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Hepatoprotective Effect of ginseng alcoholic Extract Against Ibuprofen - Induced Hepatotoxicity in Male Rats

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ABSTRACT

Background and Objective: *Panax ginseng* is a cornerstone of traditional Oriental medicine, renowned for its pharmacologically active ginsenosides, which possess potent antioxidant and anti-inflammatory properties. The present study evaluated the Hepatoprotective efficacy of an alcoholic root extract of *P. ginseng* against ibuprofen-induced liver injury in an experimental rat model. **Methods:** Histopathological analyses were performed to evaluate the Hepatoprotective efficacy of an alcoholic root extract of *P. ginseng* against ibuprofen-induced liver injury in an experimental rat model. **Results:** Histopathological analyses demonstrated that ibuprofen administration caused severe hepatic damage characterized by vacuolar degeneration, coagulative necrosis, and sinusoidal congestion, while co-treatment with ginseng extract produced amelioration of these pathological changes. Remarkably, the optimal dose of ginseng extract resulted in near-complete restoration of hepatic architecture, reduction of necrotic foci, and resolution of inflammatory infiltrates. **Conclusions:** These findings provide compelling evidence that *P. ginseng* exerts significant protective and regenerative effects against NSAID-induced hepatotoxicity, most likely mediated through its antioxidant and anti-inflammatory mechanisms, and suggest its potential as a promising adjuvant therapeutic agent in drug-induced liver disorders.

Introduction

The main way that nonsteroidal anti-inflammatory medications work is by blocking the cyclo-oxygenase enzymes (COX-1 and COX-2) to stop the production of certain prostaglandins (PG). COX catalyzes the release of prostanoids such as thromboxane (TXA) and PG from arachidonic acid [1]. These prostanoids play a crucial role in inflammation and pain signaling within the body. By inhibiting these enzymes, NSAIDs effectively reduce inflammation, alleviate pain, and lower fever, making them widely used in the treatment of various conditions. These substances are implicated in the inflammatory process and exacerbate discomfort. The effects on the gastrointestinal tract have been the main focus of most earlier research [2, 3]. Ibuprofen is one of the many antipyretic medications that are manufactured in tablet form. Ibuprofen, a non-steroidal anti-inflammatory medicine (NSAID) [4]. Ibuprofen works primarily by blocking the production of prostaglandin precursors. The enzyme phospholipase A2 causes membrane phospholipids to release arachidonic acid in response to physiological or pathological stimulation. One of three enzymatic pathways—cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP450)—receives arachidonic acid; prostaglandins, prostacyclins, and thromboxanes are produced from arachidonic acid via the cyclooxygenase pathway [5]. Finally, arachidonic acid is transformed into HETEs and epoxyeicosatrienoic acids (EET) via the cytochrome P450 pathway [5, 6]. In order to improve the risk-benefit ratio of administering NSAIDs, one study developed a risk score. This score accurately classified the one-year risk of severe toxicity among NSAID users [7]. Moreover, nothing is known about the mechanism underlying NSAID-induced liver injury. The potential for elevated rates of drug-induced liver damage and Reye syndrome should be taken into consideration due to the growing usage of ibuprofen in children [8]. It is advised to take no more than 3200 mg of ibuprofen each day. Ibuprofen overdose can be extremely harmful, especially in youngsters who consume 400 mg/kg or more. Seizures, apnea, high blood pressure, and possible liver and kidney damage are all consequences of overdosing. High-dose ibuprofen taken over an extended period of time is also linked to an elevated risk of myocardial infarction [9]. The pharmacological effects of ginseng can be understood in the light of their polyvalent actions as demonstrated by ginseng saponins with their positive anti-mutagenic, anticancer, and protective action against mammalian tumor cell lines and anti-diabetes [10]. Ginseng has immune-stimulatory, anti-inflammatory, and antihepatoxicity effects [11]. It is well known for its strong antioxidant effect, for its antioxidant property due to its ability to scavenge free radicals and to neutralize ion-induced peroxidation [12]. So, this study was aimed at studying the effect of ginseng extract against ibuprofen-induced histopathological changes of liver tissue in male rats.

