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Protective and Therapeutic Effects of Alcoholic Extract of Panax Ginseng on Hepatotoxicity Induced in Rats Model

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ABSTRACT

Panax ginseng is a widely recognized medicinal plant known for its hepatoprotective, antioxidant, and anti-inflammatory activities. These properties are largely attributed to its active constituents, the ginsenosides. Diclofenac, a commonly used nonsteroidal anti-inflammatory drug is associated with clinically significant hepatotoxicity characterized by oxidative stress, mitochondrial dysfunction, and hepatocellular injury. This study aimed to investigate the protective and therapeutic efficacy of the alcoholic extract of Panax ginseng against diclofenac-induced hepatotoxicity in adult male rats. Forty-nine rats were allocated into seven experimental groups and administered diclofenac, P. ginseng extract, or combined treatments for 30 days according to the study design. Serum biomarkers of liver function (ALT, AST, ALP) and oxidative stress (MDA, SOD) were measured, and liver tissues were subjected to histopathological evaluation. Diclofenac administration resulted in marked elevations in liver enzyme activities and significant oxidative stress, accompanied by histological alterations including vacuolar degeneration, hepatocellular necrosis, and inflammatory infiltration. In contrast, both co-administration and post-treatment with Panax ginseng extract produced substantial improvements in biochemical and histological parameters, restoring enzyme levels, reducing lipid peroxidation, enhancing antioxidant activity, and improving liver architecture. The Panax ginseng extract alone produced no adverse hepatic effects. These findings demonstrate that the alcoholic extract of Panax ginseng possesses both preventive and therapeutic hepatoprotective properties against diclofenac-induced liver injury, likely mediated through its antioxidant and anti-inflammatory mechanisms. The results support its potential use as a natural agent for mitigating drug-induced hepatotoxicity.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed therapeutic agents due to their well-established analgesic, antipyretic, and anti-inflammatory effects, which are primarily mediated through inhibition of cyclooxygenase (COX) enzymes and suppression of prostaglandin synthesis [1, 2]. Despite their clinical benefits, prolonged or excessive use of certain NSAIDs particularly

diclofenac has been strongly associated with hepatotoxic effects. These hepatic injuries range from mild hepatocellular degeneration to severe necrosis and inflammation. Multiple studies indicate that diclofenac-induced hepatotoxicity is mediated by oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways, collectively contributing to hepatocellular damage and compromised liver function [3–6]. Given the broad clinical use of diclofenac and the severity of its potential adverse effects, identifying natural agents with hepatoprotective potential remains an important research priority. Panax ginseng is a medicinal plant extensively used in traditional medicine and recognized for its wide spectrum of pharmacological activities. Its major bioactive constituents, the ginsenosides, exhibit potent antioxidant, anti-inflammatory, and anti-apoptotic effects through modulation of intracellular signaling pathways and suppression of inflammatory mediators such as NF-κB and TNF-α [7, 8]. A growing body of evidence demonstrates the hepatoprotective effects of ginseng against various chemically induced liver injuries, including toxicity from heavy metals such as cadmium and lead, as well as drug-induced hepatotoxicity caused by acetaminophen and carbon tetrachloride [9–12]. However, despite these documented benefits, the specific role of Panax ginseng particularly its alcoholic extract in mitigating diclofenac-induced hepatotoxicity has not been thoroughly investigated. This gap highlights the need for systematic studies evaluating both the protective and curative potential of ginseng in this context. Therefore, the present study aims to investigate the protective and therapeutic efficacy of the alcoholic extract of Panax ginseng against diclofenac-induced hepatotoxicity in adult male rats. By integrating biochemical assessments of liver function and oxidative stress markers with detailed histopathological evaluations, this study seeks to provide comprehensive insights into the mechanisms through which ginseng may alleviate diclofenac-mediated liver injury. The findings are expected to contribute to a better understanding of the hepatoprotective capabilities of ginseng and support its potential use as a natural agent for preventing or reducing drug-induced liver toxicity.

