**Ind. J. Pharm. Edu. Res., 2024; 58(1):198-203.**
https://www.ijper.org

Original Article

# Histopathological and Biochemical Investigation of the Effect of Shepherd's Purse (*Capsella bursa-pastoris* L.) on Ethanol-Induced Liver Damage

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## ABSTRACT

**Background:** The aim of the present study was to investigate the hepatoprotective effect of Shepherd's Purse (SP) herbal tea on ethanol (EtOH)-induced liver toxicity. **Materials and Methods:** Male Wistar rats ($n$ = 32) were divided into 4 experimental groups: control, EtOH (30% EtOH), EtOH+SP (30% EtOH+1 mL/kg SP), and SP (1 mL/kg SP orally). EtOH and SP were administered by orogastric gavage once daily. At the end of the 60-day experimental period, tissue and blood samples were obtained from the rats following necropsy. **Results:** Histopathologically, degenerative-necrotic changes in the liver of the EtOH group rats were partially reduced in the SP treatment group. Biochemical examinations revealed that SP treatment decreased aspartic transaminase, alanine transaminase, and alkaline phosphatase levels in the SP-treated rats compared to the EtOH group rats. While SP treatment had a positive effect on the triglyceride and HDL levels, it had a negative effect on the LDL and cholesterol levels. **Conclusion:** Consequently, it was determined that SP tea provides partial protection against EtOH-induced liver toxicity.

**Keywords:** Shepherd's purse, Ethanol, Histopathology, Liver, Rat.

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**Received:** 25-08-2022;
**Revised:** 18-05-2023;
**Accepted:** 14-08-2023.

## INTRODUCTION

Chronic alcohol consumption damages various organs such as the brain, liver, kidneys, pancreas, heart, lungs, skeleton muscles, and bones, and ethanol (EtOH) is regarded as a directly systemic toxin.[1-4] EtOH is mainly metabolized in the liver and partly in the brain and kidneys.[1,4] The liver is the primary target organ of alcohol-induced injury, responsible for EtOH metabolism, and is susceptible to the toxic effects of alcohol.[5] Alcoholic liver disease has a spectrum involving steatosis (fatty liver), steatohepatitis, and, in severe cases, fibrosis and/or cirrhosis.[6,7] Currently, there is no suitable treatment regime available to combat alcohol-induced liver damage or to regenerate injured tissue.[8]

Oxidative stress plays a significant role in the development of liver damage attributed to alcohol consumption.[5] The latest studies on alcohol consumption have revealed that the increase in lipid peroxidation due to alcohol metabolism and Reactive Oxygen Species (ROS) formation is the main cause of the development of acute liver damage.[8] EtOH is converted to cytotoxic acetaldehyde through alcohol dehydrogenase, and then oxidizes to acetate through aldehyde oxidase or xanthine oxidase, which leads to an excessive amount of ROS.[2,3] The role of ROS in the development of alcoholic liver damage has been acknowledged since the 1960s.[9] ROS are suppressed or excreted by cellular antioxidant defense systems consisting of enzymatic or nonenzymatic mechanisms. An excessive increase in ROS causes antioxidant deficiency. This deficiency can typically be aggravated by the inadequate intake of both supplemental and dietary antioxidants.[10]

Flavonoids, which are abundant in food sources such as fruits and vegetables, are widely used in health supplements and by being converted into medicinal agents. In previous studies, antioxidant active ingredients were reported to be effective in preventing damage resulting from EtOH exposure.[11,12]

Shepherd's Purse (SP) (*Capsella bursa-pastoris* L.) is a small, herbaceous, annual, cosmopolitan species belonging to the family Cruciferae (Brassicaceae).[13] Flavonoids, polypeptides, choline, acetylcholine, histamine, tyramine, fatty acids, sterols, organic acids, amino acids, sulforaphane, several trace elements, vitamins, and many more substances have been shown to be present in the plant.[14] Natural lipids, glucose, and phospholipids are found in the plant's leaves and roots. The presence of β-carotene and β-sitosterol in the aboveground sections was also reported.[15] SP

