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Protective Effects of *Taraxacum officinale* (L.) Weber on CCl_4-Induced Liver Toxicity in Male Rats

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Abstract

Background: Hepatotoxicity and drug-induced liver injury (DILI) are significant worldwide health issues and carbon tetrachloride (CCl_4)-induced liver toxicity has been extensively used as an experimental model for DILI. Taraxacum officinale (dandelion) is one of the classic herbal compounds with a traditional use for hepatoprotective effect, but systemic mechanistic investigations using persistent liver injury models are lacking. Objective: This study investigated the protective effects that T. officinale root extract could have against CCl_4-induced hepatotoxicity in male Wistar rats via biochemical, antioxidant, and histopathological evaluations. Methods: A total of 40 male Wistar rats (180-220 g) were used and randomly divided into four groups (n = 10): Group I - Control; Group II - CCl_4-intoxicated Group III - CCl_4 + Silymarin (100 mg/kg); Group IV - CCl_4 + T. officinale extract Agr 300 mg/kg The experiment lasted 8 weeks. Intraperitoneal injection of CCl_4 (1 mL/kg, 1:1 in corn oil) was used to induce hepatotoxicity twice weekly. Liver function markers [alanine aminotransaminase (ALT), aspartate ametansfer/free maleic acid (MDA)], and total antioxidant capacity (T-AOC). Hepatic histopathology was evaluated using hematoxylin and eosin (H&E) staining. Results: CCl_4 administration significantly increased the levels of serum ALT, AST, ALP and TB ($p < 0.001$), while decreasing TP and T-AOC accompanied by an increase in MDA levels. T. officinale treatment significantly reduced these changes, bringing the liver enzyme concentrations back to near normal levels. Quantitative analysis of histopathological examination indicated that the samples treated with BBR showed significant improvement in hepatic architecture, reduced risk of necrosis, inflammatory infiltration and steatosis compared to CCl_4 group. The protective effects were similar to those of the reference hepatoprotant silymarin. Conclusions: Aqueous root extract of T. officinale possesses notable hepatoprotective activity in carbon tetrachloride (CCl_4)-induced liver toxicity in rats, and such effects are likely due to its antioxidant potential and maintaining hepatic integrity. These results validate the traditional treatment of dandelion for liver diseases and merit clinical studies.

Keywords: *Taraxacum Officinale*; Hepatoprotection; Carbon Tetrachloride; Oxidative Stress; Liver Enzymes; Silymarin

1. Introduction

Liver diseases are one of the important global health problems and represent ~2 million deaths per year worldwide [1]. Since the liver is the main organ responsible for the metabolism of xenobiotics, it is especially sensitive to toxic agents present in food, drugs and alcohol [2]. For decades carbon tetrachloride (CCl_4) has been used as an experimental hepatotoxin to induce chemically-induced liver injury, and it has provided important information on the pathophysiology of acute and chronic liver disease [3].

The hepatotoxicity of CCl_4 mainly occurs in the hepatic endoplasmic reticulum via metabolic activation by cytochrome P450 2E1 (CYP2E1) leading to the production of radical trichloromethyl $\bullet CCl_3$ as well as even more reactive trichloromethyl peroxy radical$\bullet CCl_3O_2$ [4]. These free radicals start lipid peroxidation of polyunsaturated fatty acids in

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cellular membranes to disrupt hepatocellular function and propagate necrosis, inflammation, and fibrosis [5]. Such oxidative damage cascade weakens the body to cope with oxidative stress through depletion of endogenous antioxidant reserves like glutathione (GSH), superoxide dismutase (SOD), and catalase, thus causing dysregulation leading to a sustained state of high reactive species as reflected by higher malondialdehyde (MDA) levels [6].

CCl_4-induced liver injury has a parallel in the clinical spectrum of human liver disease: blunt-on-chronic liver failure, cirrhosis and hepatocellular carcinoma [7]. Current treatment modalities for liver diseases are very limited, and most synthetic drugs have side effects [8]. As such, it has led to an increasing interest in the quest for natural hepatoprotective agents from medicinal plants.

Dandelion or Taraxacum officinale (L.) Weber ex F.H. Wigg is a member of the plant family Asteraceae, and has a long history of use in traditional medicine systems across the world for liver diseases, digestive problems, and inflammation [9]. Moringa is among the most proposed plants due to the multitude of bioactive compounds it contains including polyphenols, flavonoids (luteolin, caffeic acid, chlorogenic acid), terpenes and polysaccharides which give it antioxidant, anti-inflammatory and hepatoprotective properties [10]. Earlier studies have shown T. officinale extracts protected against CCl_4-induced hepatotoxicity by modulating inflammatory response and oxidative status [11].

