Antioxidant-Mediated Hepatoprotective Potential of Methanolic Leaf Extract of *Cedrus deodara* against CCl_4-Induced Oxidative Liver Injury in Wistar Rats

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Abstract- Hepatotoxicity driven by oxidative stress remains a major unresolved clinical challenge. *Cedrus deodara* (Roxb.) G. Don, a Himalayan medicinal conifer, possesses a phytochemical repertoire rich in flavonoids, terpenoids, and phenolics known to modulate free radical pathways. However, hepatoprotective investigation of its leaf fraction remains unreported. To evaluate the antioxidant-mediated hepatoprotective activity of the methanolic leaf extract of *C. deodara* against carbon tetrachloride (CCl_4)-induced oxidative hepatic injury in male Wistar rats, using hepatic glutathione (GSH) and lipid peroxidation (LPO) as primary antioxidant endpoints.

Following OECD 423 acute oral toxicity assessment, extract doses of 250 and 500 mg/kg were administered orally for 14 days. CCl_4 (1 ml/kg, i.p., 1:1 v/v in olive oil) was given on days 7 and 14. Silymarin (100 mg/kg, oral) served as the reference standard. Hepatic GSH and LPO, liver weight, body weight, and histopathology were assessed. Phytochemical screening was performed using standard qualitative assays. CCl_4 administration caused a significant depletion of hepatic GSH (15.83 ± 1.47 vs. 22.83 ± 1.94 U/L in normal control; $p<0.001$) and reduction of LPO to below normal levels (16.00 ± 1.41 nmol/mg protein; $p<0.001$), accompanied by heaptomegaly and body weight loss. Treatment with the extract at 500 mg/kg significantly restored GSH (19.67 ± 1.03 U/L; $p<0.001$) and normalized LPO (21.33 ± 1.21 nmol/mg protein; $p<0.001$) in a dose-dependent manner, with efficacy statistically comparable to silymarin. Histopathology confirmed reduced hepatocyte degeneration, decreased steatosis, and regenerative changes at 50 0 mg/kg.

The methanolic leaf extract of *C. deodara* confers significant dose-depen-dent, antioxidant-driven heap-to protection in CCl_4 injured rats, establishing scientific justification for its further development as a plant-based heapto-therapeutic agent.

Keywords: *Cedrus* deodara; Heaptoprotection; Oxidative stress; Glutathione; Lipid peroxidation; Carbon tetrachloride; Antioxidant; Phytochemistry.

Introduction

Liver disease constitutes one of the foremost causes of morbidity and mortality worldwide, with toxic and oxidative hepatic injury being implicated across a spectrum of pathologies ranging from drug-induced liver injury (DILI) to non-alcoholic steatohepatitis and chronic hepatitis[1-2]. The hepatocyte, as the primary functional unit of the liver, is uniquely exposed to chemical insults by virtue of its central role in xenobiotic biotransformation. Cytochrome P450 enzymes within the hepatocyte endoplasmic reticulum convert drugs and environmental toxins into reactive electrophilic and radical intermediates, which, when generated in excess, overwhelm endogenous defenses and initiate cellular injury[3]. Oxidative stress, the net imbalance between reactive oxygen species (ROS) generation and antioxidant neutralization capacity, is the convergent mechanistic pathway through which most hepatoxins exert their damage[4]. Among endogenous antioxidants, hepatic reduced glutathione (GSH) occupies a pivotal position: it functions as a direct free-radical scavenger, a cofactor for glutathione peroxidase in the detoxification of lipid hydroperoxides, and a substrate for glutathione-S-transferase-mediated conjugation of reactive metabolites[5]. Depletion of hepatic GSH is therefore both a reliable biomarker of oxidative injury and a pathogenic amplifier that sensitizes hepatocytes to further damage. Simultaneously, lipid peroxidation of polyunsaturated fatty acids in cell membranes, measured as malondialdehyde (MDA) equivalents via the thiobarbituric acid reactive substance (TBARS) assay, reflects the downstream consequences of unchecked ROS activity on membrane integrity[6].