**DOI:** 10.5530/ijper.58.1.21

is one of the most widely used herbs in traditional medicine for a variety of reasons, in addition to its use as a food item.[16] The plant is reported to have been used in hemodialysis and as a diuretic and antipyretic in China and Japan for centuries. Tea prepared from the entire plant has been reported to have antiscorbutic, astringent, diuretic, hemostatic, hypotensive, oxytocic, stimulant, and wound-healing properties. Tea prepared from the dried plant, on the other hand, has been found to be effective in the treatment of bleeding of the stomach, lungs, uterus, and, in particular, the kidneys.[14] The antimicrobial effect of SP was reported,[17,18] as well as its anti-ulcer activity,[19,20] anti-inflammatory and diuretic effects,[20] a hemostatic effect on uterine and superficial bleeding,[21] and a hepatoprotective effect.[22] The plant extracts were determined to possess an inhibitory effect in relation to fumaric acid on Ehrlich solid tumor in rats.[23]

The aim of the present study was to investigate the protective efficiency of SP against liver toxicity induced by EtOH.

## MATERIALS AND METHODS

### Animal Material

In the present study, the Experimental Animal Research Centre at Van Yuzuncu Yil University (Van, Turkey) provided 32 male rats (Wistar albino). The rats were approximately 2 months old and weighed an average of 250 g. Randomly, 4 groups were organized including 8 rats in each group ($n$=8). The animals were housed at 20±2°C with a daily light/dark cycle. All of the animals were kept in stainless steel cages and fed a wheat-soybean-meal-based diet. Water and feed were offered *ad libitum*. Humane care according to the criteria expressed in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institute of Health were followed during the experiment period. The ethics regulations followed were in accordance with national and institutional guidelines for the protection of animal welfare during the experiments. The local ethics committee of Van Yüzüncü Yıl University Animal Experiments approved this study under decision number (06.07.2017/06).

### Plant Material

SP, obtained from herbalists in a form that is suitable for brewing, was used as the plant material. Five grams of the plant was added to 200 mL of water, brewed, and filtered. The herbal tea was prepared fresh daily. The tea prepared was administered by orogastric gavage at a dose of 1 mL/kg body weight once a day.[14,24]

### Experimental Groups

The rats used in the study were randomly divided into 4 groups containing 8 rats each:

- Group 1 (Control): Fed standard pellet feed.
- Group 2 (EtOH): 4 mL/kg 30% ethyl alcohol was administered once a day by orogastric gavage, and they were fed standard pellet feed.
- Group 3 (SP): 1 mL/kg herbal tea was administered once a day by orogastric gavage, and they were fed standard pellet feed.
- Group 4 (EtOH+SP): 4 mL/kg 30% ethyl alcohol and 1 mL/kg herbal tea were administered once a day by orogastric gavage, and they were fed standard pellet feed.

The study lasted 60 days and the rats in each group were weighed on days 0, 30, and 60 of the experiment to determine their weight changes. Their feed intake was also recorded. The rats in each group were monitored daily for potential complications.

### Biochemical Analyses

Following the completion of the 60-day experiment, the rats were anesthetized with 50 mg/kg of ketamine hydrochloride+10 mg/kg of xylazine hydrochloride and euthanized by cervical dislocation. Blood samples of each animal were taken intracardially, and their serum and plasma were removed and stored in a deep freezer (–80°C) until the relevant analyses were performed. Alanine Transaminase (ALT), Aspartic Transaminase (AST), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), cholesterol, triglyceride, HDL cholesterol, and Fasting Blood Glucose (FBG) activities were observed in the blood samples taken.