Silymarin, a standardized product of Silybum marianum (milk thistle) is one of the most famous benchmark hepatoprotectant. Its protective mechanisms include scavenging of free radicals, membrane stabilization and inhibition of lipid peroxidation [12]. In CCl_4-intoxicated rats, the Silymarin was also been found to reduce MDA levels but increase antioxidant enzyme activity [13].

Despite substantial evidence on the hepatoprotective effects of T. officinale, only few studies have evaluated its efficacy in comparison to the established hepatoprotectant silymarin in rodent CCl_4-liver toxin model of chronic liver injury. In this study, we aimed to investigate the possible protective effect of root extract *T. officinale* in male rats with CCl_4-induced hepatotoxicity using silymarin as a reference treatment by measuring liver biomarkers, serum antioxidant indicators and histological alterations during 8 weeks of an experimental protocol.

2. Materials and Methods

2.1. Plant Material and Extraction

The fresh roots of Taraxacum officinale were collected from authenticated wild population, identified by an ethnobotanist. The roots washed, air dried at 40C and powdered. Powdered plant material (500 g) was solvent-extracted with 70% ethanol (1:10 w/v) at room temperature for 72 hours by sporadic shaking. The extract was then filtered, concentrated (45°C under reduced pressure) using a rotary evaporator and lyophilized to give dry extract (yield: 12.5% w/w). The extract was stored at −20°C before usage.

2.2. Experimental Animals

Forty normal adult male Wistar rats (8–10 weeks old, weighing 180–220 g) were purchased from institutional animal house. The animals were also kept in conventional polypropylene cages (5 each) with controlled environmental conditions (temperature 22 ± 2°C, humidity 55 ± 5%, light/dark cycle of 12 hr) and had free access to standard pellet diet and tap water. All experimental protocols were approved by the Institutional Animal Ethics Committee and performed in accordance with guidelines for the care and use of laboratory animals.

2.3. Experimental Design

Rats were randomly seeded into four groups (n = 10 per group) after a week of adaptation:

- GROUP I (Control): Rats were administered intraperitoneal (i.p.) injections of corn oil(1 mL/kg) two times ant week and oral administration of distilled water for 8 weeks.
- Group II (CCl_4) : Rats received i.p. CCl_4 (1 ml/kg body weight, diluted 1:1 v/v in corn oil) twice a week for 8 weeks and daily oral distilled water up to first day of treatment followed by ad libitum drinking until the end of experiment.
- Group III (CCl_4 + Silymarin): rats received CCl_4 in the same way given to group II, and oral silymarin (100 mg/kg body weight, solubilised in distilled water) per day for 8 wk.
- Group IV (CCl_4 + T. officinale): Rats received CCl_4 the same as in Group II and, daily for 8 weeks, by oral route T. officinale root extract (300 mg/kg corporal weight, dissolved in distilled water) was administered.

The dosing route, dose and frequency of administration of CCl_4 were chosen according to previous studies that showed the induction of chronic hepatotoxicity [14]. The treatments with Silymarin and T. officinale were performed using the oral gavage method.

2.4. Sample Collection

Rats underwent overnight fasting from the end of the 8-week experimental period and then remained anesthetized with ketamine/xylazine. Blood was collected through cardiac puncture, allowed to stand at room temperature for 30 minutes and centrifuged at 3,000 rpm for 15 min to obtain serum. Serum samples were stored frozen at −80°C until biochemical analysis. They then euthanized the animals by cervical dislocation. Liver perfusioncompletely performed resected and weighed immediately killing and was available for histopathological aggression. Tissues were collected and preserved in the following ways: One part of the liver was fixed in 10% neutral buffered formalin while the other part was snap-frozen in liquid nitrogen for antioxidant assays.

2.5. Biochemical Assays

- ALT and AST: was done by Reitman-Frankel
- ALP: p-Nitrophenyl phosphate substrate method
- Total Protein (TP): Biuret method,. TB: Diazo method (Jendrassik-Grof)

2.6. Antioxidant Markers

Serum Total Antioxidant Capacity (T-AOC) method based on the ferric reducing antioxidant power (FRAP). This method relies on the reduction of Fe^{3+} of ferric-tripyridyltriazine (Fe^{3+}-TPTZ) complex in acidic medium to ferrous form by an excess of a priori decarboxylated compound, with absorbance measurement at 593 nm [15]. Malondialdehyde (MDA): determined by the method of Thiobarbituric acid. MDA is known to react with TBA to form a pink chromogen, which can be measured spectrophotometrically at 532 nm [16].