Carbon tetrachloride (CCl_4) is the most extensively validated experimental model of oxidative hepatic injury. Following hepatic uptake, CCl_4 undergoes cytochrome P450 2E1-catalyzed homolytic cleavage to yield the trichloromethyl radical (CCl_3•), which rapidly reacts with dissolved oxygen to form the trichloromethylperoxy radical (CCl_3OO•). These radical species initiate lipid peroxidation cascades, deplete hepatic GSH, and cause hepatocyte necrosis indistinguishable histologically from human toxic hepatitis, making this model uniquely suitable for pre-clinical hepatoprotection evaluation[7-8].

Current pharmacotherapeutic options for toxic liver injury remain limited. Silymarin, a standardized flavonolignan complex from Silybum marianum, is the most widely used heaptoprotective agent in clinical practice, primarily through free-radical scavenging and GSH preservation[9].

Nevertheless, silymarin's modest oral bioavailability, inconsistent efficacy in advanced liver disease, and the complete absence of any regulatory approved synthetic agent specifically for toxic hepatic injury collectively define a substantive therapeutic gap that has sustained global investigation into plant derived hepatoprotective compounds[10-11].

Medicinal plant research has yielded numerous hepatoprotective leads, with polyphenols, flavonoids, and terpenoids consistently identified as the principal

active compound classes[12]. These phyto-constituents exert multi-mechanistic antioxidant effects: direct hydrogen atom donation to terminate radical chain reactions, chelation of pro-oxidant metal ions, inhibition of lipid peroxidation chain propagation, and transcriptional up regulation of endogenous antioxidant enzymes via the Nrf2/ARE pathway[13-14]. This multi-target profile is recognized as pharmacologically superior to single mechanism antioxidants and aligns with the complex, self-amplifying pathogenesis of oxidative hepatotoxicity. *Cedrus Deodara* (Roxb.) G. Don (family Pinaceae), the Himalayan deodar cedar, is a large evergreen conifer distributed between 1,200 and 3,200 metres across the western Himalayan range[15]. It occupies a well-documented position in Ayurvedic therapeutics, referenced in the Charaka Samhita under multiple drug categories relevant to inflammation, metabolic dis-orders, and detoxification[16]. Phytochemical investigations of its wood and bark have identified sesquiterpene alcohols (himachalol, allo himachalol, beta-himachalene), di-terpenes, bioactive lignans (deodarone, *Cedrus*in), flavonoids and phenolic acids[17-18]. Documented pharmacological activities include anti-inflammatory[19], anti-oxidant[20], anti-hyperglycemic[21] and anti-cancer effects[22].

Despite this pharmacological profile, the leaf fraction of *C. deodara* has received minimal scientific attention and has never been investigated for heapto-protective activity. This represents a clear gap in the literature, since leaves offer a renewable, sustainably harvested plant resource and are known to concentrate bioactive phenolics amenable to methanolic extraction[23]. The present study was designed specifically to address this gap by evaluating the anti-oxidant mediated hepatoprotective potential of the methanolic *C. deodara* leaf extract in the CCl_4 rat model, with hepatic GSH and LPO as primary endpoints, alongside liver weight, body weight, and histo-pathological assessment.

The mechanistic basis of CCl_4 heapto-toxicity has been characterized with precision. Weber et al; established the molecular sequence from CYP2E1-mediated radical generation to self-propagating lipid peroxidation and centrilobular necrosis. Recknagel et al. confirmed that depletion of hepatic GSH and membrane lipid peroxidation are the earliest and most sensitive biochemical events, preceding overt histological damage, making them ideal pre-clinical efficacy endpoints for hepatoprotective agents.

Glutathione biochemistry in the context of hepatic oxidative injury was comprehensively characterized by Meister and Anderson, who demonstrated that intracellular GSH depletion below a critical threshold eliminates the heaptocyte's principal defence against reactive metabolites. Subsequent investigations established that the Nrf2/ARE signalling pathway governs transcriptional induction of GSH synthesis and antioxidant enzyme expression in response to oxidative challenge, and that plant flavonoids and polyphenols are potent Nrf2 activators, suggesting a molecular mechanism for their GSH-restorative hepatoprotective effects.