Materials and Methods

Ibuprofen

Was obtained from General Company for the Manufacture of Pharmaceuticals and Medical Appliances Samarra Iraq.

Panax ginseng roots extraction

The ginseng roots were purchased from the Agricultural Supplies Market, Baghdad, and were packaged by IKO Company, Iraq-Baghdad. The method used in extraction is maceration. The dried ginseng roots were ground into a fine powder then sieved to obtain a uniform particle size. The ginseng powder was extracted 3 times with 70% ethanol, with a solvent to solid material ratio of 3:1 (15 mL ethanol: 5 g ginseng). The extracts were filtered using a Whatman no. 2 filter paper to remove any debris. The filtrates were concentrated using a rotary evaporator at 40°C then dried in an oven to obtain the powdered extract and stored at - 80°C in a deep-freezer. [13].

Animals

This investigation was conducted from August 24 to September 26, 2024, in the animal house of Veterinary Medicine College at Tikrit University. Seventy mature male Albino rats that appeared to be in good health were acquired. The creatures are 8–10 weeks old and weigh between 200 and 250 g, with an average of 225 g. Standard cages made of plastic measuring 46*28*13 cm were used to house the animals. They were maintained in an atmosphere that was suitable for them (20–25 C°).

General Experimental Design

The animals used in the current study were divided into 7 groups, and each group contained 10 rats, as follows:

- G1: control group received normal saline (orally) for 30 days.
- G2: rats received (5ml/kg) dimethyl sulfoxide (DMSO) [14] (orally) daily for 30 days.
- G3: rats received Ibuprofen (120mg/kg) (orally) [15] daily for 10 days.

- G4: rats received Ibuprofen (120mg/kg) daily for 30 days.
- G5: rats received ginseng extract (20mg/kg) [16] (orally) daily for 30 days.
- G6: rats received Ibuprofen (120mg/kg) for 10 days and followed by ginseng extract (20mg/kg) daily for 20 days.
- G7: rats received Ibuprofen (120mg/kg) and ginseng extract (20mg/kg) daily for 30 days.

Histological study

Rat liver pieces were taken, fixed with 10% formalin, paraffin-processed, cut with a rotary microtome to a thickness of six micrometers, and stained with Hematoxylin and Eosin (H&E) histological stains [17]. Through the use of an Optica microscope (Italy), sections were inspected.

Results & Discussion

Control group

Microscopic examination revealed a normal liver structure. The liver lobule was observed with a central vein, surrounded by blood sinusoids at the periphery. These sinusoids contained Kupffer cells and red blood cells. The liver tissue consisted of columns of polyhedral cells, each with spherical basophilic nuclei. (figure:1).

Dimethyl sulfoxide group

Histological examination revealed cytoplasmic vacuolar degeneration in the liver parenchyma. Necrotic liver cells lacking nuclei were observed, and the blood sinusoids contained Kupffer cells. The portal area of the liver showed a congested portal vein and branches of the bile duct surrounded by infiltration of white blood cells. Liver cells were present around the portal area. (Figure 2).

Ibuprofen (10 days) group

The cross section of this group showed that the portal area had portal vein, engorged with frothy blood and WBC's The wall of vein was Surrounded by a great number of inflammatory WBC, the liver cells were hypertrophied and Containing cytoplasmic vacuolation, Certain nuclei of liver cells were pykontic (figure 3).

Ibuprofen (30 days) group

Under microscope, the liver lobule had Central vein which demonstrated with hyperemic hemolyzed blood, The Inflammatory WBC's were infiltrated around the wall of central vein. Most of liver Cells Were degenerated with vacuolation in its cytoplasm, the blood sinusoid was containing few Kupffer cells (figure 4).

Ginseng (30 days) group

The microscope examination showed that the liver tissue had great Central vein containing masses of frothy clot, the central vein was surrounded with columns liver cells which containing Spherical nuclei, there was of cytoplasmic vacuolation of certain liver cells, blood sinusoid had Kupffer cells. (figure 5).

Ibuprofen (10 days) and ginseng (20 days) group

The liver cells appeared as Columns extended toward the central vein, those cells were polyhedral with Spherical nuclei, the blood sinusoid were present around the columns of liver cells and passing toward the central vein with presence of Kupffer cells. (figure 6).