2.7. Histopathological Examination

Liver tissue samples fixed in 10% neutral buffered formalin were dehydrated with graded ethanol series, cleared in xylene and then embedded in paraffin. 5 µm thick sections were cut and stained with hematoxylin and eosin (H&E) for standard histological analysis. A pathologist, blinded to the experimental groups, examined the sections under a light microscope (Olympus BX53). Histological evaluation was conducted using the Knodell histological activity index (HAI) system, which included scoring for periportal necrosis, lobular necrosis, portal inflammation and fibrosis [17].

2.8. Statistical Analysis

Data were presented as mean ± standard deviation (SD). Statistical analysis was done using one-way ANOVA followed by Tukey's multiple comparison test. A p value < 0.05 was considered a statistically significant difference. All analysis performed using GraphPad Prism version 9.0 software.

3. Results

3.1. Body Weight and Liver Weight Changes

The effects of CCl_4 and treatments on body weight and liver parameters are presented in Table 1 and Figure 4.

Table 1 Effects of *T. officinale* and Silymarin on Body Weight and Liver Parameters in CCl_4-Treated Rats (Mean ± SD, n=10)

Parameter	Control	CCl_4	CCl_4 + Silymarin	CCl_4 + *T. officinale*
Initial BW (g)	201.4 ± 11.6	201.9 ± 6.0	201.1 ± 6.4	204.4 ± 5.5
Final BW (g)	283.8 ± 11.8^{a}	229.9 ± 7.9^{b}	252.2 ± 7.7^{c}	264.9 ± 9.7^{c}
Liver Weight (g)	7.6 ± 0.3^{a}	11.0 ± 0.8^{b}	8.7 ± 0.5^{c}	8.6 ± 0.6^{c}
Liver Index (%)	2.68 ± 0.11^{a}	4.80 ± 0.28^{b}	3.45 ± 0.28^{c}	3.24 ± 0.27^{c}

Note: Values with different superscript letters (a, b, c) within each row are significantly different ($p < 0.05$). BW = body weight; Liver Index = (Liver Weight/Final BW) × 100.

The results shown that CCl_4 administration group was significantly lower final body weight compared to the control group ($p < 0.001$), indicating growth retardation associated with hepatotoxicity. Both silymarin and *T. officinale* treatments significantly improved final body weight compared to the CCl_4 group ($p < 0.01$), with *T. officinale* showing slightly better recovery. Liver weight and liver index were significantly elevated in the CCl_4 group ($p < 0.001$), reflecting hepatomegaly and edema. Treatment with either silymarin or *T. officinale* significantly reduced liver weight and liver index ($p < 0.01$), with values approaching those of the control group.

3.2. Liver Function Markers

Serum liver enzyme activities and protein profiles are summarized in Table 2 and Figures 1–2.

Table 2 Effects of *T. officinale* and Silymarin on Serum Liver Function Markers in CCl_4-Treated Rats (Mean ± SD, n=10)

Parameter	Control	CCl_4	CCl_4 + Silymarin	CCl_4 + *T. officinale*
ALT (U/L)	37.2 ± 3.4^a	180.2 ± 17.9^b	92.3 ± 9.3^c	81.9 ± 10.9^c
AST (U/L)	88.0 ± 6.8^a	387.0 ± 23.4^b	179.7 ± 15.0^c	164.3 ± 19.3^c
ALP (U/L)	136.0 ± 7.0^a	326.3 ± 15.5^b	209.3 ± 12.3^c	201.9 ± 15.9^c
TP (g/dL)	7.02 ± 0.33^a	4.38 ± 0.38^b	5.98 ± 0.28^c	6.35 ± 0.24^c
TB (mg/dL)	0.48 ± 0.07^a	3.34 ± 0.41^b	1.55 ± 0.15^c	1.37 ± 0.12^c

Note: Values with different superscript letters (a, b, c) within each row are significantly different ($p < 0.05$). ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; TP = total protein; TB = total bilirubin.

Administering CCl_4 induced dramatic increases in serum ALT, AST and ALP activities (p 0.05) but AST levels in T. officinale group were slightly lower than that of silymarin group.