Silymarin, the reference hepato-protective compound, achieves hepato-protection primarily through free radical scavenging, inhibition of lipid per-oxidation, and GSH preservation, as demonstrated in multiple CCl_4 and other hepatotoxin models[24]. Vargas-Mendoza et al[25]; confirmed that silymarin maintained hepatic GSH and attenuated lipid peroxidation markers in experi-mentally stressed animals. Satyam et al[26]; further showed that antioxidant-anti-inflammatory combinatorial appro-aches produced superior histological recovery in CCl_4 models compared to silymarin alone, supporting the trans-lational advantage of multi-mechanism plant extracts. Investigative work on Himalayan medicinal plants has gene-rated relevant parallels. Nirmalkar et al[27]; demonstrated that the methane-olic leaf extract of *Lathyrus sativus* restored hepatic antioxidant status and serum biochemical markers in paracetamol hepatotoxic Wistar rats over 14 days with confirmed histopathological tissue recovery, providing a method-logical template for leaf extract evaluation. Within the genus *Cedrus*, Adinarayana and Subbaraju[28] isolated bioactive lignans from *C. deodara* wood with antioxidant structural features, and Zhang and Shi[29] provided a compre-hensive review identifying sesqui-terpenes as the pharmacologically dominant fraction. Sharma and Singh[28] confirmed the presence of flavonoids, alkaloids, tannins, and saponins in *C. deodara* leaves, establishing the phytochemical basis for the antioxidant pharmacology expected from this fraction. Sharma and Prasad reported significant anticancer activity mediated through antioxidant mechanisms in vivo. No published study, however, has evaluated the hepatoprotective efficacy of the leaf fraction, identifying the specific scientific gap this work addresses.

Materials and Methods

Ethical Clearance and Animal Care

All experimental procedures were conducted in accordance with CPCSEA guidelines and approved by the Institutional Animal Ethics Committee (IAEC) of Siddhartha Institute of Pharmacy, Dehradun (IAEC Form B)[29]. Healthy adult male Wistar rats (150-200 g; 10-12 weeks) were procured from Shri Guru Ram Rai University, Dehradun, and housed under standard laboratory conditions (25 ± 2°C, 12-hour light/dark cycle) with free access to standard pellet diet and drinking water. A 7-day acclimatization period preceded all procedures.

Plant Material and Authentication

Fresh leaves of *Cedrus Deodara* were collected from Berinag, Uttarakhand, India, shade-dried, and coarsely powdered. The plant material was authenticated by the Botanical Survey of India, Dehradun (Authentication No. 1775).

Preparation of Methanolic Extract

Forty grams of dried leaf powder was subjected to Soxhlet extraction using methanol (400 mL) as solvent over 48 hours until the siphonate became colour-less[30]. The extract was concentrated under reduced pressure and stored at 4°C. OECD 423 acute oral toxicity eva-luation at 2000 mg/kg revealed no mortality or observable toxicity, and working doses of 250 and 500 mg/kg were selected accordingly[31].

Phytochemical Screening

Qualitative phytochemical tests were performed on the extract for alkaloids (Dragendorff's, Mayer's, and Hager's tests), flavonoids (alkaline reagent and lead acetate tests), carbohydrates (Molisch's, Benedict's, and Fehling's tests), glycosides (Keller Killiani and Legal's tests), and tannins (ferric chloride test[32]).

Experimental Methods

Thirty male Wistar rats were randomly assigned to five groups (n = 6):

Group I (Normal Control): No treatment.

Group II (Disease Control): CCl_4 (1ml/ kg i.p., 1:1 v/v in olive oil) on days 7 and 14.

Group III *C. deodara* extract 250 mg/kg/day (oral, 14 days) + CCl_4.

Group IV *C. deodara* extract 500 mg/kg/day (oral, 14 days) + CCl_4.

Group V (Standard): Silymarin 100 mg/kg/day (oral, 14 days) + CCl_4.

Doses were calculated daily on body weight. Confirmatory hepatotoxicity induction was verified by retro-orbital blood sampling from one disease control animal after day 7.

BiochemicalandAntioxidant Estimation

At study termination (day 14), animals were sacrificed under anesthesia. Liver tissue was homogenized in 0.1M phosphate buffer (pH 7.4) and used to estimate:

(a) Hepatic GSH by Ellman's method[33] (U/L).