Ibuprofen and ginseng group

The histological sections of this group showed the liver parenchyma had hypertrophic liver cells with extensive vacuolation of its cytoplasm pyknotic nuclei, certain liver cells were lost its nuclei and demonstrated necrotic cells, few Kupffer cells were Seen in the blood sinusoid narrow. (figure 7).

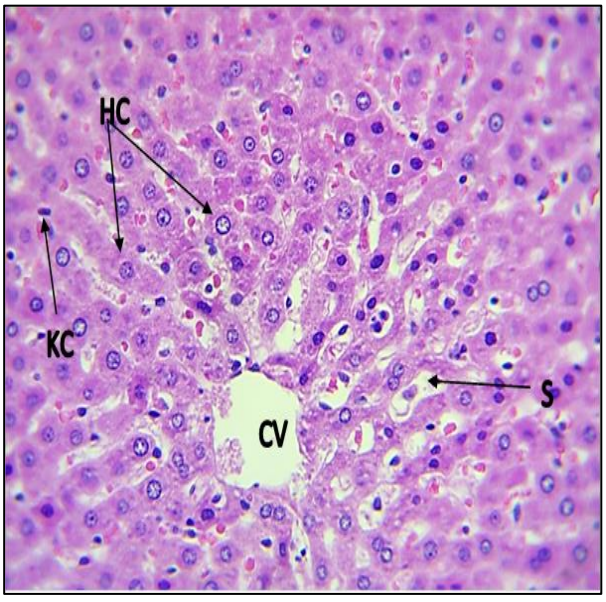

Fig (1): Liver cross section of control group showed normal central vein (CV), hepatocytes (HC), sinusoids (S), with Kupffer cells (KC) H&E, X40.

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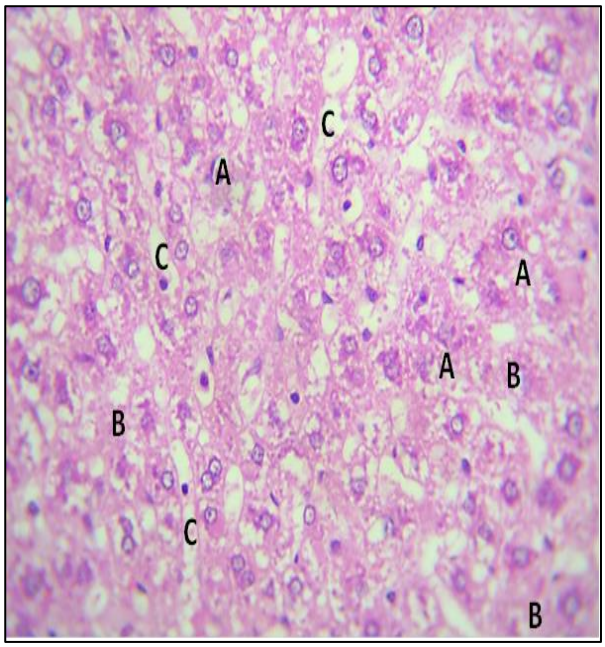

Fig (2): Liver cross section of DMSO group showed cytoplasmic vacuolar degeneration of liver cells (A), Necrotic liver cells with devoid nuclei (B), Narrow blood sinusoids with Kupffer cells (C).H&E, X40.

