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Pharmacological Evaluation of Cedrus Deodara leaves extract on Carbon tetra-chloride induced Hepatotoxicity in Wistar Rats

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ABSTRACT

Background: Carbon tetrachloride (CCl_4) is a well-established agent for inducing oxidative liver injury. While *Cedrus deodara* holds traditional relevance in hepatoprotection, its leaves extract remains scientifically underexplored. This study evaluates the biochemical and histological effects of its methanolic extract in a CCl_4-induced hepatotoxicity model.

Methods: Leaves were methanol-extracted via Soxhlet apparatus. Male Wistar rats were divided into five groups: normal control, CCl_4 control, two *Cedrus Deodara* extract-treated groups (250 and 500 mg/kg, p.o.), and a silymarin (100 mg/kg, p.o.) standard group. Extract and silymarin was administered once daily for 14 days. Hepatotoxicity was induced via CCl_4 (1 ml/kg i.p. 1:1 v/v in olive oil) on Days 7 and 14. Biochemical parameters (SGOT, SGPT, ALP, bilirubin), and liver histopathology were evaluated.

Results: CCl_4 significantly elevated hepatic markers. Treatment with C. deodara extract, especially at 500 mg/kg, restored biochemical levels ($p < 0.001$) and improved hepatic architecture, with outcomes comparable to silymarin.

Conclusion: Methanolic leaves extract of C. deodara confers dose-dependent hepatoprotection, likely via free radical scavenging and membrane stabilization. Its safety profile and efficacy validate its traditional use and warrant further pharmacodynamic investigation.

Keywords: *Cedrus deodara, Hepatoprotective activity, Carbon tetrachloride (CCl_4), Wistar rats, Liver toxicity*

1. INTRODUCTION

Liver injury mediated by xenobiotics remains a major concern in toxicological research. Carbon tetrachloride (CCl_4), once widely used as a solvent, induces liver damage through reductive dehalogenation by cytochrome P450 enzymes, generating trichloromethyl and trichloromethyl peroxy radicals (H., 2022). These reactive species initiate lipid peroxidation and disrupt hepatocellular membranes, leading to necrosis and inflammation. Conventional hepatoprotective agents are limited by adverse effects and inconsistent outcomes, prompting intensified interest in herbal formulations characterized by safety and multi-targeted effects (Pandey, 2023), (Służały, 1985). Polyphenolic compounds from plant sources exhibit antioxidant, anti-inflammatory, and membrane-stabilizing actions relevant to hepatic protection (Dutta, 2021) .

Cedrus deodara (Roxb. ex D. Don), known as Devadaru in Ayurveda, has documented use in traditional medicine for treating inflammation, skin ailments, and metabolic imbalances (Meena, 2024). Its wood-derived oil and bark have shown antimicrobial and antioxidant activity, while the leaves—rich in flavonoids, phenolics, and terpenoids—are comparatively under characterized (Kumari, 2022). Taxifolin, cedrol, and himachalol have been isolated from various parts of the plant, contributing to its pharmacological profile (Harsh Pathak, 2023). However, the methanolic extract of the leaves in particular remains unexplored for hepatoprotective efficacy in contemporary models. This study was designed to evaluate the extract's role in counteracting CCl_4-induced hepatic damage using biochemical, and histological parameters.

Materials and Methods

Plant Material and Extraction

Fresh leaves of C. Deodara were collected from Berinag, Distt- Pithoragarh, Uttarakhand, and shade-dried. Methanolic extraction was performed using Soxhlet apparatus for 48 hours (40 g plant material in 400 mL solvent). The extract was concentrated under reduced pressure and stored at 4 °C.