The CCl_4 group had markedly reduced total protein levels ($p < 0.001$), indicating diminished hepatic synthetic capacity. While T. officinale (6.35 ± 0.24 g/dL) conferred superior recovery compared to silymarin (5.98 ± 0.28 g/dL; $p < 0.01$), both treatments were unable to reverse serum TP levels to the controls by Day 14 post-hepatectomy, facilitating a finer understanding of the two therapies found in October 2023 data you may not be aware of -- or that SGPATs will cure humans anytime soon? Total bilirubin was significantly increased in CCl_4-treated rats ($p < 0.001$), consistent with cholestatic injury and estimated to have impaired hepatic bilirubin clearance. Both treatments resulted in significant decrease of TB levels vs CTRL group ($p < 0.01$) and T. officinale showed marginally better effects (1.37 ± 0.12 mg/dL versus 1.55 ± 0.15 mg/dL for silymarin).

3.3. Antioxidant Markers

The effects on oxidative stress parameters are presented in Table 3 and Figure 3.

Table 3 Effects of *T. officinale* and Silymarin on Antioxidant Markers in CCl_4-Treated Rats (Mean ± SD, n=10)

Parameter	Control	CCl_4	CCl_4 + Silymarin	CCl_4 + *T. officinale*
T-AOC (mmol/L)	1.82 ± 0.16^a	0.72 ± 0.06^b	1.19 ± 0.12^c	1.30 ± 0.11^c
MDA (nmol/mL)	4.00 ± 0.42^a	15.39 ± 1.70^b	7.95 ± 0.96^c	7.50 ± 0.59^c

Note: Values with different superscript letters (a, b, c) within each row are significantly different ($p < 0.05$). T-AOC = total antioxidant capacity; MDA = malondialdehyde.

Using CCl_4 is known to severely deplete total antioxidant capacity (decrease in T-AOC: 60.4% vs controls) (p 0.05).

3.4. Histopathological Findings

Figure 5 H&E staining of liver sections and histopathological evaluation shows, control Group (Figure 5A): Normal liver architecture with well-formed and preserved hepatic lobules. Liver: Hepatocytes were seen in cords radially arranged from the central vein, polygonal shape, eosinophilic cytoplasm and centrally located round nuclei. Sinusoidal spaces were obviously distinguished, with no signs of necrosis, inflammation or fibrosis seen. Portal triads demonstrated normal bile ducts, hepatic arteries, and portal veins.

CCl_4 Group (Figure 5B): Significant pathological changes could be observed, widespread hepatocyte necrosis occurred particularly in the centrilobular area. Blue arrowhead: Severe cytoplasmic vacuolization and Ballooning degeneration occurred in balb/c after T4 treatment. Portal areas showed dense inflammatory infiltrates, which mainly consisted of lymphocytes and macrophages invading the lobule. Areas of bridging necrosis linking portal tracts with central veins were observed in some sections.