(b) Hepatic LPO by the TBARS assay[34] (nmol MDA/mg protein).

Liver weight was recorded immediately after excision. Body weights were measured on days 1, 7, and 14.

Histopathological Examination

Liver specimens were fixed in 10% neutral buffered formalin, paraffin-embedded, sectioned at 5 μm, and stained with haematoxylin and eosin. Sections were examined at 45× magnification under light microscopy[35].

Statistical Analysis

Data are expressed as mean ± SEM (n = 6). Statistical significance was assessed by one-way ANOVA followed by Tukey's multiple comparison test. $p < 0.05$ was considered significant[36].

Results

Phytochemical Screening

Phytochemical screening of the methanolic leaf extract confirmed the presence of alkaloids, flavonoids, carbohydrates, glycosides, and tannins **(Table-1)**. The presence of flavonoids, tannins, and phenolic constituents is of particular relevance to the antioxidant pharmacological profile of the extract.

Table-1 Phytochemical screening of methanolic leaf extract of *Cedrus deodara*

Phytochemical Class	Test Applied	Result
Alkaloids	Dragendorff's, Mayer's, Hager's tests	Present (+)
Flavonoids	Alkaline reagent test, Lead acetate test	Present (+)
Carbohydrates	Molisch's, Benedict's, Fehling's tests	Present (+)
Glycosides	Keller-Killiani test, Legal's test	Present (+)
Tannins	Ferric chloride test	Present (+)

(+) denotes presence of phytoconstituent

Body Weight- Normal control animals showed consistent weight gain throughout the study period. Disease control animals receiving CCl_4 exhibited progressive body weight loss from day 7, reflecting systemic catabolic effects of hepatotoxic inflammation. Both extract-treated groups and the silymarin group showed attenuated weight loss, with the 500 mg/kg group maintaining body weight most closely to the normal trajectory **(Table-2)**.

Table-2 Body weight (g) of rats across treatment groups on days 1, 7, and 14

Group	n	Day 1 (g)	Day 7 (g)	Day 14 (g)
Normal Control	6	132 ± 25.6	145 ± 26.8	138 ± 31.9
Disease Control (CCl_4)	6	130 ± 18.4	118 ± 19.2	110 ± 21.5
C. deodara 250 mg/kg	6	128 ± 17.3	125 ± 18.4	120 ± 19.7
C. deodara 500 mg/kg	6	131 ± 16.8	138 ± 15.2	125 ± 14.9
Silymarin 100 mg/kg	6	161 ± 12.2	163 ± 12.4	149 ± 10.8

Values expressed as mean ± SEM. Individual rat weights given in thesis raw data.

Liver Weight

CCl_4 caused significant hepatomegaly in the disease control group (17.39 ± 0.34 g) versus normal control (11.02 ± 0.31 g; $p<0.001$). Extract treatment reduced liver weight dose-dependently (250 mg/kg: 8.18 ± 0.16 g; 500 mg/kg: 10.24 ± 0.31 g; both $p<0.001$ vs. disease control). The 500 mg/kg group was comparable to silymarin (11.21 ± 0.14 g; $p<0.001$ vs. disease control) (Table-3, Figure-1).

Table-3 Effect of various treatments on liver weight (g) (mean ± SEM, n=6)

S. No.	Group	Liver Weight (g)	Significance
1	Normal Control	11.02 ± 0.31	---
2	Disease Control (CCl_4)	17.39 ± 0.34	$p<0.001$ vs. NC
3	*C. deodara* 250 mg/kg + CCl_4	8.18 ± 0.16	$p<0.001$ vs. DC
4	*C. deodara* 500 mg/kg + CCl_4	10.24 ± 0.31	$p<0.001$ vs. DC
5	Silymarin 100 mg/kg + CCl_4	11.21 ± 0.14	$p<0.001$ vs. DC

NC = Normal Control; DC = Disease Control. One-way ANOVA + Tukey's post-hoc.