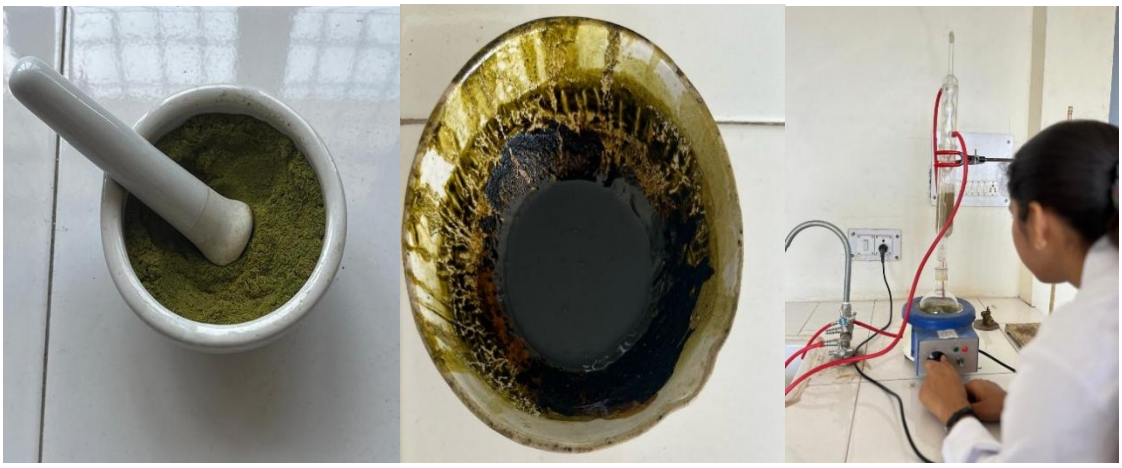


Figure 1. Methanolic extraction of *Cedrus deodara* leaves using a Soxhlet apparatus

Experimental 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 I: Normal control group

Group II: Disease control group (CCl_4 1 ml/kg i.p. in 1:1 olive oil, Days 7 & 14)

Group III: Treatment group (C. Deodara Extract 250 mg/kg + CCl_4)

Group IV: Treatment group (C. Deodara Extract 500 mg/kg + CCl_4)

Group V: Standard group (Silymarin 100 mg/kg + CCl_4)

Plant extract and silymarin was administered orally from Day 1 to Day 14. This prophylactic model is recognized for assessing the ability of agents to mitigate or prevent hepatic insult through preconditioning mechanisms (Ugwu, 2021).

Biochemical and Oxidative Stress Markers

On Day 15, animals were anaesthetized and sacrificed. Blood and liver samples were collected for estimation of SGOT, SGPT, ALP, total bilirubin levels.

Histopathology

Liver tissues were fixed in 10% formalin for histopathological evaluation.

2. 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 and Antioxidant Effects

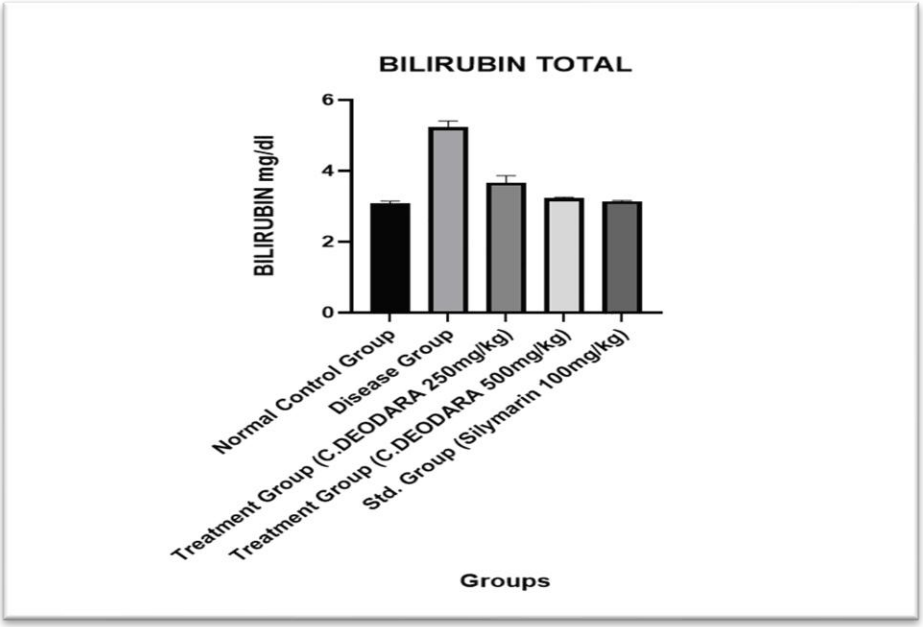
Liver enzymes—SGOT, SGPT, ALP, and total bilirubin—were estimated as per the lab's standard validated protocols and internal quality controls.