### Histopathological Examination

Following the 60-day experimental period, necropsy was performed for each of the animals, and following the detection of the tissue samples taken from the liver in 10% buffered formalin, they were embedded in paraffin blocks and sections of 4 µm were taken using a microtome. Afterwards, the samples were stained with Hematoxylin-Eosin (HE) for histopathological examination and examined under a light microscope. The liver tissue was examined in terms of inflammation, steatosis, vacuolar degeneration, and fibrosis.

### Statistical Analysis

The biochemical analysis results, as the mean and standard deviation (X±SD), were performed based on standard methods using a ready program (Minitab for Windows). The difference between the group averages and live weights was specified based on one-way ANOVA. The differences between the pathological changes were determined using the chi square test.

## RESULTS

### Body Weight

The effects of SP and EtOH on the body weights of the rats are given in Table 1.

### Histopathological Findings

The livers of the rats from the control (Figure 1a) and SP group (Figure 1b) had a normal histological appearance. Marked histopathological findings were present in the livers of all of the rats from the EtOH-treated group. It was observed that the remark cord structures were dissociated. Steatosis and vacuolar degeneration were detected, particularly in hepatocytes in the centrilobular regions. Common necrotic hepatocytes were detected in the liver parenchyma. Bile duct epithelial hyperplasia and a mild increase in fibrous tissue were observed in the periportal area (Figures 1c). Histopathological findings similar to those in the livers of the rats in the alcohol group were detected in the livers of the rats in the EtOH+SP group. However, these findings were significantly reduced. While hepatocellular degeneration was significantly reduced, the number of necrotic hepatocytes was also observed to decrease significantly in the livers of the rats in the EtOH+SP group (Figure 1d).

### Biochemical Findings

Following the applications carried out for 60 days, the serum AST, ALT, ALP, and LDH enzyme levels, which are biomarkers of liver damage, were observed. Table 2 shows the mean values of the liver damage biomarkers of the control and study groups along with standard errors. In comparison with the control, there was an increase in the serum AST, ALT, and ALP activities in the EtOH group. The increase in ALT and ALP activities was statistically significant ($p < 0.05$). There was no significant difference in the LDH activity between the EtOH and control groups ($p > 0.05$). Compared with the EtOH group, it was determined that the serum AST, ALT, LDH, and ALP activities of the rats in the EtOH+SP group were lower. A statistically significant difference was found only in AST and ALT levels ($P < 0.05$). Compared with the control group, the serum ALT activity in the EtOH+SP group decreased significantly ($p < 0.05$), while there was no significant difference between the AST, LDH, and ALP activities ($p > 0.05$). There was no significant difference between the serum AST, ALT, LDH, and ALP activities of the rats in the SP group when compared with the control group ($p > 0.05$). No significant difference was found in the LDH levels between the groups (Table 2).

Table 3 shows the triglyceride, LDL, HDL, and cholesterol levels of the control and study groups. In comparison with the control group, there was a decrease in the triglyceride, HDL, and cholesterol levels of the rats in the alcohol group, while there was an increase in the LDL levels. However, these changes were not significant ($p > 0.05$). In comparison with the EtOH group, there was a decrease in the triglyceride levels of the rats in the EtOH+SP group ($p > 0.05$), while there was an increase in the LDL, HDL, and cholesterol levels ($p > 0.05$). In comparison with the control group, an increase was observed in the LDL, HDL, and cholesterol levels of the rats in the SP group, while there was a decrease in the triglyceride levels (Table 3).

