Vol. 4 No. 4 (2025)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Taraxerol Acetate: A Natural Hepatoprotective Agent against Drug-Induced Liver Damage.

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Keywords: Taraxerol Acetate, Ccl4-Induced Hepatotoxicity, Hepatoprotective Agents

Received on 20 Nov 2025
Accepted on 20 Dec 2025
Published on 31 Dec 2025

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Abstract

Background: Drug-induced liver injury is a significant clinical concern, often resulting in acute or chronic liver dysfunction. Carbon tetrachloride (CCl_4) serves as a widely used experimental model to induce hepatotoxicity and evaluate the protective efficacy of therapeutic agents. Taraxerol acetate (TA), a natural compound with promising antioxidant and anti-inflammatory properties, has demonstrated hepatoprotective potential in preclinical studies. This study investigates the hepatoprotective effects of TA against CCl_4-induced liver damage in Wistar albino rats.

Methods: A total of 25 adult Wistar albino rats were divided into five groups: normal control, negative control (CCl_4-only), positive control (silymarin-treated), and two test groups receiving TA at doses of 20 mg/kg and 40 mg/kg. Treatments were administered orally or intraperitoneally for three days, with subcutaneous CCl_4 administration on the third day to induce hepatotoxicity. Blood samples were collected post-treatment to measure biochemical markers of liver injury, including serum glutamate oxaloacetate

transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (ALP), and total bilirubin (TB). Statistical analysis was performed using ANOVA with a significance threshold of $p < 0.05$.
Results: CCl_4 exposure significantly elevated liver enzyme levels and reduced liver weight in the negative control group. TA treatment at 20 mg/kg and 40 mg/kg doses markedly decreased SGOT, SGPT, ALP, and TB levels ($p < 0.05$) and improved liver weight compared to the negative control. The hepatoprotective effect of TA was comparable to the standard drug silymarin. Notably, the 20 mg/kg dose exhibited the most pronounced reduction in liver enzyme levels.
Conclusion: Taraxerol acetate demonstrated significant hepatoprotective effects against CCl_4-induced liver damage, with reductions in biochemical markers of liver injury and improved liver weight. These findings suggest that TA is a promising candidate for the prevention and management of drug-induced liver injury. Further clinical investigations are warranted to confirm its therapeutic potential in humans.

Introduction:

Drug-induced liver injury is a significant concern in clinical practice and pharmaceutical development. [1,2] Liver plays a crucial role in drug metabolism and detoxification, making it susceptible to damage from various pharmacological agents and environmental toxins. [3,4] Hepatotoxicity can lead to acute liver failure, chronic liver disease, and even hepatocellular carcinoma, posing a major health risk. [5] Identifying hepatoprotective agents that can mitigate liver damage is therefore essential for improving patient health outcomes and preventing drug-induced liver injury.

Carbon tetrachloride (CCl_4) has long been used as a model compound for inducing hepatotoxicity in experimental settings. [6,7] Its metabolic activation produces highly reactive free radicals, which can damage cellular macromolecules, including lipids, proteins, and DNA, leading to hepatocyte death. [8,9] The resulting inflammation and oxidative stress contribute to the progression of liver injury. Several studies have demonstrated that CCl_4 exposure can lead to significant alterations in liver function tests, including increased levels of serum aminotransferases (SGOT and SGPT), alkaline phosphatase (ALP), and total bilirubin. These markers serve as critical indicators of hepatic injury and are commonly used to evaluate the effectiveness of potential therapeutic agents. [10,11]

Taraxerol, a natural pentacyclic triterpene found in various plants, has garnered researcher's attention for its potential hepatoprotective properties. [12] Preliminary studies suggest that taraxerol possesses antioxidant, anti-inflammatory, and anti-fibrotic effects, and may play a crucial role in protection against liver injury. [13,14] Given the pressing need for effective hepatoprotective strategies, this study aims to evaluate the protective effects of taraxerol against CCl_4-induced hepatotoxicity in Wistar albino rats.

By assessing biochemical markers of liver injury and liver weight, this study seeks to establish the hepatoprotective role of taraxerol and its efficacy as a promising candidate for the prevention of drug-induced liver damage.

Materials and Methods

Isolation of the taraxerol compound: The Taraxerol acetate compound was obtained from the aerial part of the plant Artemesia roxburghiana found in the Hazara University Campus, Mansehra, KPK, Pakistan and was donated to us by Mr. Ishtiaq who works in the Department of Biochemistry of the same university.