Histological Observations

The CCl_4 control group exhibited widespread hepatocellular degeneration, necrosis, and inflammatory infiltration. Extract-treated groups, particularly at 500 mg/kg, showed improved preservation of hepatic cords, reduced necrotic zones, and restoration of sinusoidal structure. The silymarin group revealed near-normal hepatic architecture with signs of regeneration.

S. No	Group Name	Total Bilirubin Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	3.093 ± 0.04719	**1**	Normal vs. Disease	-2.140	-2.344 to -1.936	yes	<.001
2	Disease Control (CCl_4)	5.233 ± 0.1751	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	1.567	1.362 to 1.771	yes	<.001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	3.667 ± 0.1966	**3**	Disease vs. Treatment (C. Deodara) 500mg/kg	2.003	1.799 to 2.208	yes	<.001
4	Treatment group (*Cedrus Deodara*)500mg/kg+ CCl_4	3.230 ± 0.02608	**4**	Disease vs. Standard (Silymarin 100mg/kg)	2.090	1.886 to 2.294	yes	<.001
5	Standard Group (Silymarin) 100mg/kg+ CCl_4	3.143 ± 0.02160	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	0.4367	0.2322 to 0.6411	yes	<.001
			6	Treatment 500mg/kg vs Silymarin 100mg/kg	0.08667	-0.1178 to 0.2911	No	.726

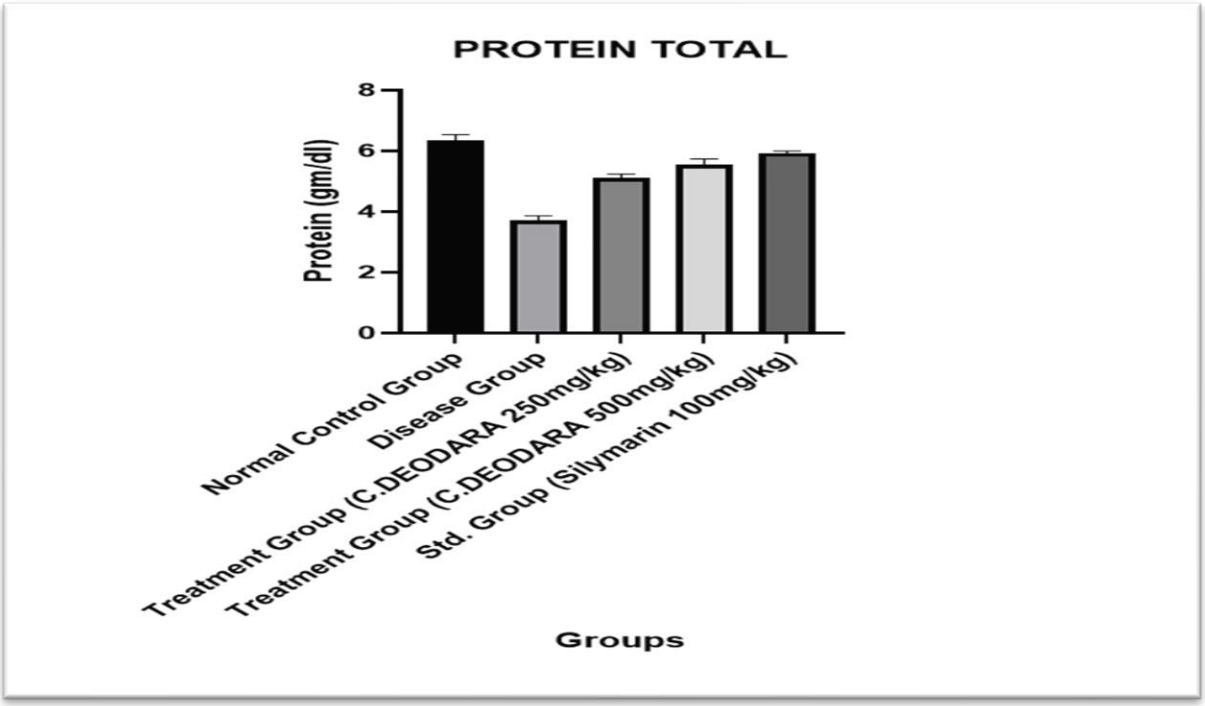
Table 1. Shows Effect of various pharmacological interventions on level of Total Bilirubin (mg/dl)