MATERIALS AND METHODS

Chemicals and Plant Material

Diclofenac sodium pure powder was obtained from the General Company for the Manufacture of Pharmaceuticals and Medical Appliances, Samarra, Iraq. Panax ginseng roots purchased from local markets in Duhok, Iraq. Roots were washed, shade-dried for 5–7 days, powdered, and extracted using 99% ethanol (200 mL per 20 g powder) for 24–72 hours with intermittent shaking. The extract was concentrated using a rotary evaporator at 40–50 °C and dried at room temperature [13].

Animals

Forty-nine adult male albino rats (175–250 g) were obtained from the Animal House, College of Veterinary Medicine, University of Duhok. Rats were housed under standard laboratory conditions (temperature 18–24 °C; 10/14 h light/dark cycle) with free access to food and water. Animals were acclimatized for 14 days before the experiment.

Ethical approval was obtained from the Animal Ethics Committee, College of Veterinary Medicine, University of Duhok (CVM2024\0111UoD).

Experimental Design

Rats were randomly divided into seven groups (n = 7 for each) and treated orally as follows:

G1 (Negative control): Distilled water (5 mL/kg) for 30 days.

G2 (Positive control): Carbon tetrachloride (CCl_4)1000 mg/kg daily for 30 days [14, 15].

G3: Diclofenac 10 mg/kg daily for 10 days [16].

G4: Diclofenac 10 mg/kg daily for 30 days.

G5: Ginseng extracts 100 mg/kg daily for 30 days [17].

G6: Diclofenac 10 mg/kg for 10 days, followed by ginseng 100 mg/kg for 20 days.

G7: Diclofenac 10 mg/kg and ginseng 100 mg/kg concurrently for 30 days.

Biochemical Analysis

Blood samples were obtained from the retro-orbital plexus under light anesthesia. Serum levels of ALT, AST, and ALP were determined as biochemical markers of liver function, while MDA and SOD were assessed as indicators of oxidative stress, using commercial diagnostic kits (BIOLABO, France). Data are expressed as Mean ± SD. Statistical analysis was conducted using one-way ANOVA followed by Tukey's post hoc test, with $p \leq 0.05$ was considered statistically significant.

Histological Examination

Liver samples were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 6 µm, and stained with Hematoxylin and Eosin. Sections were examined under a light microscope for hepatocyte morphology, vacuolation, necrosis, and inflammatory infiltration [18].

RESULTS

Biochemical Findings

Diclofenac significantly increased ALT, AST, and ALP levels compared to controls, with higher elevations in the 30-day group. Ginseng alone did not alter enzyme levels. Co-administration (G6 and G7) significantly altered enzymes compared with the + ve control, and diclofenac-alone administrations. (Table 1).

Antioxidant Effects of Panax ginseng

As shown in Table 2, diclofenac administration significantly increased MDA levels and decreased SOD activity compared to the control group (G1). Short-term diclofenac treatment (G3, 10 days) caused moderate significant oxidative stress, while prolonged treatment (G4, 30 days) resulted in more pronounced alterations compared with the – ve control group. Panax ginseng alone (G5) did not significantly affect MDA or SOD levels compared with the (–ve control group) with significant alteration competed with group 2 and 3. Treatment with ginseng following diclofenac exposure (G6) significantly reduced MDA levels and restored SOD activity. Concurrent administration of diclofenac and ginseng (G7) also improved oxidative markers. There was no statistically significant difference between G6 and G7.

Table1. Serum liver enzyme levels (ALT, AST and ALP) in different experimental groups.