Animals: Adult Wistar rats of either sex, weighing approximately 180 ± 10 grams, were used for this study. The animals were housed in groups of five under standard laboratory conditions with a 12-hour light-dark cycle and provided with water and

standard rat feed ad libitum. All established ethical principles for the care and use of laboratory animals were strictly observed throughout the study. Prior to the commencement of the experiment, the rats were acclimatized to the laboratory environment for seven days.

CCl_4-Induced Hepatotoxicity Model: Hepatotoxicity was induced using carbon tetrachloride (CCl_4). Five groups of Wistar albino rats were established to study the hepatoprotective effects of taraxerol acetate (TA). Each group consisted of five animals (n = 5).
Group 1 (Normal Control): Animals in this group received only the vehicle (sodium carboxymethyl cellulose and olive oil in a 1:1 ratio) at a dose of 1 milligram per kg body weight orally, once daily for three days.
Group 2 (Negative Control): Animals in this group were administered CCl_4 (1 ml/kg, s.c.) and the vehicle. The vehicle was given once daily for the first and second days, followed by CCl_4 injection on the third day.
Group 3 (Positive Control): This group received silymarin (50 mg/kg, i.p.) as the standard drug along with CCl_4. Silymarin was suspended in sodium carboxymethyl cellulose and administered intra-peritoneally once daily for three days, with CCl_4 injected subcutaneously on the third day.
Group 4 (TA 20 mg/kg): Animals in this group received taraxerol at a dose of 20 mg/kg orally, suspended in sodium carboxymethyl cellulose, once daily for three days, followed by a subcutaneous injection of CCl_4 on the third day.
Group 5 (TA 40 mg/kg): Animals in this group received taraxerol at a dose of 40 mg/kg orally once daily for three days, followed by CCl_4 administration on the third day.
After 24 hours of the final treatment, blood samples were collected via cardiac puncture from each animal in all groups. The blood was stored in appropriate tubes at room temperature, and then centrifuged at 3200 rpm for 15 minutes to separate the serum. The serum was subsequently used to estimate the markers of hepatotoxicity, including SGOT, SGPT, ALP, and total bilirubin (TB).
Statistical Analysis: Statistical analysis was performed to evaluate the obtained data. Data were analyzed using analysis of variance (ANOVA) for comparison among the study groups, followed by appropriate post hoc tests to determine specific group differences. For the evaluation of differences between two groups, a t-test was employed. All analyses were conducted using SPSS version 22. A significance level of $p < 0.05$ was established to indicate statistically significant differences.

Results:

General Distribution

A total of 25 Wistar albino rats were utilized in this study, divided into five groups of five animals each. Each group was monitored for a standard period following treatment to evaluate the effects on liver health.

Serum Biochemical Markers

Table.1 summarizes the effect of TA on liver enzymes in rats with CCl_4-induced hepatotoxicity. The administration of CCl_4 significantly increased the levels of all biochemical markers of hepatic injury investigated in this study compared to the control group. The normal control group animals, which received neither CCl_4 nor the drugs, had normal levels of SGOT, SGPT, ALP, and TB. In contrast, the negative control group, which received only CCl_4 and the vehicle, showed a marked increase (two to tenfold) in the values of all biochemical parameters.
Group III animals treated with the standard drug Silymarin and the hepatotoxin CCl_4 showed better liver profile as compared to group II i.e the negative control. The animals

treated with TA at oral dose of 20 mg per kg exhibited a marked improvement of liver profile with decrease in the values of all biochemical parameters. Another group receiving 40 mg per kg oral dose of taraxerol showed a further decrease in values of all parameters. Although the values in group V (40 mg/Kg TA) decreased arithmetically, however no significant difference was noted between the two TA-treated groups. No significant difference was observed when the enzyme levels of group III, positive control group treated with silymarin, were compared with group IV and V (TA treated groups)

Table 1: Effect of taraxerol acetate on serum levels of liver enzymes in rats with CCl_4 induced hepatotoxicity

Treatment group	Biochemical parameters			
	SGOT (1U/L)	SGPT (1U/L)	ALP (1U/L)	TB (mg/dl)
Normal	85.76±2.34	45.41±1.16	158.82±1.83	0.29±0.02
Negative control (CCl_4, 1 ml/kg s.c.)	541.62± 11.97	451.83± 1. 47	369.27±2.53	1.82±0.01
Silymarin (50 mg/kg i.p.)	122.91±1.18*	91.43± 1.52*	195.68±1.98*	0.36±0.03*
TA (20 mg/kg p.o)	347.43±1.94*	312.95± 1.36*	278.33±1.18*	0.72±0.03*
TA (40 mg / kg p.o)	232.53±1.54*	296.44±1.07*	213.46±1.37*	0.64±0.01*

P<0.01 when compared to toxic (CCl_4 treated) group; n = 5

Table 2 shows the percentage- wise effect of taraxerol acetate on liver function tests performed in this study.

