Health Sciences Quarterly
eISSN: 2791-6022

Health Sci Q
e-ISSN: 2791-6022, DOI: 10.26900/hsq.3106
2026; 6(2):345-353, Frequency: Quarterly

HOLISTENCE PUBLICATIONS

ORIGINAL ARTICLE

Hepatoprotective effects of Scoparone in an experimental mouse model of liver fibrosis

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Article History:

Received: 2026-01-21

Accepted: 2026-04-08

Online Published: 2026-04-27

Abstract

Scoparone, a key ingredient isolated from *Artemisia capillaris*, has important therapeutic properties. In our study, it was aimed to investigate the therapeutic effects of systemic administration of Scoparone on liver fibrosis after the formation of liver fibrosis with Thioacetamide. In order to create a chronic fibrosis model, Swiss albino mice were injected intraperitoneally with Thioacetamide. Serum levels of AST and ALT were investigated in all groups, and TGF-β1, HGF and TNFAIP6 gene expressions from mRNA isolated

Citation: Kurtoğlu EL, Aslan S, Göçer S, Özdemir Erdoğan M, Yıldız SH, Solak M. Hepatoprotective effects of Scoparone in an experimental mouse model of liver fibrosis. Health Sci Q. 2026;6(2): 345-353. doi: 10.26900/hsq.3106

Keywords:

Scoparone, liver fibrosis, gene expression

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from liver tissues were examined. According to our findings; ALT and AST levels of mouse serum samples in the fibrosis groups were significantly increased compared to the control, DMSO and Scoparone groups. It was observed that Scoparone injection in the fibrosis group decreased ALT and AST levels, but there was no statistically significant difference. While HGF gene expression was found to be significantly higher in liver mRNA samples in which Scoparone treatment was applied to the fibrous group, compared to all other groups, Scoparone injection to the fibrotic subjects caused a decrease in TGF-β1 gene expression (p<0.05). Injection of Scoparone into the liver fibrosis group caused a decrease in TNFAIP6 levels, but this decrease was not statistically significant. In conclusion; although scoparone does not completely regress fibrosis, it has been found to be beneficial and this is reflected in molecular analyzes. However, further studies are needed to determine the effect of different doses, to clarify its molecular mechanisms and targets, and to elucidate its toxicity.

Introduction

Chronic liver failure is a slowly progressive liver injury process and is a common health problem worldwide with significant morbidity and mortality rates. In this process, normal liver tissue is replaced by fibrotic tissue with regeneration nodules [1]. If fibrotic tissue is left untreated, cirrhosis, which is associated with organ shrinkage and nodule formation, may occur, ultimately leading to organ failure and death [2,3]. In general, liver transplantation is the most effective treatment for chronic liver failure, but it is not widely practiced due to a lack of donor organs, costs and specialists. It also has the disadvantage of requiring lifelong immunosuppression. Therefore, *in vivo* and *in vitro* models of drug toxicity and chronic liver failure are critical for identifying new drug targets and testing new therapeutic interventions [4]. Hepatoprotective agents, especially natural products and herbs, are important against chemical liver injury [5]. However, in recent years, extensive research on the application of traditional Chinese medicine in the treatment of liver diseases has become increasingly common. These investigations are generally aimed at protecting hepatocytes and inhibiting hepatic inflammation [6]. In the light of recent data obtained from various *in vitro* and *in vivo* studies, Scoparone, an important component isolated from *Artemisia capillaris*, is reported to have important therapeutic properties [7]. Scoparone has been used in Chinese herbal medicine to treat neonatal jaundice [8]. Various studies have reported that Scoparone has hypolipidemic, antiallergic, anti-tumor, anti-oxidant, anti-inflammatory and hepatoprotective effects [9,10]. In our study, it was aimed to biochemically investigate the effect of systemic administration of Scoparone on liver damage after TAA (Thioacetamide)-induced liver fibrosis, to molecularly determine the expression of genes associated with liver regeneration.