Group	ALT (U\L)	AST (U\L)	ALP (U\L)
G1	**35 ± 3,1 A**	**40 ± 4.4 A**	**85 ± 7.4 A**
G2	**120 ± 10 B**	**135 ± 12.2 B**	**210 ± 15.2 B**
G3	**90 ± 8.2 C**	**105 ± 9.2 C**	**150 ± 10.2 C**
G4	**140 ± 12 D**	**160 ± 15.4 D**	**230 ± 18.6 D**

G5	**40 ± 4.1 A**	**45 ± 5.8 A**	**90 ± 8.2 A**
G6	**45 ± 7.3 A**	**51 ± 8.9 A**	**95 ± 12.3 A**
G7	**51 ± 9.6 A**	**59 ± 10.2 A**	**92 ± 12.4 A**

Values are expressed as Mean ± SD (n = 7). Different superscripts within the same column indicate significant differences between groups at ($p \leq 0.05$). Groups sharing the same letter are not significantly different from each other. LSD=0.05

Table 2. Effect of treatment groups on hepatic oxidative stress markers (MDA and SOD) in experimental rat groups

Group	MDA nmol/mg	SOD U/mg
G1	**1.8 ± 0.2 a**	**12.5 ± 1.1 a**
G2	**4.9 ± 0.3 b**	**6.2 ± 0.8 b**
G3	**3.5 ± 0.3 c**	**8.5 ± 0.9 c**
G4	**4.3 ± 0.3 d**	**7.1 ± 0.8 d**
G5	**1.9 ± 0.2 a**	**13.0 ± 1.0 a**
G6	**2.5 ± 0.3 a**	**11.8 ± 1.0 a**
G7	**2.7 ± 0.3 a**	**11.5 ± 0.9 a**

Values are expressed as Mean ± SD (n = 7). Different superscripts within the same column indicate significant differences between groups at ($p \leq 0.05$). Groups sharing the same letter are not significantly different from each other.

Histological Findings

Histopathological examination of liver sections revealed distinct alterations across experimental groups. The control group (G1) exhibited normal hepatic architecture, with polyhedral hepatocytes, basophilic nuclei, and well-defined central veins and sinusoids (Fig. 1). In contrast, rats treated with carbon tetrachloride (G2) showed marked hepatocellular vacuolar degeneration, necrosis, and prominent inflammatory cell infiltration (Fig. 2). Diclofenac administration induced notable hepatocyte vacuolation, necrosis, and inflammatory infiltration, with more severe lesions observed in the 30-day treatment group (G3 and G4; Figures 3and 4). Treatment with ginseng alone (G5) preserved liver architecture, showing only minimal cytoplasmic vacuolation (Fig. 5). Therapeutic administration of ginseng following diclofenac exposure (G6) improved hepatocyte morphology and reduced inflammatory cell presence (Figure 6). Concurrent treatment with diclofenac and ginseng (G7) partially mitigated hepatotoxic effects, although some hepatocellular necrosis remained (Fig. 7).

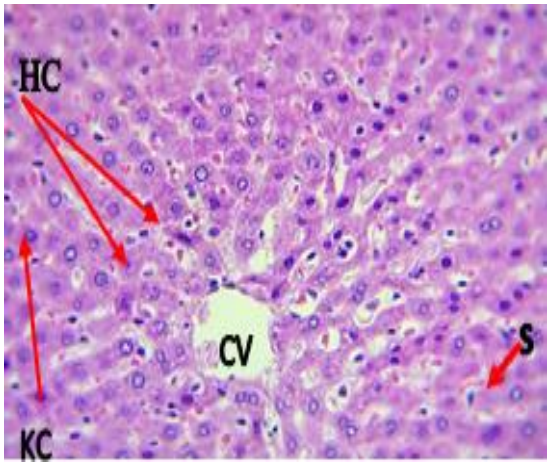

Fig. 1. Liver section of control group(G1) showed normal central vein (CV), hepatocytes (HC), sinusoids (S), with kupffer cells (KC) H&E, 40X

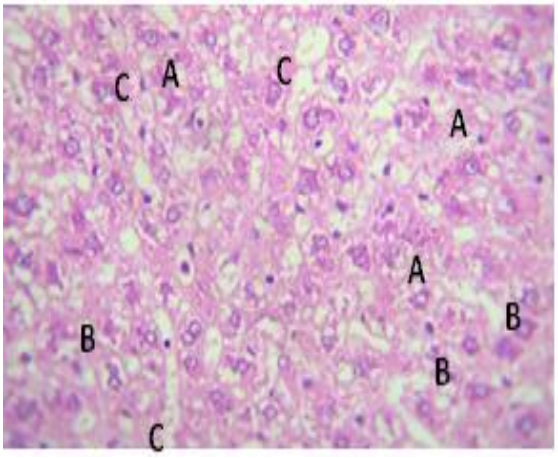

Fig. 2. Liver section of CCl_4 group (G2) exhibiting cytoplasmic vacuolar degeneration of liver cells (A), Necrotic liver cells with devoid nuclei (B), Narrow blood sinusoids with Kupffer cells (C).H&E, 40 X