## DISCUSSION

Nutrients that are rich in terms of the bioactive phytochemicals obtained from fruits and vegetables not only improve the health of an individual, but also contribute positively to the human diet.[25] Flavonoids, a group of bioactive polyphenolic phytochemicals, play a significant role in healthy food supplements due to their abundance in plant-based diets and potential beneficial pharmacological effects.[26,27] Today, due to the fact that EtOH poisoning can cause many metabolic disorders[28] or sudden death[29] in humans, it is clear that an effort should be made to establish effective protection against the harmful effects of this substance.[12] EtOH interacts with cell components, triggering protein oxidation and lipid peroxidation in the cell membrane. Thus, it causes the formation of ROS that form free radicals.[30] EtOH-induced

**Table 1: Effects of the ethanol and SP on the body weights of the rats.**

| Gropus | Beginning | Finally |
|---|---|---|
| Control | 200.75±9.06[a] | 306.25±20.16[b] |
| SP | 196.12±14.06[a] | 310.75±22.60[b] |
| Ethanol | 219.71±20.89[a] | 304.00±36.23[b] |
| Ethanol+SP | 210.63±21.18[a] | 304.14±28.63[b] |

Each value represents the Mean±SD. Different letters in each row represents statistics significance ($p<0.05$).

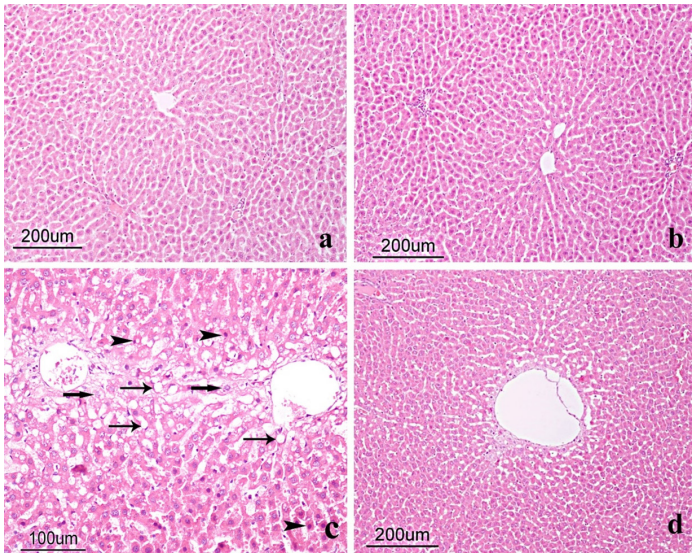


**Figure 1:** Histopathological appearance of cross-sections of the rat liver. Control (a) and SP (b) groups showed normal normal histological aspects of the liver H&E Bar = 200 µ. Ethanol group (c) showed steatosis (thin arrows) vacuolar degeneration (thick arrows) and coagulation necrosis (arrowheads) in hepatocytes H&E. Bar = 100 µ. Ethanol+SP (d) group showed less histopathologic changes than ethanol group H&E. Bar = 200 µ.

**Table 2: Liver serum enzyme activities of rats in control, SP, ethanol, and ethanol+SP groups.**

| | Control | SP | Ethanol | Ethanol+SP |
|---|---|---|---|---|
| AST (U/L) | 115.17±13.28$^{a,b}$ | 115.00±11.08$^{a,b}$ | 140.50±35.79$^{b}$ | 97.67±16.35$^{a}$ |
| ALT (U/L) | 45.50±.2.51$^{b}$ | 44.13±1.72 $^{a,b}$ | 58.00±2.74$^{c}$ | 40.57±4.64$^{a}$ |
| LDH (U/L) | 1797.57±576.56$^{a}$ | 1352.13±217.32$^{a}$ | 1691.20±433.18$^{a}$ | 1202.57±765.50$^{a}$ |
| ALP (U/L) | 193.60±44.99$^{a}$ | 203.13±25.82$^{a,b}$ | 256.29±67.66$^{b}$ | 215.57±37.77$^{a,b}$ |

Each value represents the Mean±SD. Different letters in each row represents statistics significance ($p$<0.05).