Graph 1. Effect of C. Deodara with CCl_4 on Total Bilirubin level

S. No	Group Name	Total Protein Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	6.350 ± 0.1871	**1**	Normal vs. Disease	2.633	2.381 to 2.886	yes	<.001
2	Disease Control (CCl_4)	3.717 ± 0.1472	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	-1.400	-1.652 to -1.148	yes	<.001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	5.117 ± 0.1169	**3**	Disease vs. Treatment (C. Deodara) 500mg/kg	-1.833	-2.086 to -1.581	yes	<.001
4	Treatment group (*Cedrus Deodara*)500mg/kg+ CCl_4	5.550 ± 0.1871	**4**	Disease vs. Standard (Silymarin 100mg/kg)	-2.207	-2.459 to -1.954	yes	<.001
5	Standard Group (Silymarin) 100mg/kg+ CCl_4	5.923 ± 0.07394	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	-0.4333	-0.6857 to -0.1809	yes	<.001

Table 2. Effect of various pharmacological interventions on level of Total Protein. (gm/dl)

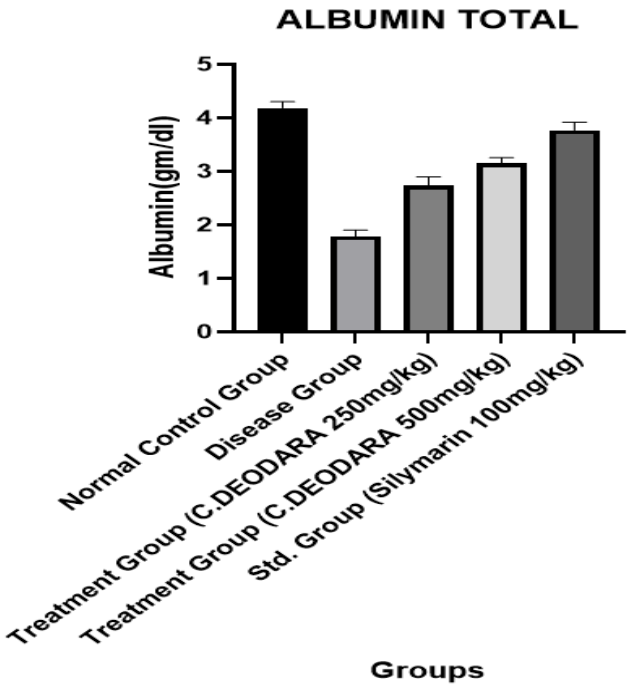


Graph 2. Effect of C. Deodara with CCl_4 on Total Protein level.

S. No	Group Name	Total Albumin Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	4.183 ± 0.1169	**1**	Normal vs. Disease	2.400	2.175 to 2.625	yes	<.001
2	Disease Control (CCl_4)	1.783 ± 0.1169	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	-0.9500	-1.175 to -0.7255	yes	<.001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	2.733 ± 0.1633	**3**	Disease vs. Treatment (C. Deodara) 500mg/kg	-1.367	-1.591 to -1.142	yes	<.001
4	Treatment group (*Cedrus Deodara*)500mg/kg+ CCl_4	3.150 ± 0.1049	**4**	Disease vs. Standard (Silymarin 100mg/kg)	-1.983	-2.208 to -1.759	yes	<.001