Materials and Methods

Experimental design

For this study, ethical approval was obtained from the local ethics committee of Afyon Kocatepe University-Experimental Animals Application and Research Center on 24.06.2020 with the protocol number 49533702/282. A total of 40 male Swiss albino mice, 8-10 weeks old, 18-20 g, were used in the study. During the experiment, the mice were kept in rooms with a temperature of 21 ^{o}C and an ambient humidity of 55-60%, 12 hours of light and 12 hours of darkness, and all mice were fed ad libitum with standard mouse chow during the experiment. The chemicals used in this study were Scoparone (≥98% purity, Sigma-Aldrich®, USA) and Thioacetamide (TAA) (≥99% purity, Sigma-Aldrich®, USA). Mice

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were divided into 5 groups (n=8 per group) as control group (Group 1), DMSO (Dimethyl sulfoxide) group (Group 2), Scoparone group (Group 3), TAA group (Group 4), TAA+Scoparone group (Group 5). Control Group (Group 1): Nothing was applied to the subjects for 12 weeks. DMSO Group (Group 2): DMSO, in which Scoparone chemical was dissolved, was administered to the subjects at the same rate (0.04%) for 2 weeks [7]. Scoparone Group (Group 3): Scoparone agent was dissolved in 0.04% DMSO and administered i.p. at a dose of 40 mg/kg daily for 2 weeks [11]. TAA Group (Group 4): TAA agent at a dose of 100 mg/kg was dissolved in PBS (Phosphate-buffered saline) and administered i.p. 3 days a week for 12 weeks (11). TAA+Scoparone Group (Group 5): TAA agent at a dose of 100 mg/kg was dissolved in PBS and administered i.p. 3 days a week for 12 weeks [11]. After 12 weeks of TAA administration, Scoparone agent was administered i.p. daily at a dose of 40 mg/kg for 2 weeks. Scoparone dose (40 mg/kg) was selected based on practices reported in previous studies within the effective and safe dose range [7].

Serum liver enzyme levels

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using commercially available ELISA (Enzyme Linked Immunosorbent Assay) kits (Sunred®, Shanghai, China; Cat. No: 201-02-0330) in accordance with the manufacturer's protocols.

Real time-polymerase chain reaction

RNeasy Plus Mini kit (QIAGEN®, Germany) was used for RNA isolation from mouse liver tissues. Quality of RNA (OD260/280) was evaluated using the nanodrop device (NanoDrop/ND-1000 UV/USA). cDNA synthesis followed the instructions in the RT2 HT First Strand Kit (QIAGEN, Germany). β-actin was used as a reference gene. RT2 SYBR Green qPCR Mastermix kit (QIAGEN, Germany) was used for determination of gene expression by Real-time polymerase chain reaction (RT-PCR). PCR mix was prepared for each sample (HGF, TNFAIP6, TGFB1, ACTB) according to the instructions in the kit. RT-PCR conditions were determined as 95 ^{o}C for 10 minutes (1 cycle), 40 cycles of 15 seconds at 95 ^{o}C and 30 seconds at 60 ^{o} C in Biorad device. Relative gene expression levels were calculated using the $2^{-\Delta Ct}$ method (normalized to β-actin) and expressed as relative expression values [12].

Statistical analysis

The data of the research was analyzed using SPSS 22.0 (IBM) software. The suitability of the data for normal distribution was evaluated by Shapiro–Wilk test. Levene test was used to determine whether the variances were homogeneous. Additionally, one-way ANOVA were used. Tukey's test was performed when variances were homogeneous. For nonnormal distributed data, intergroup comparisons were performed using the Kruskal–Wallis test. $p<0.05$ was considered statistically significant. Sample size and power: Group sizes (n=8) were sufficient to detect biologically meaningful differences. Post-hoc power analysis using ALT values indicated statistical power ≈75–80% (α=0.05, two-tailed).

Results

Serum AST ve ALT levels

ALT and AST levels were significantly increased in fibrosis groups compared to control, DMSO and Scoparone groups. Scoparone injection in the fibrosis group decreased ALT and AST levels, but there was no statistically significant difference (Table 1).

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Table 1. Biochemical analysis of the experimental groups.

Groups	Mean AST (U/L)	Mean ALT (U/L)
Control	81,91±11,59	27,51±8,42
DMSO	86,66±12,45	28,11±3,54
Scoparone	87,99±15,48	30,81±3,54
TAA	118,07±16,09*	36,02±6,04**
TAA+Scoparone	95,30±28,07	31,45±3,29

*The values of the groups in the table show the mean±standard deviation of the ELISA analysis results obtained from the samples. *: Represents the statistical difference between TAA group and control, DMSO and Scoparone groups (p<0.05). **: Represents the statistical difference between the TAA group and the control and DMSO groups (p<0.05).*

Gene expression results

HGF gene expression was found to be significantly higher in Scoparone-treated samples of the TAA-induced liver fibrosis group compared to all groups. TAA administration did not change HGF mRNA levels compared to the control group (Figure 1).

