear superiority in lowering inorganic phosphorus levels (8.520± 0.4105 mg/dl compared to the low-dose group (10.53± 0.4204 mg/dl, showing an efficacy profile similar to the standard chelation agent, EDTA (7.550± 0.3619 mg/dl.

These functional improvements correlate strongly with histopathological observations. The disease control group exhibited extensive acute tubular necrosis, interstitial lymphoplasmacytic infiltration, and severe vascular hemorrhage. In contrast, groups treated with *Cedrus deodara* leaf extract demonstrated structural preservation, characterized by an "almost recovered" tissue state with only focal, minimal tubular necrosis and reduced inflammatory cell infiltration.

This therapeutic potential is attributed to the presence of active secondary metabolites in the extract, including flavonoids (such as taxifolin), phenolics, and sesquiterpenes. These phytoconstituents function via multi-targeted pathways: scavenging free radicals, stabilizing epithelial membranes to prevent crystal or fibrinous deposition, and replenishing endogenous antioxidant reserves to mitigate chemical-induced cell death.

Conclusion-

The present study demonstrates that the methanolic leaf extract of *Cedrus deodara* effectively mitigates lead acetate-induced nephrotoxicity in Wistar rats. The extract possesses strong nephroprotective properties, as demonstrated by the significant, near-complete normalization of blood urea, BUN, serum creatinine, and inorganic phosphorus levels, alongside the reversal of severe tubular necrosis and glomerular congestion. The dose-dependent therapeutic improvement shown at 500 mg/kg supports its potential as a safe, natural alternative or adjunct strategy against heavy metal-induced renal injury, justifying further research into its downstream molecular targets.

Conflict of Interest: The author has no conflict of interest.

Acknowledgement:

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Author Contribution

AKS- Writing originalDraft RSD- Original concept SS- Supervision

Ethical Approval:

The research study was conducted at Siddhartha institute of pharmacy, Near IT park, Dehradun 248001. The animal house is CPCSEA approval. And the registration no. of the animal house – 1435/PO/RE/S/11/CPCSEA.

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