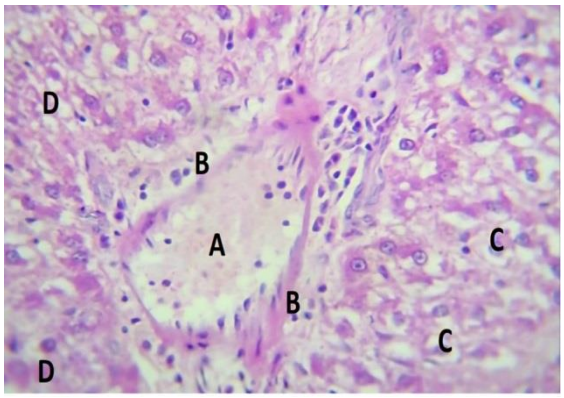

Fig. 3. Liver section of diclofenac 10 days group (G3) showing portal vein with frothy blood (A), WBC's infiltration (B), hypertrophic liver cells (C), with vacuolation , pyknotic nucleic (D), H&E 40X.

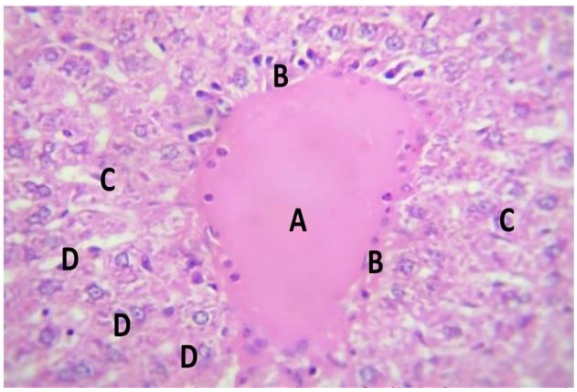

Fig. 4. Liver section of diclofenac 30 days group (G4) with showing central vein with hyperemia (A), WBC's infiltration (B), degenerated liver cells (C). Kupffer cells in the blood sinusoid (D), H&E 40X.

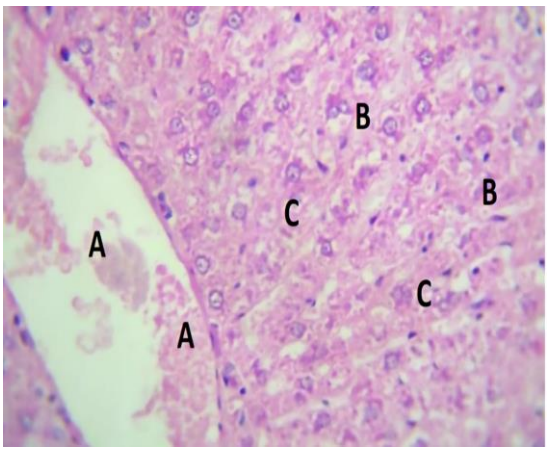

Fig. 5. Liver section of ginseng 30 days group (G5) showing Central vein of liver with mild frothy blood (A), normal columns of liver cells (B), narrow blood sinusoid (C), H&E 40X.