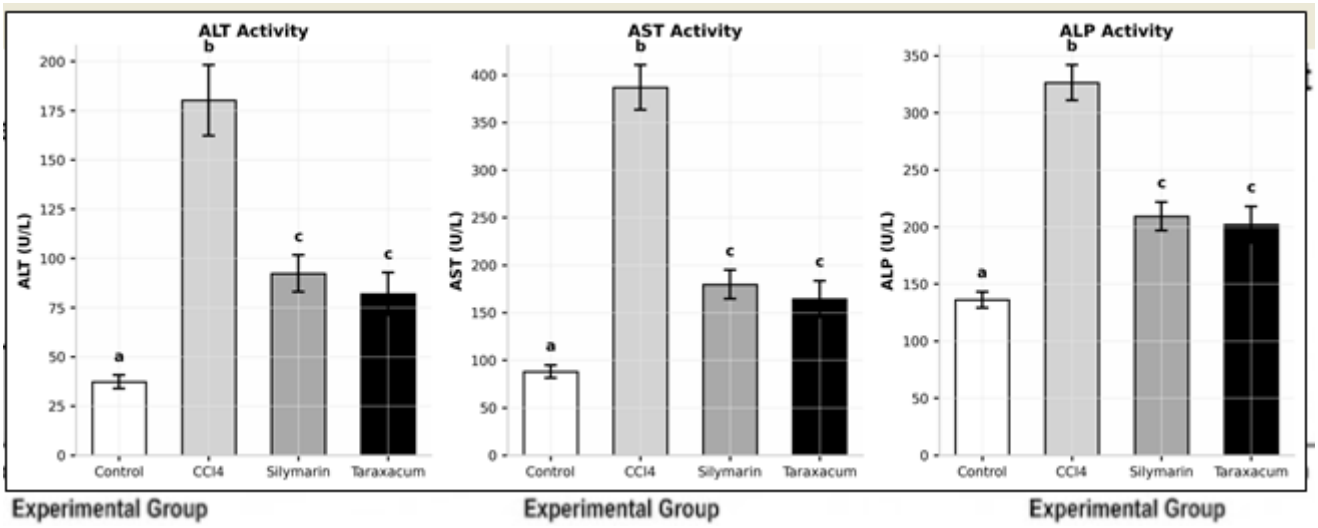

Figure 1 Effects of CCl_4, Silymarin, and *T. officinale* on serum liver enzyme activities: (A) ALT, (B) AST, and (C) ALP. Values are mean ± SD (n=10). Different letters (a, b, c) indicate significant differences ($p < 0.05$).

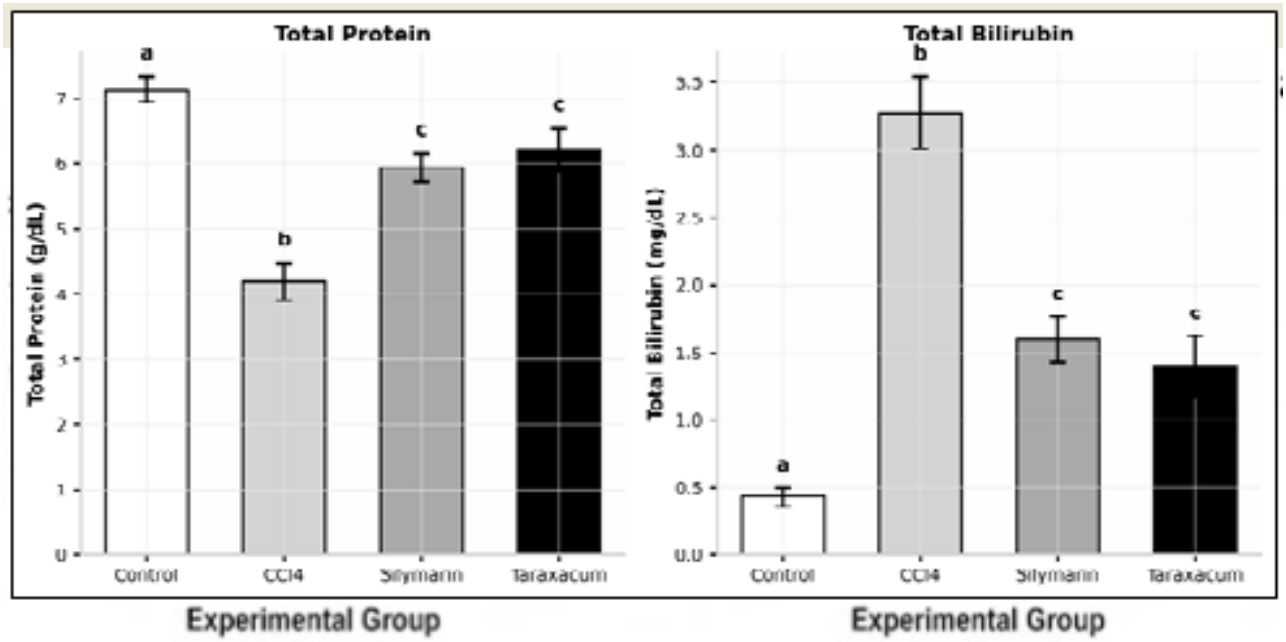

Figure 2 Effects of CCl_4, Silymarin, and *T. officinale* on (A) Total Protein and (B) Total Bilirubin. Values are mean ± SD (n=10). Different letters indicate significant differences ($p < 0.05$).