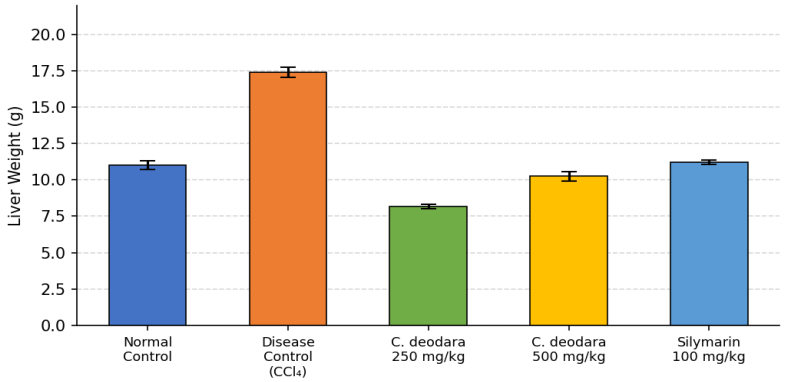

Figure-1 Effect of *C. deodara* extract on liver weight in CCl_4 induced hepatotoxicity

Hepatic Glutathione (GSH)

Hepatic GSH was significantly depleted in the disease control group (15.83 ± 1.47 U/L) relative to normal control animals (22.83 ± 1.94 U/L; $p<0.001$), reflecting consumption of the glutathione pool during free-radical detoxification. Treatment with the extract produced dose dependent, statistically significant GSH restoration: 250 mg/kg yielded 18.50 ± 1.05 U/L ($p<0.001$ vs. disease control), and 500 mg/kg yielded 19.67 ± 1.03 U/L ($p<0.001$ vs. disease control). Importantly, there was no significant difference between the 500 mg/kg group and silymarin (21.50 ± 1.05 U/L; $p=0.165$), confirming comparable antioxidant efficacy at this dose (Table-4, Figure-2).

Table-4 Effect of various treatments on hepatic GSH level (U/L) (mean ± SEM, n=6)

S. No.	Group	GSH (U/L)	Mean Diff.	Adjusted p Value
1	Normal Control	22.83 ± 1.94	---	---
2	Disease Control (CCl_4)	15.83 ± 1.47	+7.00 vs. NC	<0.001
3	*C. deodara* 250 mg/kg + CCl_4	18.50 ± 1.05	-2.67 vs. DC	<0.001
4	*C. deodara* 500 mg/kg + CCl_4	19.67 ± 1.03	-3.83 vs. DC	<0.001
5	Silymarin 100 mg/kg + CCl_4	21.50 ± 1.05	-5.67 vs. DC	<0.001

500 mg/kg vs. Silymarin: mean diff. = -1.83; p = 0.165 (NS). One-way ANOVA + Tukey's post-hoc.

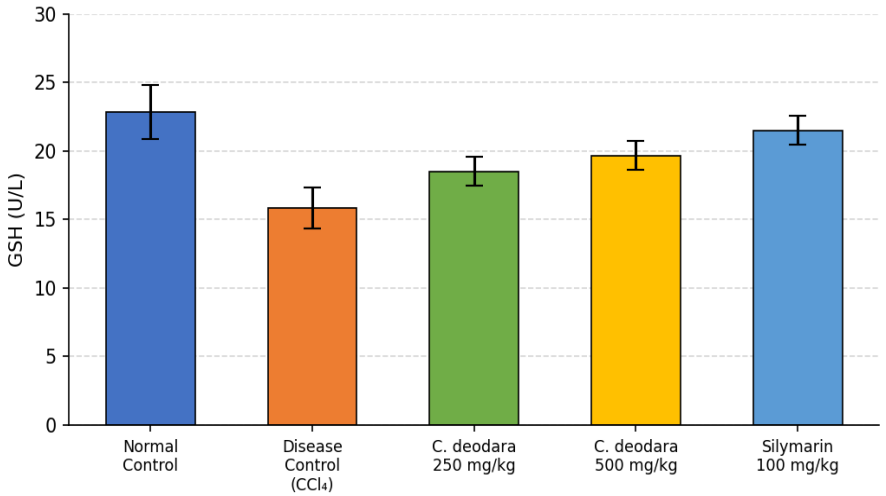

Figure-2 Effect of *C. deodara* extract on hepatic GSH level (U/L)

Hepatic Lipid Peroxidation (LPO)