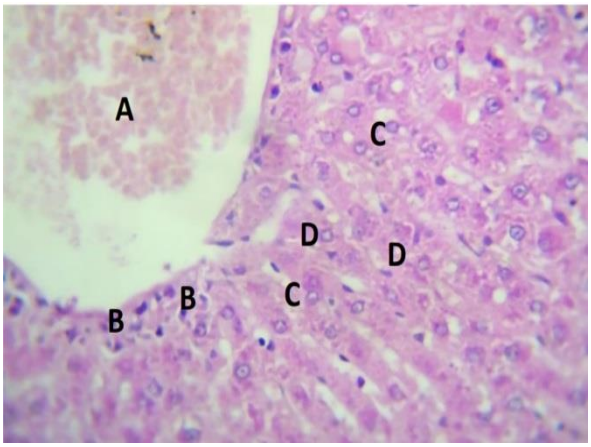

Fig. 6. Liver section of diclofenac (10 days) with ginseng (20 days) group showing Central vein with mass of blood clot (A), WBC's diffusion around the wall of central vein (B) Radial pattern of liver cells (C), blood sinusoid with Kuptter cells (D), H&E 40 X.

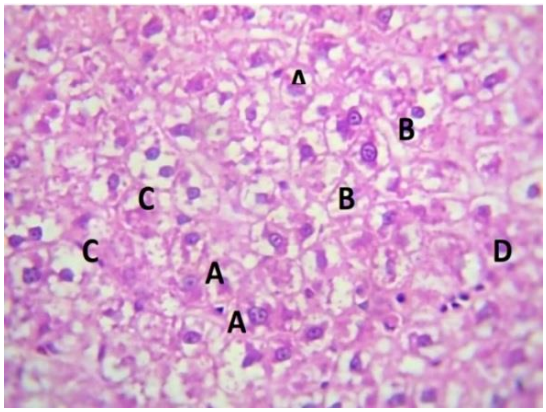

Fig. 7. Liver section of diclofenac with ginseng group showing liver parenchyma, hypertrophic liver cells (A) with cytoplasmic vacuolar degeneration (B) pyknotic nuclei (C) Kupffer cells (D), H&E 40 X.

DISCUSSION

The present study confirms that diclofenac administration induces significant hepatotoxicity, evidenced by both histopathological alterations and elevated serum liver enzymes. CCl_4-treated rats exhibited classical hepatocellular injury including vacuolation, necrosis, and inflammatory infiltration, consistent with previous studies [19]. Diclofenac caused hepatocyte vacuolation, necrosis, and inflammatory infiltration, in line with prior reports [20-22]. The hepatotoxicity of diclofenac is mainly attributed to oxidative stress and mitochondrial dysfunction [23].

Administration of Panax ginseng extract significantly restored liver function, normalized ALT, AST, and ALP levels, and ameliorated histological damage. These results confirm its dual protective and therapeutic roles, supporting previous findings demonstrating ginseng's hepatoprotective effects against chemical-induced liver injury [24-26]. The mechanisms likely involve reduction of reactive oxygen species, stabilization of hepatocyte membranes, and modulation of inflammatory mediators such as NF-κB and TNF-α [7, 8].

In addition, Panax ginseng exhibited a significant antioxidant effect in diclofenac-exposed rats. Both post-treatment (G6) and concurrent administration (G7) improved oxidative stress markers compared to controls (G1), indicating effective mitigation of oxidative damage. No significant difference was observed between G6 and G7, suggesting that the antioxidant activity of ginseng is effective regardless of the timing of administration. These findings align with previous studies reporting that ginseng reduces oxidative stress and enhances endogenous antioxidant defenses in chemically induced toxicity models [27, 28]. However, other studies have noted inconsistent effects on antioxidant enzymes under normal conditions, likely due to differences in ginseng type, extraction methods, dosage, or experimental models [29, 30]. Therapeutic administration after diclofenac exposure (G6) was more effective than concurrent treatment (G7) in improving liver function and reducing oxidative stress, suggesting that Panax ginseng not only prevents liver injury but also supports recovery after hepatotoxic damage. This highlights its potential as a post-injury therapeutic agent rather than solely a prophylactic one.

CONCLUSIONS

Panax ginseng alcoholic extract effectively reduced diclofenac-induced hepatotoxicity by improving liver enzymes, restoring antioxidant balance, and ameliorating tissue damage. Both preventive and therapeutic administration demonstrated significant hepatoprotective activity. These findings support ginseng as a promising natural agent against drug-induced liver

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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