5	Standard Group (Silymarin) 100mg/kg+ CCl_4	3.767 ± 0.1506	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	-0.4167	-0.6412 to -0.1921	yes	<.001
			6	Treatment 500mg/kg vs Silymarin 100mg/kg	-0.6167	-0.8412 to -0.3921	yes	<.001

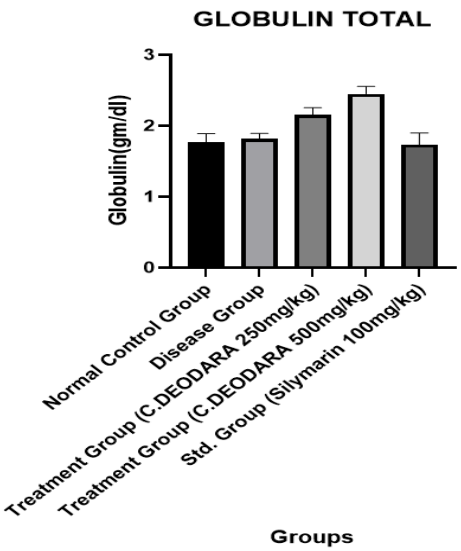
Table 3. Effect of various pharmacological interventions on level of Albumin (gm/dl)



Graph 3. Effect of C. Deodara with CCl_4 on Albumin level

S. No	Group Name	Total Globulin Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant ?	Adjusted P Value
1	Normal Control	1.767 ± 0.1211	**1**	Normal vs. Disease	-0.05000	-0.2492 to 0.1492	NO	.946
2	Disease Control (CCl_4)	1.817 ± 0.07528	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	-0.3333	-0.5325 to -0.1341	yes	<.001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	2.150 ± 0.1049	**3**	Disease vs. Treatment (C. Deodara) 500mg/kg	-0.6333	-0.8325 to -0.4341	yes	.320
4	Treatment group (*Cedrus Deodara*)500mg/kg + CCl_4	2.450 ± 0.1049	**4**	Disease vs. Standard (Silymarin 100mg/kg)	0.08333	-0.1159 to 0.2825	No	.735
5	Standard Group (Silymarin) 100mg/kg+ CCl_4	1.733 ± 0.1633	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	-0.3000	-0.4992 to -0.1008	yes	.001
			6	Treatment 500mg/kg vs Silymarin 100mg/kg	0.7167	0.5175 to 0.9159	yes	<.001

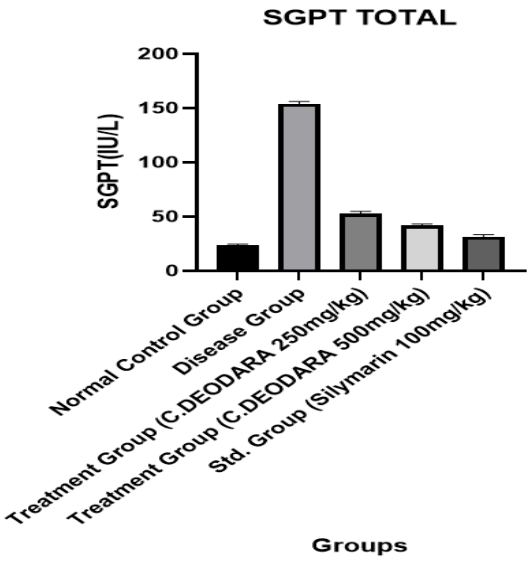
Table 4. Effect of various pharmacological interventions on level of Globulin (gm/dl)



Graph 4. Effect of C. Deodara with CCl_4 on Globulin level.