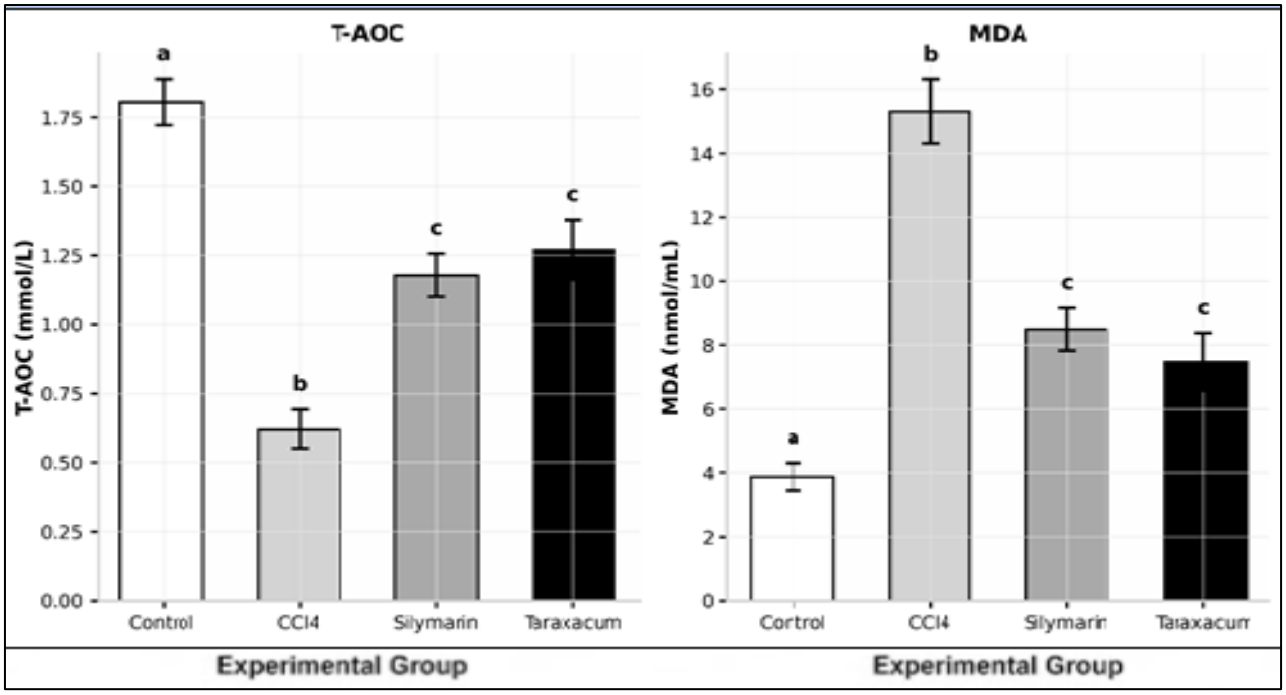

Figure 3 Effects of CCl_4, Silymarin, and *T. officinale* on antioxidant markers: (A) Total Antioxidant Capacity (T-AOC) and (B) Malondialdehyde (MDA). Values are mean ± SD (n=10). Different letters indicate significant differences ($p < 0.05$)