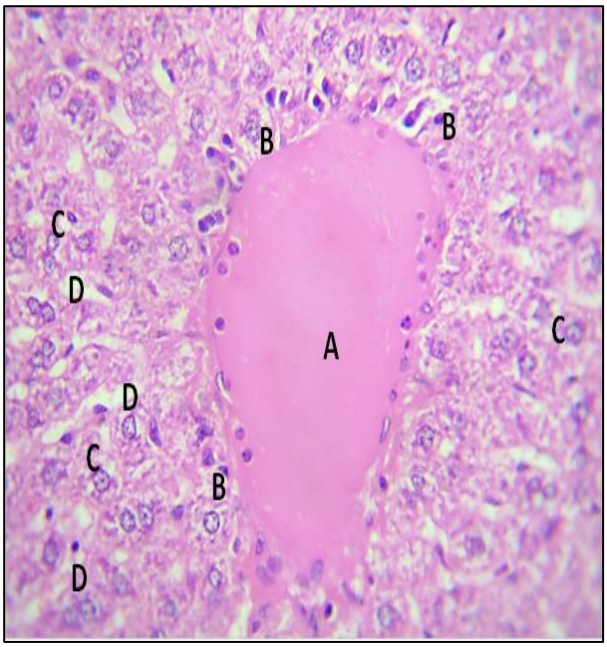

Fig (4): Liver cross section of Ibuprofen (30 days) group showed central vein with hyperaemic hemolyzed blood (A), WBC's infiltration (B), degenerated liver cells (C). Kupffer cells in the blood sinusoid (D), H&E X40.

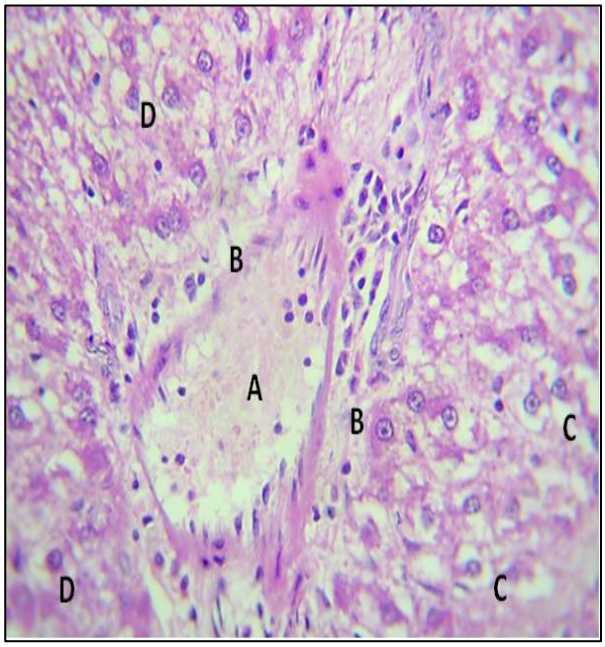

Fig (3): Liver cross section of Ibuprofen (10 days) group showed portal area, portal vein with frothy blood (A), WBC's infiltration (B), hypertrophic liver cells (C), with vacuolation, pyknotic nucleic (D), H&E X40.

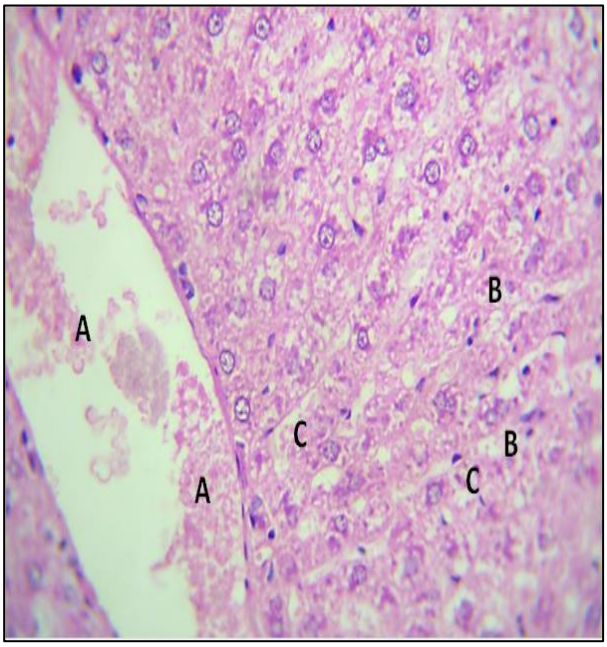

Fig (5): Liver cross section of Ginseng (30 days) group showed Central vein of liver with frothy blood (A), columns of liver cells (B). Which had vacuolation in its cytoplasm, narrow blood sinusoid (B), H&E X40.