Hepatic LPO values in the disease control group (16.00 ± 1.41 nmol/mg protein) were significantly lower than normal controls (24.00 ± 1.79 nmol/mg protein; $p<0.001$). This pattern reflects the known consequence of severe CCl_4-induced necrosis: depletion of peroxidable lipid substrate and suppression of microsomal enzyme activity eliminate the substrate for ongoing peroxidation at the 14-day endpoint. Extract treatment restored LPO values toward normal in a dose-dependent manner: 250 mg/kg produced 17.33 ± 1.63 nmol/mg ($p=0.562$ vs. disease control; NS), while 500 mg/kg produced 21.33 ± 1.21 nmol/mg ($p<0.001$ vs. disease control). The silymarin group achieved 25.33 ± 1.51 nmol/mg, near normal. LPO normalization in treated groups reflects

recovery of membrane lipid homeostasis during hepatocellular regeneration, confirmed histopathologically (Table-5, Figure-3).

Table-5 Effect of various treatments on hepatic LPO level (nmol/mg protein) (mean ± SEM, n=6)

S. No.	Group	LPO (nmol/mg)	Mean Diff.	Adjusted p Value
1	Normal Control	24.00 ± 1.79	---	---
2	Disease Control (CCl_4)	16.00 ± 1.41	+8.00 vs. NC	<0.001
3	*C. deodara* 250 mg/kg + CCl_4	17.33 ± 1.63	-1.33 vs. DC	0.562 (NS)
4	*C. deodara* 500 mg/kg + CCl_4	21.33 ± 1.21	-5.33 vs. DC	<0.001
5	Silymarin 100 mg/kg + CCl_4	25.33 ± 1.51	-9.33 vs. DC	<0.001

NS = Not significant. One-way ANOVA + Tukey's post-hoc.

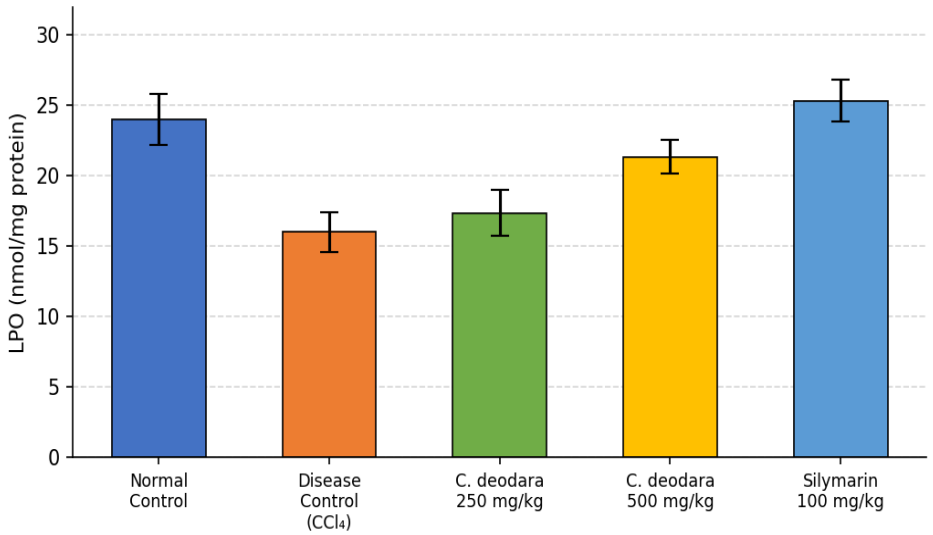

Figure-3 Effect of *C. deodara* extract on hepatic LPO level (nmol/mg protein)

Histopathology

Normal control liver sections (Fig.a) showed intact hepatic cords, well-defined central veins, and normal portal triads with no cellular damage. Disease control sections (Fig.-b) revealed moderate hepatocyte degeneration with dropout necrosis, ballooning predominantly in the periportal zone, prominent fatty change, mononuclear inflammatory infiltration, congestion, and marked cholestasis, consistent with classical CCl_4 oxidative hepatic injury. The 250 mg/kg group (Fig. c) showed mild-to-moderate degeneration with vesicular change, reduced but persistent necrosis and steatosis. The 500 mg/kg group (Fig.d) demonstrated minimal hepatocyte degeneration, moderate Kupffer cell hyperplasia, mild fatty change, and scant hemorrhage, indicating substantially preserved hepatic architecture. The silymarin group (Fig. e) showed only occasional hepatocyte degeneration with regenerative changes and prominent Kupffer cell hyperplasia, a near normal histological profile closely paralleled by the 500 mg/kg group.