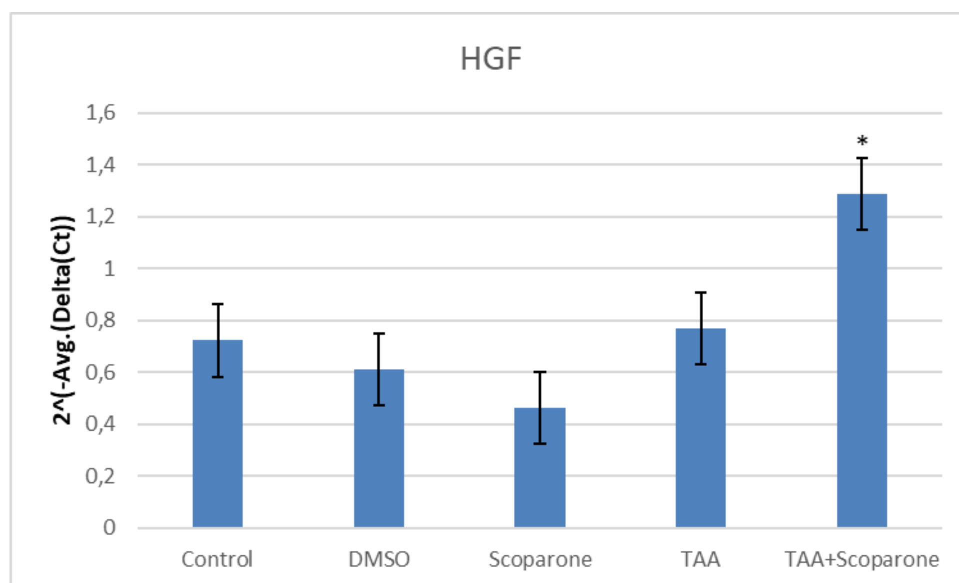

Figure 1. Comparison of HGF gene expressions according to groups (n=8 per group). The data represent the mean ± SD of 2^ (-Avg.(Delta(Ct)). **: Symbolizes the statistical difference between TAA+Scoparone group and other groups (p<0.05).*

TGF-β1 gene expression was found to be increased in the fibrosis group compared to the control group. Scoparone injection into subjects with liver fibrosis caused a decrease in TGF-β1 gene expression (Figure 2).

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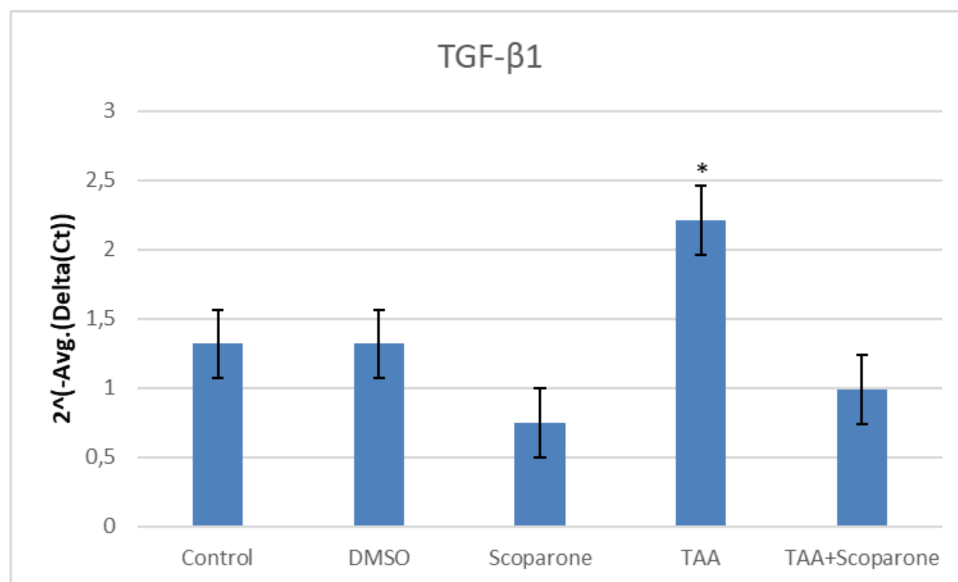

Figure 2. Comparison of TGF-β1 gene expressions according to groups (n=8 per group). The data represent the mean ± SD of 2^ (-Avg.(Delta(Ct)). **: Symbolizes the statistical difference between TAA group and other groups (p<0.05).*

Induction of liver fibrosis by TAA caused a significant increase in TNFAIP6 levels compared to the healthy group. Injection of Scoparone into the liver fibrosis group caused a decrease in TNFAIP6 levels, but this decrease was not statistically significant (Figure 3).