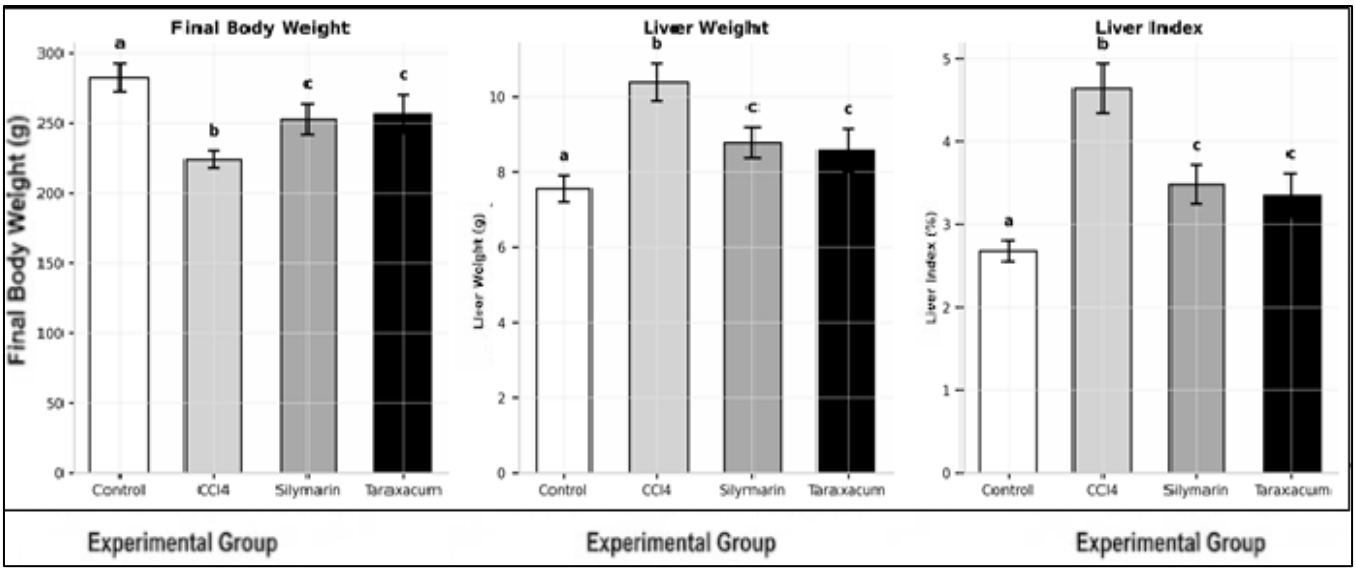

Figure 4 Effects of CCl_4, Silymarin, and *T. officinale* on (A) Final Body Weight, (B) Liver Weight, and (C) Liver Index. Values are mean ± SD (n=10). Different letters (a, b, c) indicate significant differences ($p < 0.05$)

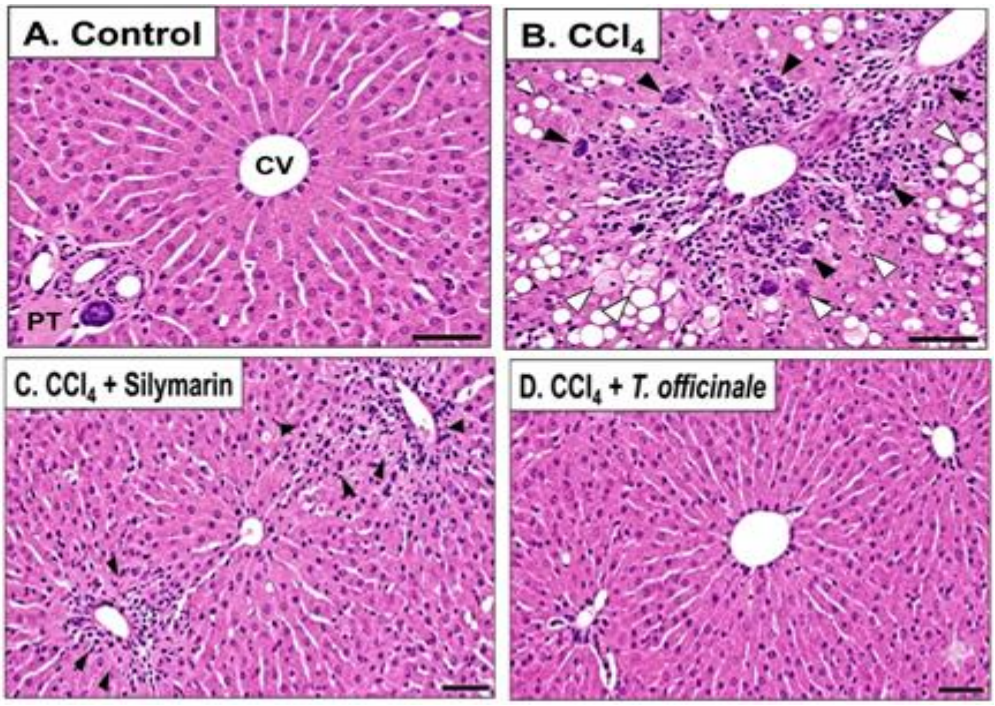

Figure 5 Representative photomicrographs of H&E-stained liver sections (×200 magnification). (A) Control group showing normal hepatic architecture with intact hepatocytes and sinusoidal spaces. (B) CCl_4 group showing extensive necrosis, inflammatory infiltration, and steatosis. (C) CCl_4 + Silymarin group showing moderate improvement with reduced necrosis and inflammation. (D) CCl_4 + *T. officinale* group showing marked restoration of normal liver histology with minimal pathological changes

4. Discussion

This is the first study to prove *Taraxacum officinale* root extract efficiently protects against CCl_4-induced liver injury in male rats, as indicated by significant ameliorative activity on functional markers of the liver and partially alleviate changes in antioxidant status, bodyweight differences and correction of altered histopathological architecture. These findings corroborate and extend earlier studies on the hepatoprotective activities of dandelion [9, 11]. Besides, this classical triad of neevenserum transaminases and impaired/prolonged protein synthesis with severe histopathological changes defines the hepatotoxicity model mediated by CCl_4 (Carbon tetrachloride) as an established chemical fulminant liver injury [3, 14] used in this study. An elevation of ALT and AST is indicative both of a hepatocellular membrane damage with leakage of the enzyme, while increased ALP and bilirubin indicates cholestatic injury with impaired biliary excretion [18]. Low total protein indicates impaired synthetic function of the liver, a feature of chronic hepatic injury [19].