**Table 3: Effects of the ethanol and SP on the triglyceride, LDL, HDL, cholesterol and FBG values.**

| | Control | SP | Ethanol | Ethanol+SP |
|---|---|---|---|---|
| Triglyceride (mg/dL) | 72.71±31.44$^{a}$ | 62.00±15.11$^{a}$ | 69.80±32.70$^{a}$ | 62.29±22.22$^{a}$ |
| LDL (mg/dL) | 3.33±2.80$^{a}$ | 4.13±2.63$^{a}$ | 5.03±2.09$^{a}$ | 5.58±3.56$^{a}$ |
| HDL (mg/dL) | 37.68±5.54$^{a,b}$ | 41.96±3.36$^{b}$ | 34.36±3.68$^{a}$ | 38.38±8.06$^{a,b}$ |
| Cholesterol (mg/dL) | 52.57±9.37$^{a}$ | 58.50±4.92$^{a}$ | 49.80±3.96$^{a}$ | 56.43±12.27$^{a}$ |
| FBG (mg/dL) | 113.63±3.73$^{a}$ | 107.25±3.13$^{a}$ | 115.57±3.47$^{a}$ | 110.13±3.09$^{a}$ |

Each value represents the Mean±SD. Different letters in each row represents statistics significance ($p$<0.05).

oxidative stress is believed to play a key role in the pathogenesis of liver injury.[8] In recent years, it has been emphasized that certain natural products have an inhibitory effect on EtOH absorption and, therefore, can be used as an alternative to synthetic drugs for the prevention of diseases caused by alcohol.[31] Based on the current information in the literature, the present study is the first to determine the effects of SP on EtOH poisoning by monitoring the histopathological findings in the livers of rats and certain serum biomarkers.

The main metabolite of the initial oxidation reaction of EtOH is acetaldehyde. Acetaldehyde is more toxic than EtOH and also plays an important role in alcohol-induced liver damage.[32] Acetaldehyde accumulates in hepatocytes as a result of protein degradation and degeneration of the structures of the liver enzyme systems, causing hepatocellular degeneration, necrosis, and steatosis.[33,34] After EtOH administration, hydropic and vacuolar degeneration of hepatocytes, mononuclear cell infiltration, sinusoidal dilatation and congestion were observed in the alcohol group rats.[12,17,35] In the present study, similar findings were found with previous studies. The hepatocytes around the vena centralis were especially more severely affected. Because they are more exposed to the hypoxic environment and are rich in mitochondria, hepatocytes near the vena centralis are more vulnerable to toxic damage. In the case of exposure to alcohol or other toxic substances, this is the primary area of concern.[36]

Many plant extracts and their bioactivities have the potential to be applied as protective agents against alcoholic liver injury. Foods rich in phytochemicals have been shown to protect the liver from EtOH toxicity.[11] The hepatoprotective effect of mulberry juice extracts on EtOH-induced liver injury through antiinflammation and inhibition of lipogenesis has been reported.[37] Saffron aqueous extract has been shown to have protective effects on rat liver through antioxidant, anti-apoptosis and anti-inflammatory effects against EtOH toxicity.[38] In this presented study, the findings observed in the alcohol group were significantly reduced in the rats in the treatment group. This conclusion is assumed to be attributable to the fact that SP is a flavonoid-rich plant. According to Ma *et al*.,[39] four of the nine flavonoids isolated from the SP extract demonstrated anti-hepatotoxic properties.

Serum transaminases are highly sensitive for detecting hepatocyte damage, and serum levels rise in cases when cellular degeneration or destruction occurs in liver.[40] Because they are found in considerable concentrations in the liver, AST, ALT, ALP, and LDH levels in particular are tested to determine the existence of liver disorders.[41] Chronic exposure to high doses of EtOH can result in damage to the hepatocyte membrane. This may result in the release of intracytoplasmic enzymes into the serum. Elevated ALT levels in the serum indicate reversible hepatocyte damage, whereas increased AST levels indicate hepatic necrosis and mitochondrial damage.[42] Hepatocellular necrosis can also produce elevated ALP activity.[43] Previous studies have found elevated activities of these enzymes in rats chronically treated with EtOH, showing the biochemical manifestation of EtOH toxic activity.[44-49] In the present study, increases in the serum AST, ALT, and ALP activities of the rats as a result of EtOH toxicity indicates that these enzymes occur as a result of leakage from the cell cytoplasm (especially hepatic cells) into the bloodstream. The presence of hepatic damage as a result of EtOH toxicity in liver tissue was confirmed by histological examination, as well as AST and ALT data. SP co-administration significantly attenuated the AST and ALT release induced by EtOH. The results showed that SP co-administration could protect the integrity of liver cell membrane significantly.