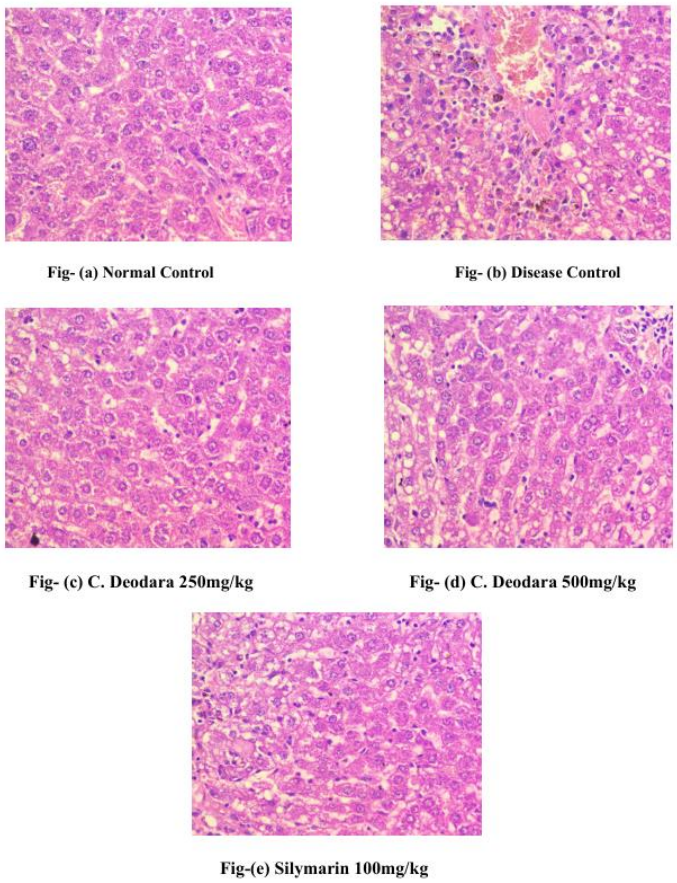

Figure-4 Photomicrographs (45×) of H&E-stained rat liver sections. (a) Normal Control: normal hepatic architecture; (b) Disease Control (CCl_4): necrosis, ballooning degeneration, steatosis, cholestasis; (c) *C. deodara* 250 mg/kg: mild-moderate degeneration with reduced injury; (d) *C. deodara* 500 mg/kg: minimal degeneration, Kupffer cell hyperplasia; (e) Silymarin 100 mg/kg: regenerative changes, near-normal architecture.

Discussion

This study provides the first systematic pre-clinical evidence that the methanolic leaf extract of *Cedrus Deodara* confers significant antioxidant mediated heapto-protection against CCl_4 induced oxidative liver injury in a dose-dependent manner. The coherent pattern of GSH restoration, LPO normalization, liver weight reduction, and histopathological recovery across both treatment doses, with the 500 mg/kg dose achieving equivalence with silymarin on the primary antioxidant endpoint, constitutes robust pre-clinical evidence of hepatoprotective efficacy. The hepatic GSH depletion observed in the group is the predictable biochemical signature of CCl_4 toxicity. As trichloromethyl radicals are generated by CYP2E1 biotransformation, GSH is consumed both enzymatically through glutathione peroxidase catalyzed hydroperoxide reduction and non-enzymatically through direct adduct formation with radical intermediates. Once depleted, the glutathione pool can no longer buffer subsequent oxidative insults, creating a vicious cycle of amplifying damage. The significant and dose dependent restoration of hepatic GSH by *C. deodara* extract, with statistical equivalence to silymarin at 500 mg/kg, indicates that the