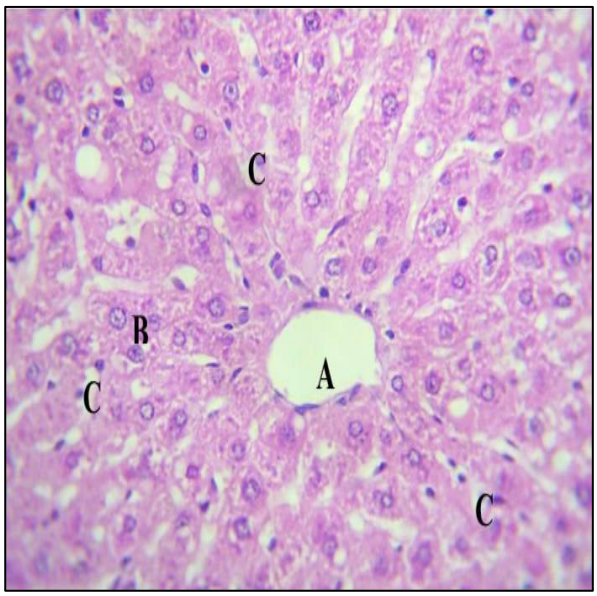

Fig (6): Liver cross section of ibuprofen (10 days) with ginseng (20 days) group showed Central vein (A), radial pattern of liver cells of polyhedral Shape (B), blood sinusoid with Kupffer cells (C), H&E X40.

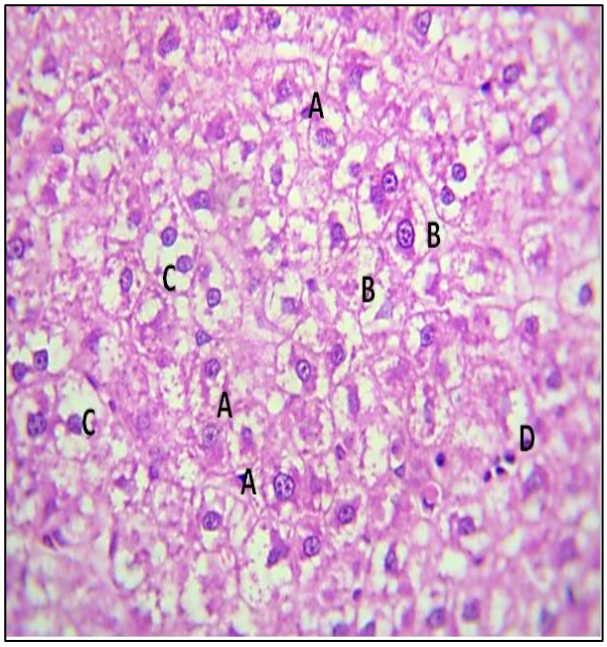

Fig (7): Liver cross section of ibuprofen with ginseng group showed liver parenchyma, hypertrophic liver cells (A) with cytoplasmic vacuolar degeneration (B) pyknotic nuclei (C) Kupffer cells (D), H&E X40.

The findings of the present study also indicated that administration of DMSO resulted in certain histological alterations in the liver, which were the loss of cytoplasmic vacuolar degeneration of the liver cells, blood congestion, and infiltration of WBC. These results were consistent with what [18] reported in the sense that the Dimethyl Sulfoxide (DMSO) treatment triggered several histological changes, including lymphocytic infiltration and the destruction of some liver cells. In addition to degeneration of the wall of the blood vessels in the liver, came rupture of cytoplasm of some cells and lipid droplets. That it was caused by DMSO leading to oxidative stress and production of free radicals in liver that affect the histology.

The histological results from this study showed that ibuprofen led to several changes in the liver tissue of the experimental animals. [19] also found that ibuprofen at 500 mg/kg body weight caused notable changes in normal liver cells, such as vacuolization, hepatomegaly, and centrilobular necrosis. Other research has shown that ibuprofen can alter the structure and permeability of liver cells. Increased levels of liver marker enzymes are often linked to ibuprofen-induced liver cell damage, which results from cell leakage and loss of membrane integrity [20].

In this study, ibuprofen administration caused histological abnormalities in the liver tissue. These disturbances were visible as vascular blockage in the central venule and mild swelling in the portal tract, which appeared in both treated groups.

According to [21], liver problems caused by taking ibuprofen may happen because of the production of free radicals.