S. No	Group Name	SGPT Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	23.50 ± 1.049	**1**	Normal vs. Disease	-130.5	-133.6 to -127.4	yes	<.001
2	Disease Control (CCl_4)	154.0 ± 2.098	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	101.3	98.27 to 104.4	yes	<.001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	52.67 ± 2.160	**3**	Disease vs. Treatment (C. Deodara) 500mg/kg	112.3	109.3 to 115.4	yes	<.001
4	Treatment group (*Cedrus Deodara*)500mg/kg+ CCl_4	41.67 ± 1.633	**4**	Disease vs. Standard (Silymarin 100mg/kg)	122.5	119.4 to 125.6	yes	<.001
5	Standard Group (Silymarin) 100mg/kg+ CCl_4	31.50 ± 1.871	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	11.00	7.935 to 14.06	yes	<.001
			6	Treatment 500mg/kg vs Silymarin 100mg/kg	10.17	7.102 to 13.23	yes	<.001

Table 5. Effect of various pharmacological interventions on level of SGPT (IU/L)

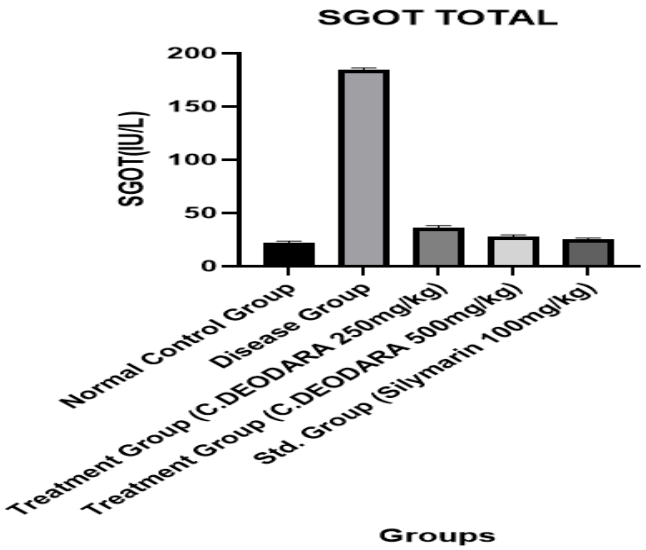


Graph 5. Effect of C. Deodara with CCl4 on SGPT level

S. No	Group Name	SGOT Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	22.17 ± 1.472	**1**	Normal vs. Disease	-162.3	-165.4 to -159.3	yes	<.0001
2	Disease Control (CCl_4)	184.5 ± 1.871	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	148.7	145.6 to 151.7	yes	<.0001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	35.83 ± 2.317	**3**	Disease vs. Treatment (C. Deodara) 500mg/kg	157.0	153.9 to 160.1	yes	<.0001
4	Treatment group (*Cedrus Deodara*)500mg/kg+ CCl_4	27.50 ± 1.871	**4**	Disease vs. Standard (Silymarin 100mg/kg)	159.5	156.4 to 162.6	yes	<.0001

5	Standard Group (Silymarin) 100mg/kg+ CCl_4	25.00 ± 1.414	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	8.333	5.250 to 11.42	yes	<.0001
			6	Treatment 500mg/kg vs Silymarin 100mg/kg	2.500	-0.5833 to 5.583	no	0.1536

Table 6. Effect of various pharmacological interventions on level of SGOT (IU/L)

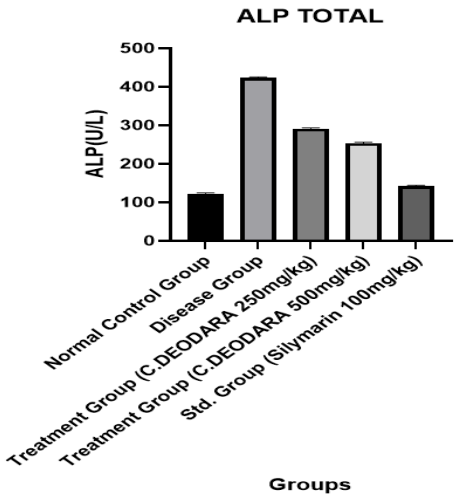


Graph 6. Effect of C. Deodara with CCl_4 on SGOT level

S. No	Group Name	Total GSH Level	S.no	Tukey's multiple comparison tests	Mean Difference	95.00% CI of diff.	Significant?	Adjusted P Value
1	Normal Control	122.5 ± 1.871	**1**	Normal vs. Disease	-301.3	-305.0 to -297.7	yes	<.001
2	Disease Control (CCl_4)	423.8 ± 1.722	**2**	Disease vs. Treatment (C.Deodara) 250mg/kg	132.3	128.7 to 136.0	yes	<.001
3	Treatment group (*Cedrus Deodara*) 250mg/kg+ CCl_4	291.5 ± 1.871	**3**	Disease vs. Treatment (C. Deodara)	281.3	277.7 to 285.0	yes	<.001