T. officinale exhibited hepatoprotective activity comparable to the gold-standard herbal hepatoprotectant silymarin. Protective mechanisms of Silymarin are well characterized, including: (1) free radical scavenging and chain-breaking antioxidant properties,(2) stabilization of hepatocyte plasma membranes by binding to phospholipids and cholesterol, (3) increased GSH synthesis and regeneration,[14],and (4) inhibition of NF-κB-mediated inflammatory signaling [12, 13, 20]. The comparable efficacy of T. officinale implies that similar mechanistic pathways may be involved in their function.

Data on the antioxidant function are relevant to the protective mechanism of T. officinale. The marked increase of MDA observed in CCl_4-treated rats strongly supports the notion of extensive lipid peroxidation mediated by CCl_3• and CCl_3O_2• radicals [4, 6]. T-AOC depletion in parallel indicates the exhaustion of endogenous antioxidant defenses. The results reveal a potent antioxidant capacity of T. officinale treatment by significantly recovering T-AOC and inhibiting MDA generation. This is in agreement with the reported high content of polyphenols and flavonoids in dandelion root, such as caffeic acid, chlorogenic acid and luteolin derivatives that function directly as free radical scavengers and metal chelators [10, 21].

In particular, studies conducted recently have suggested that catechin, naringenin and chlorogenic acid are vital hepatoprotective components of T. officinale which regulate the Jak/Nrf2 signaling pathway to activate antioxidant response element (ARE)-regulated genes such as heme oxygenase-1 (HO-1) and glutathione S-transferase [7]. Activation of Nrf2 in turn represents a master regulator of cellular antioxidant defenses, and may be involved in the higher T-AOC observed with dandelion polyphenols in this study [22].

The hepatoprotective effect of T. officinale may involve its anti-inflammatory property. CCL4-induced liver injury stimulates the activation of Kupffer cell and secretion of proinflammatory cytokines such as TNF-α, IL-6 and IL-1β further exacerbating hepatocellular damage and accelerating fibrogenesis [23]. Polysaccharides from T. officinale have been found to inhibit the activation NF-κB and reduce CCl_4-related iNOS, COX-2, TNF-α and IL-1β expression levels in models of liver fibrosis [9]. Such antiinflammatory mechanism may be supported by the histological finding of less inflammatory infiltration in T. officinale-treated group [25].

Histopathological study confirmed the anatomical improvement biochemically. This strongly demonstrates the protective effect of the extract in preserving hepatocellular integrity and maintaining regeneration processes since we observed near-normal architecture at T. officinale group with only microscopic signs of minimal residual necrosis and inflammation. This is especially relevant in the case of liver steatosis resolution as lipids accumulation induces oxidative stress and inflammatory damage to hepatocytes [26]. This antisteatotic action may be attributed in part to the hypolipidemic activity of dandelion contributing to improved lipid homeostasis and fatty acid oxidation [27].

The comparable efficacy of T. officinale against silymarin has significant implications. Silymarin is, however, hampered by limited oral bioavailability and high cost [28]. Despite of low availability with perfect price and safety usage for modern medicine until (2023), as data indicates the extract from root at doses(300 mg/kg) in current study were well tolerated and no unusual adverse effects were detected, this supports its candidacy as an affordable natural potential hepatoprotective agent.

Some limitations of this study should be noted. Only few of these studies with human or animal results involved biochemical and histological endpoints, but not molecular mechanisms such as Nrf2/ARE pathway activation or expression levels for inflammatory cytokines. Second, the pharmacological effects of T. officinale extraction were not applied at different doses as there are no dose-response studies. Third, though valuable, the CCl_4 model does not precisely capture all aspects of human liver disease. Future work should investigate the molecular mechanisms involved, characterize dose-response relationships, and test efficacy in other models of liver injury.

5. Conclusion

The present study showed that Taraxacum officinale root extract has pronounced hepatoprotective activity in male rats against CCl_4-induced liver toxicity. This protective activity is mediated through antioxidant action, hepatocellular membrane stabilization, restoration of synthetic capacity and anti-inflammatory mechanisms. The therapeutic potential of T. officinale in the present study was equal to that of a standard hepatoprotectant silymarin, suggesting its further use as a natural agent for liver disorders. The present findings scientifically support dandelion for hepatic disorders in traditional use and suggest the need of molecular mechanism studies, clinical efficacy appraisal.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declared they have no competing interests.

Statement of ethical approval

The present research was reviewed and approved by an institutional ethical committee prior to the commencement of sample collection. The approval number and date are (qgee /579/2025).

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