extract's polyphenolic and flavonoid constituents either scavenge radicals upstream, sparing GSH from consumption, or activate Nrf2/ARE-driven transcriptional induction of GSH synthesis, as reported for structurally similar flavonoids. The LPO pattern requires contextual mechanistic interpretation. Reduced LPO in the disease control relative to normal animals at the 14 day endpoint, rather than the elevated values often assumed, reflects known biophysical consequences of severe heaptocellular necrosis: extensive cellular destruction depletes the polyunsaturated lipid substrate available for peroxidation and suppresses the CYP 2E1 driven radical generation that sustains the peroxidative cascade. The acute MDA burst characteristic of CCl_4 injury resolves substantially within 48-72 hours, leaving reduced residual values at the chronic endpoint that reflect substrate depletion rather than antioxidant recovery. The dose dependent restoration of LPO toward normal values in extract treated animals, most signifycantly at 500 mg/kg, is therefore correctly interpreted as a marker of membrane lipid replenishment and restoration of normal hepatocellular lipid metabolism during regeneration, a conclusion fully supported by the parallel histopathological observations of reduced steatosis and improved hepatocyte architecture.

The multi-component phytochemical profile of the extract provides a mechanistically coherent basis for the observed effects. Flavonoids, the principal antioxidant compound class identified, act through at least four complementary mechanisms: direct hydrogen atom donation to terminate lipid radical chain reactions, chelation of redox-active iron and copper ions that catalyze Fenton-type hydroxyl radical formation, allosteric inhibition of prooxidant enzymes including xanthine oxidase and NADPH oxidase, and Nrf2-mediated transcriptional upregulation of glutamate cysteine ligase and glutathione reductase[37]. Tannins contribute additional membrane stabilizing and astringent effects that limit hepatocyte membrane permeabilization. Sesquiterpene terpe-noids characteristic of C. deodara, particularly himachalol, exert anti-inflammatory activity through inhibition of prostaglandin synthesis and neutrophil margination, addressing the inflamematory amplification phase of CCl_4-induced injury. Alkaloids may further contribute through membrane stabilizing effects that reduce lysosomal enzyme release. Kupffer cell hyperplasia in the 500 mg/kg and silymarin groups reflects active phagocytic clearance of necrotic debris and initiation of hepatocyte regeneration, and may additionally reflect immune-modulatory modulation of the resident macrophage pool by the extract's terpenoids and flavonoid constituents[38]. The absence of acute toxicity at 2000 mg/kg (OECD 423) and excellent tolerability at therapeutic doses over 14 days establishes an adequate preclinical safety profile for further development.

Conclusion

The methanolic leaf extract of *Cedrus Deodara* demonstrates significant, dose dependent, antioxidant mediated hepatoprotection against CCl_4 induced oxidative liver injury in male Wistar rats. The extract significantly restored hepatic

GSH and normalized LPO in a dose-dependent fashion, with the 500 mg/kg dose-achieving efficacy statistically equivalent to silymarin (100 mg/kg) on the primary antioxidant endpoint. Liver weight normalization, body weight preservation, and histopathological evidence of reduced necrosis, decreased steatosis, and hepatocyte regeneration comprehensively corroborate these findings. The phytochemical profile, including flavonoids, tannins, alkaloids, and terpenoids, provides a mechanistically coherent multi-target antioxidant and anti-inflammatory basis for these effects. These results validate, for the first time, the hepatoprotective potential of the *C. deodara* leaf fraction and establish a rigorous pre-clinical foundation for further pharmacological development.

Future Perspectives

Future research should employ HPLC-MS and GC-MS-based phytoconstituent profiling to identify the specific bioactive molecules responsible for hepatoprotection and enable standardization of the extract. Mechanistic pathway studies targeting Nrf2/ARE, NF-κB, and TNF-α signaling will clarify the molecular basis of action. Sub-chronic and chronic toxicity evaluation across multiple species is essential before clinical translation. Nano-formulation or other delivery system development may improve the oral bioavailability of the active constituents. Parallel investigation of nephron-protective and neuro-protective activities would capitalize on the established antioxidant profile of the extract. Ultimately, well-designed pilot clinical trials in patients with hepatic dysfunction, subject to regulatory approval, represent the translational goal that these pre-clinical findings now justify.

Conflict of Interest

The authors declare no conflicts of interest.

Disclaimer Statement

Authors declare that no competing interest exists. The products used for this research are commonly used products in research. There is no conflict of interest between authors and producers of the product.

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