Table 2: Percentage-wise effect of taraxerol acetate on liver enzymes in rats with carbon tetrachloride induced hepatotoxicity

Treatment group	Biochemical parameters			
	SGOT (1U/L)	SGPT (1U/L)	ALP(1U/L)	TB (mg/dl)
Negative control (CCl_4, 1 ml/kg s.c.)	-	-	-	-
Silymarin (50 mg/kg i.p.)	22.6%	20.2%	57.8%	19.7%
TA (20 mg/kg p.o)	64.1%	69.2%	75.3%	39.5%
TA (40 mg / kg p.o)	42.9%	65.6%	57.8%	19.7%

P<0.01 when compared to toxic (CCl_4 treated) group; n = 5; *Percentage reduction of various serum biochemical parameters due to treatment with TA against CCl_4 induced hepatotoxicity in rats

Table 3 presents the liver weight and volume measurements of the animals in each group. Following CCl_4 exposure, the liver weight decreased from 4.1 g in normal rats to 3.2 g in the CCl_4-treated group. Treatment with TA at doses of 20 mg/kg and 40

mg/kg significantly recovered liver weight, approaching the values seen in rats treated with the standard drug, indicating the hepatoprotective role of TA.

Treatment Group	Weight of liver (g)	% Recovery in Weight	Volume of liver (cc)	% Recovery in volume
Normal	4.1	--	4.9	--
Negative control (CCl_4)	3.2	--	3.6	--
Silymarin 50 mg/kg	3.9	88.8	4.4	61.5
TA 20 mg/kg	3.3	11.1	3.8	15.3
TA 40 mg/kg	3.7	55.5	4.2	46.1

Table 3.3 Effect of TA on Liver weight and volume against carbon tetrachloride induced hepatotoxicity in rats

Discussion

The results of the current study provide compelling evidence that taraxerol acetate (TA) significantly improvesa liver damage induced by carbon tetrachloride (CCl_4) in adult Wistar albino rats. Treatment with TA led to a marked reduction in serum levels of liver enzymes, including SGOT, SGPT and ALP, and total bilirubin, as well as an improvement in liver weight, suggesting its potential as a hepatoprotective agent. These findings are consistent with prior studies that have documented the hepatoprotective properties of natural compounds. For instance, silymarin, a well-known hepatoprotective agent, reduced SGOT levels by 22.6% in our study, whereas TA at 20 mg/kg exhibited a remarkable 64.1% reduction. This significant difference in efficacy underscores the potential of TA as a more effective alternative or adjunctive therapy in the management of liver injury.

Mechanistically, the hepatoprotective effects of TA can be attributed to its antioxidant properties, which may help mitigate oxidative stress—a critical factor in CCl_4-induced liver damage. Previous research has shown that antioxidants can scavenge free radicals, thereby reducing lipid peroxidation and subsequent cellular injury in hepatic tissues [(15).] Moreover, natural compounds known for their hepatoprotective properties, such as flavonoids and silymarin, have been shown to positively influence liver enzyme activity and enhance liver function, suggesting a potentially similar mechanism of action for TA [(16-18)]. This aligns with our findings where taraxerol effectively reduced the levels of liver enzymes in treated rats.

In terms of clinical relevance, the promising results of TA in this animal model may have implications for human liver health, particularly in conditions characterized by oxidative stress and inflammation, such as alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD). The use of natural products like TA could offer a complementary approach to conventional therapies, potentially improving patient outcomes and reducing side effects associated with synthetic medications [(19,20)] . However, it is essential to note that while animal studies provide valuable insights, the direct translation of these findings to humans requires further investigation through well-designed clinical trials.

Limitations

Despite the strengths of this study, including the robust experimental design and the use of multiple dosing regimens, there are limitations that should be acknowledged. The relatively small sample size may limit the generalizability of the findings, and the choice of a rat model may not entirely replicate human hepatic responses to injury and

treatment. Moreover, the lack of long-term monitoring post-treatment raises questions about the sustainability of the observed effects.

Recommendation

Future studies should aim to address these limitations by incorporating larger sample sizes and exploring the long-term effects of TA on liver health.

Conclusion

This study adds to the growing body of evidence supporting the hepatoprotective effects of taraxerol acetate against CCl_4-induced liver injury. Given the significant reductions in liver enzyme levels and the improvement in liver weight observed with TA treatment, further research is warranted to elucidate its mechanism of action and potential clinical application in liver disease management.

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