Shahryari *et al*. showed that the consumption of 6 g/kg EtOH for 30 days increased cholesterol, triglyceride, and HDL levels.[50] In another study, the serum triglyceride level was found to be lower

than the rats in the control group that consumed 5 g/kg alcohol for 30 days.[51] Justice *et al*. showed that the total cholesterol, HDL, and LDL levels were lower in Wistar rats that consumed 30% EtOH for 13 weeks compared to the control group. The reason for the decrease in the lipid profiles in the EtOH group may have been due to the decrease in the expression of genes involved in cholesterol synthesis.[52] In addition, moderate alcohol consumption may reduce serum triglyceride levels due to its beneficial effects on insulin resistance and insulinemia.[53] In the presented study, although the serum triglyceride, HDL, and cholesterol levels were low in the rats in the EtOH group compared to the control group, this decrease was not significant ($p > 0.05$). When the EtOH group was compared with the EtOH+SP group, there was no significant difference in the lipid profiles ($p > 0.05$). The effect of EtOH on lipids depends on the amount of alcohol consumed as well as the duration of consumption. Alcohol exerts its effects on lipid metabolism in different ways. Acute alcohol consumption may decrease lipoprotein lipase activity or lipolysis of circulating chylomicron and LDL. Conversely, chronic consumption of low concentrations of EtOH prevents hyperglycemia by increasing lipoprotein lipase activity.[54]

## CONCLUSION

In conclusion, treatment with SP reduced certain histological abnormalities in the liver and improved specific hepatic serum enzyme activity in the toxicity induced by EtOH in the rats. The exact protective efficacy of SP in EtOH-induced liver damage could not be specified since its effect on the lipid levels and cholesterol values varied.

## ACKNOWLEDGEMENT

Ethical approval was obtained from the Animal Experiments Local Ethics Committee of Van Yuzuncu Yil University (06.07.2017/06).

## FUNDİNG

This study was funded by the Van Yuzuncu Yil University Scientific Research Projects Foundation (Grant number TYL-2018-6759). This study was prepared from Orhan POLAT's Master's thesis.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**SP:** Shepherd's purse; **ALT:** Alanine transaminase; **AST:** Aspartic transaminase; **ALP:** Alkaline phosphatase; **LDH:** Lactate dehydrogenase; **FBG:** Fasting blood glucose.

## SUMMARY

*Capsella bursa-pastoris* (shepherd's purse, SP) is a small, herbaceous, annual, cosmopolitan species belonging to the Cruciferae (Brassicaceae) family,[13] containing flavonoids, polypeptides, choline, acetylcholine, fatty acids, sterols, organic acids, amino acids, various trace elements, and vitamins.[14]

The aim of the present study was to investigate the protective efficiency of SP against liver toxicity induced by EtOH.

In this study, male Wistar rats ($n = 32$) were divided into 4 experimental groups. Biochemical and histopathological alterations in all of the groups were examined.

Treatment with SP reduced certain histological abnormalities in the liver and improved specific hepatic serum enzyme activity in the toxicity induced by EtOH in the rats. Its effect on the lipid levels and cholesterol values varied.

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**Cite this article:** Polat O, Yaman T, Kömüroğlu AU. Histopathological and Biochemical Investigation of the Effect of Shepherd's Purse (*Capsella bursa-pastoris* L.) on Ethanol-Induced Liver Damage. Indian J of Pharmaceutical Education and Research. 2024;58(1):198-203.