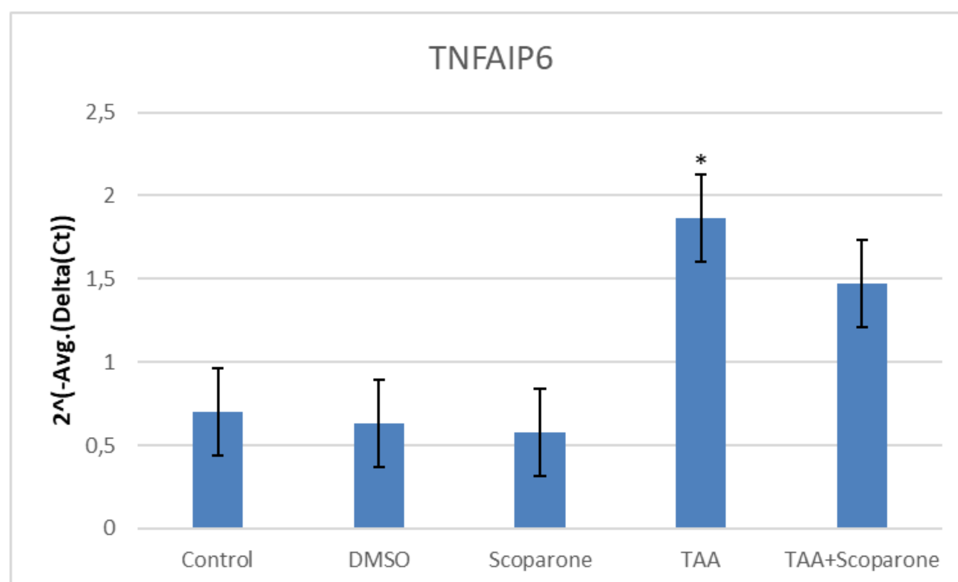

Figure 3. Comparison of TNFAIP6 gene expressions according to groups (n=8 per group). The data represent the mean ± SD of 2^ (-Avg.(Delta(Ct)). **: Symbolizes the statistical difference between TAA group and control, DMSO and Scoparone groups (p<0.05).*

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Discussion

In this study, the effect of Scoparone, a naturally occurring bioactive compound isolated from *Artemisia capillaria*, on liver fibrosis was investigated at the molecular level. Liver fibrosis is a reversible wound healing response and may occur in patients with chronic liver injury [2,13,14]. AST and ALT enzymes, which are found at low levels in circulation in healthy individuals, leave the cell membrane due to increased hepatocyte destruction in liver injury and their levels in serum increase [15]. In our study, a statistically significant increase was observed in AST and ALT values in TAA- administration groups compared to control, DMSO groups and Scoparone-treated group (p<0.05). According to these findings, it was concluded that TAA administration caused damage in mouse livers and as a result of this damage, AST and ALT enzymes were released from the cells and their serum concentrations increased. In the TAA + Scoparone treatment groups, serum AST and ALT values were lower than the TAA group, but there was no statistically significant difference. In the study by Liu et al. investigating the effects of Scoparone in non-alcoholic steatohepatitis, it was observed that Scoparone administered at a dose of 20, 40 and 80 mg/kg for four weeks significantly reduced the increased AST and ALT levels in mice induced by MCD (methionine and choline deficiency) in a dose-dependent manner [7]. Bilgin et al. showed that Scoparone administered orally at a dose of 35 mg/kg to rats in which acute hepatoxicity was induced by CCl4 caused a decrease in serum AST and ALT levels [16,17]. In our study, Scoparone was administered intraperitoneally to mice only at a dose of 40 mg/kg for two weeks. This finding indicates that the effect of Scoparone administration on biochemical parameters remains limited.