				500mg/kg				
4	Treatment group (*Cedrus Deodara*)500mg/kg+ CCl_4	253.5 ± 3.082	**4**	Disease vs. Standard (Silymarin 100mg/kg)	38.00	34.37 to 41.63	yes	<.001
5	Standard Group (Silymarin) 100mg/kg+ CCl_4	142.5 ± 1.871	**5**	Treatment 250 mg/kg vs Treatment 500mg/ kg	111.0	107.4 to 114.6	yes	<.001
			6	Treatment 500mg/kg vs Silymarin 100mg/kg	-0.7167	-0.9463 to-0.4871	yes	<.001

Table 7. Effect of various pharmacological interventions on level of ALP (U/L)



Graph 7. Effect of C. Deodara with CCl4 on ALP level

Histopathology of Rat Liver

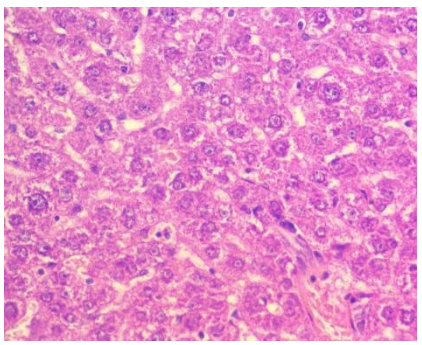


Fig- (a) Normal Control

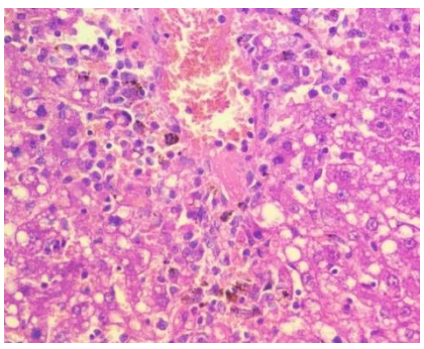


Fig- (b) Disease Control

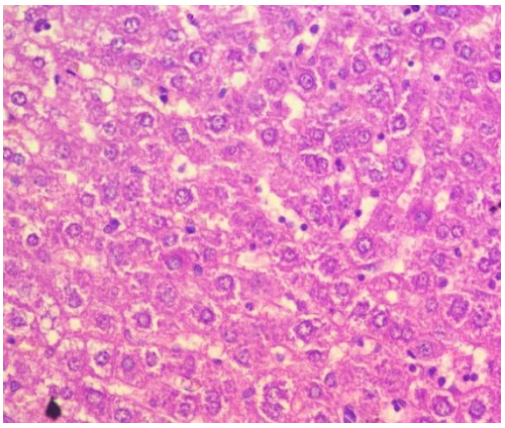


Fig- (c) C. Deodara 250mg/kg

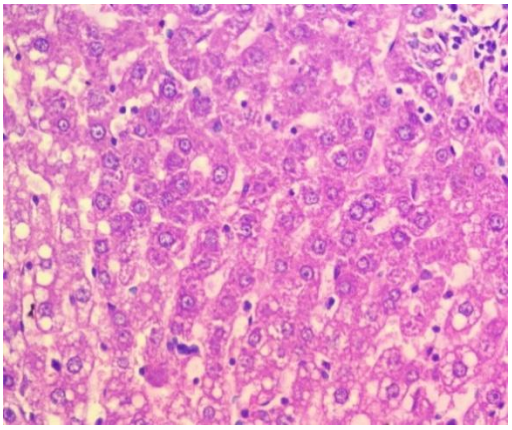


Fig- (d) C. Deodara 500mg/kg

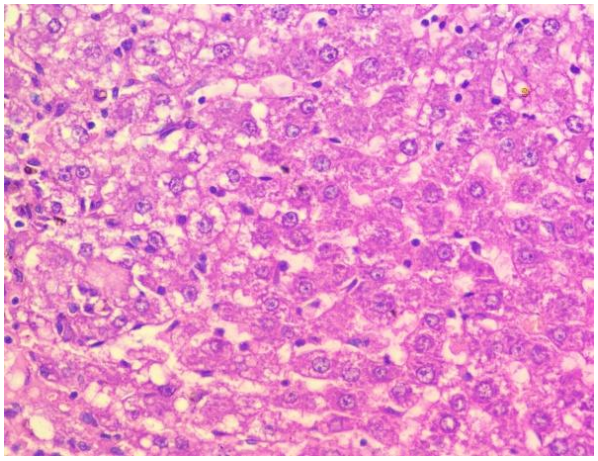


Fig-(e) Silymarin 100mg/kg

Figure. Photomicrographs (original magnification 45×) showing histopathological changes in rat liver tissue across different groups.

(Fig. a) Liver section showing normal portal architecture; areas surrounding the hepatic vein appear intact.

(Fig. b) Liver section showing moderate hepatocytic degeneration with dropout necrosis and ballooning, primarily in the periportal region and occasionally around the hepatic vein. Prominent fatty changes, congestion, mononuclear cell infiltration, and marked cholestasis are evident.

(Fig. c) Liver section displaying mild to moderate hepatocytic degeneration with vesicular changes, predominantly in the periportal zone. Dropout necrosis, hemorrhage, congestion, steatosis, and mononuclear cell infiltration are present.

(Fig. d) Liver section exhibiting minimal hepatocytic degeneration with moderate Kupffer cell hyperplasia. Mild fatty changes, scant hemorrhage, congestion, and mild steatosis with minimal mononuclear cell infiltration are noted.

(Fig. e) Liver section showing occasional hepatocytic degeneration with regenerative changes and pronounced Kupffer cell hyperplasia. Mild to moderate fatty changes are observed around the periportal area, along with scant hemorrhage, congestion, mild steatosis, and minimal mononuclear infiltration.