The current study found that ginseng helps repair liver damage caused by ibuprofen, showing clear improvements in liver cells and tissue. [22] confirmed ginseng's antioxidant benefits by showing it reduces ROS, which are the main cause of oxidative stress and tissue damage. Aminotransferases are sensitive markers for liver cell damage and can help identify acute liver disorders like hepatitis. The pattern of aminotransferase increase can also be useful for diagnosis.

When ginseng extract was utilized, it was evident that it improved the texture of the liver, which was destroyed by ibuprofen. This improvement was greater when ibuprofen was administered. The Hepatoprotective effect of ginseng extract against lead-induced liver damage in rats is consistent with the observation made in [23, 24] that the inflammatory effect of root ginseng has been responsible for the hepatic cells, including the production of inflammatory cytokines (TNF-Y, IL-IB), which inhibit tumor necrosis factor alpha (TNF-&). NF-KB activation was stimulated. By preventing the activation of proliferation with collagen fiber expression and inhibiting metallo-proteinase-1 in hepatic stallic

cells, which is the primary source of tissue fibrosis, ginsenosides' ameliorating effects considerably reduce liver fibrosis [25,26]. Similar research has also been published on the root ginseng extract's ability to modulate liver cytochrome P450 activation and protein phosphorylation, as well as its regulation of inducible hepatic enzymes [27].

Conclusions

It's concluded that the alcoholic extract of ginseng roots shows a protective effect for liver tissue injuries and improves the functions and enzymes of liver.

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Declaration of interests

The authors declare that there are no conflicts of interest.

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Publication consent

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Data and material availability

All data analyzed and generated in this study are included in this published research.

Author contribution

All authors participated in the study design and conception. Data analysis, data collection, performance of the results, and assent to the final version.

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التأثير الوقائي للكبد لمستخلص الجينسنغ الكحولي ضد السمية الكبدية الناجمة عن الإيبوبروفين في ذكور الجرذان

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الملخص

الخلفية والهدف: يُعد الجينسنغ (*Panax Ginseng*) أحد الركائز الأساسية في الطب الشرقي التقليدي، ويشتهر باحتوائه على مركبات الجينسينوسيدات الفعالة دوائيًا، والتي تمتلك خصائص قوية مضادة للأكسدة ومضادة للالتهابات. هدفت الدراسة الحالية إلى تقييم الفعالية الوقائية للكبد للمستخلص الكحولي لجذور *P. ginseng* ضد إصابة الكبد المستحثة بالإيبوبروفين في نموذج تجريبي باستخدام الجرذان.

المواد وطرائق العمل: أُجريت تحليلات نسيجية مرضية لتقييم الفعالية الوقائية للكبد للمستخلص الكحولي لجذور *P. ginseng* ضد إصابة الكبد المستحثة بالإيبوبروفين في نموذج تجريبي باستخدام الجرذان.

النتائج: أظهرت التحليلات النسيجية المرضية أن إعطاء الإيبوبروفين أدى إلى حدوث تلف كبدي شديد، تميز بالتنكس الفجوي، والنخر التخثري، واحتقان الجيوب الكبدية، في حين أدى العلاج المتزامن بمستخلص الجينسنغ إلى التخفيف من هذه التغيرات المرضية. ومن اللافت للنظر أن الجرعة المثلى من مستخلص الجينسنغ أسفرت عن استعادة شبه كاملة للبنية الطبيعية للكبد، مع انخفاض البؤر النخرية وزوال الارتشاحات الالتهابية.

الاستنتاجات: توفر هذه النتائج دليلًا قويًا على أن *P. ginseng* يمتلك تأثيرات وقائية وتجديدية ملحوظة ضد السمية الكبدية المستحثة بمضادات الالتهاب غير الستيرويدية، ويرجح أن يكون ذلك من خلال آلياته المضادة للأكسدة والمضادة للالتهابات، مما يشير إلى إمكاناته كعامل علاجي مساعد واعد في حالات اضطرابات الكبد الناجمة عن الأدوية.

الكلمات المفتاحية: الجينسنغ، الإيبوبروفين، الكبد، خلايا كوفر، الجرذان.