According to the results of our study, TGF-β gene expression, which activates hepatic stellate cells and transforms them into myofibroblastic cells, was determined by RT-PCR method as a fibrosis marker. TGF-β is the main regulator of fibrosis [18,19]. A pathological increase in TGF-β signaling is central to HSC activation [14]. Moreover, other hepatic cell types, including hepatocytes, also secrete TGF-β1, critically contributing to the profibrotic shift of HSCs [20-23]. In our study, TGF-β1 gene expression was found to be increased in mouse livers of the fibrosis group compared to the control group. This result shows that we have established the fibrosis model correctly. Scoparone injection into subjects with liver fibrosis caused a significant decrease in TGF-β1 gene expression (p<0.05). TNFAIP6 (TSG-6) is an important antifibrotic cytokine gene of mesenchymal stem cells [24]. Recent studies have reported that TNFAIP6 reduces inflammation and fibrosis in mice with acute liver injury and supports liver regeneration [25,26]. Wang et al. investigated whether TNFAIP6 promotes liver regeneration by inducing autophagic clearance in damaged livers. In the study, TSG-6 was injected into mice fed a methionine choline deficient diet for two weeks. According to the data obtained, it was observed that increased liver enzymes and histomorphologic injury in mice with liver damage decreased with TSG-6 treatment [26]. According to the results of our study; induction of liver fibrosis by TAA caused a significant increase in TNFAIP6 levels compared to the healthy group. It is thought that the anti-inflammatory effect of TNFAIP6 promotes healing in damaged tissue and therefore, there is an increase in gene expression. Injection of Scoparone into the liver fibrosis group did not cause a significant decrease in TNFAIP6 levels. Plasma concentrations of HGF increase after partial hepatectomy, liver injury and fulminant liver failure. In liver tissue, HGF and its mRNA levels correlate better with the degree of injury [27]. According to the results of our study; no significant change was observed in HGF gene expression in the samples of the TAA-induced fibrosis group compared to the control group, probably due to increased hepatic TGF-β1 expression. In TAA+Scoparone groups, Scoparone increased the gene expression of HGF. The signaling mechanism by which this occurs will be determined by further studies. There is no study in the literature on the effects of Scoparone on HGF gene expression. However, according to the results of our study, Scoparone's antifibrotic It is conceivable that an HGF-mediated mechanism at least partially underlies its effect. HGF exerts biological and physiological activities through the Met receptor tyrosine kinase and the anti-fibrotic effect of the HGF-Met pathway has been demonstrated in different models for different tissues. In the liver, selective loss of the Met

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receptor in hepatocytes accelerates the development of liver fibrosis in response to chronic hepatic injury induced by CCl_4 [28-30]. In contrast, administration of HGF and expression of the HGF gene suppresses the development of liver fibrosis/cirrhosis. HGF treatment has been shown to accelerate resolution of fibrosis in experimental animal models, including kidney and lung fibrosis [29,31,32]. It should also be emphasized that HGF and TGF-β1 balance each other in their signaling and expression. HGF represses TGF-β1 expression and TGF-β1 represses HGF expression [32-35]. When these data are evaluated together, it is thought that Scoparone's antifibrotic effect occurs through multifaceted molecular mechanisms and is particularly mediated through the TGF-β1/HGF balance.

Along with these findings, some limitations of the study should also be considered. First, the limited sample size may affect statistical power and restrict the generalizability of the results. Furthermore, the use of only male animals did not allow for the evaluation of sex-related biological differences. This can be considered a significant methodological limitation when considering the potential effects of hormonal regulation on liver fibrosis and regeneration. Another important point to consider in interpreting the study is that the findings are largely based on gene expression levels. The absence of confirmatory analyses at the protein level (e.g., Western blot or ELISA) prevents the direct determination of the functional counterparts of the observed molecular changes. Similarly, the lack of histopathological evaluations limits the confirmation of the fibrotic process at the tissue level. While this restricts the translational interpretability of the study, it necessitates that the data obtained be considered as preliminary for further experimental studies. Additionally, the application of a single-dose and relatively short-term treatment protocol in the study limits a comprehensive evaluation of the potential effects of Scoparone. Experimental designs involving different doses and longer application periods are needed to elucidate dose-response relationships and time-dependent effects. In this context, mechanistic interpretations of the current findings should be carefully considered, as they are based on gene expression data and existing literature rather than direct mechanistic or protein-level validation, and should therefore be supported by further studies.

Conclusion

This study suggests that Scoparone may exhibit modulatory effects on antifibrotic and regenerative processes in TAA-induced liver fibrosis. Particularly when the significant decrease in TGF-β1 expression is considered alongside the increase in HGF levels, it is thought that Scoparone may have an effect profile targeting the biological balance between fibrogenesis and regeneration. These findings indicate that the agent can not only limit damage but also support repair processes. However, the observation of more pronounced changes in gene expression levels despite limited improvement in biochemical parameters suggests that the effects of Scoparone are time-dependent. It is clear that longer-term studies with different dosage regimens are needed to determine whether these molecular-level changes translate into clinical improvement. In this context, dose, duration of administration, and timing of treatment initiation stand out as critical determinants. In conclusion, Scoparone can be considered a promising candidate molecule in the treatment of liver fibrosis; however, the current findings are preliminary. Further studies with larger sample sizes, multiparameters, and translational design are needed to validate this efficacy and demonstrate its clinical applicability. Additionally, investigating potential combinations with different antifibrotic agents presents a significant area of research for strategies that could enhance treatment efficacy.

Funding

This study was supported by Afyonkarahisar Health Sciences University Scientific Research Projects Coordination Unit project number 20.GENEL.020.

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Conflict of interest

The authors have no conflicts of interest to declare.

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