3. DISCUSSION

The protective effects observed may be attributed to the flavonoids and phenolics present in the methanolic leaf extract, which likely counteracted free radical damage and preserved membrane integrity (Dutta, 2021), (Kumari, 2022). Similar plant-based compounds have been documented to upregulate endogenous antioxidant enzymes and modulate pro-inflammatory cytokines via the Nrf2 signaling cascade (Ugwu, 2021), (Li R, 2021).

Taxifolin and related flavonoids isolated from C. deodara have shown hepatocyte stabilization in previous models (Harsh Pathak, 2023). The present study reinforces these findings, showing that the extract not only normalizes serum biomarkers but also conserves hepatic architecture.

The prophylactic administration allowed the extract's constituents to bolster antioxidant reserves prior to CCl_4 exposure, a design justified in phytotherapeutic evaluations of hepatic injury (Ugwu, 2021).

4. CONCLUSION

Methanolic leaf extract of Cedrus deodara effectively mitigates CCl_4-induced hepatic damage in rats through hepatocellular protective mechanisms. Its safety profile and dose-dependent efficacy affirm its therapeutic potential and support further studies into its molecular targets.

5. LIST OF ABBREVIATIONS

1. C. deodara: Cedrus deodara
2. CCl_4: Carbon Tetrachloride
3. OECD: Organisation for Economic Co-operation and Development
4. SGPT: Serum Glutamate Pyruvate Transaminase
5. SGOT: Serum Glutamate Oxaloacetate Transaminase
6. ALP: Alkaline Phosphatase
7. H&E: Hematoxylin and Eosin
8. CPCSEA: Committee for the Purpose of Control and Supervision of Experiments on Animals
9. i.p.: Intraperitoneal
10. p.o.: Oral administration
11. SEM: Standard Error of Mean
12. ANOVA: Analysis of Variance
13. Nrf2: Nuclear factor erythroid 2–related factor 2
14. n: Sample size
15.

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

Acknowledgement:

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Author Contribution

PJ- Writing original

Draft 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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