

Exploring the Therapeutic Potential of (+)-Catechin Gallate: An *In Vivo* Approach to Combat Liver Fibrosis

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Abstract: Liver fibrosis occurs as a result of the progression of chronic liver diseases, regardless of underlying causes such as hepatitis virus infection, alcohol intake, and metabolic fatty liver disorder. It is often associated with liver damage, inflammation, and cell death. In the current study, the potential of (+)-catechin gallate was checked against liver fibrosis in rat models. Carbon tetrachloride (CCl₄) was administered to induce liver fibrosis, and 0.7 mL/kg of CCl₄ with olive oil was injected into rats for six weeks twice a week. The analysis of liver markers (i.e., alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT)) was found to be increased in rats treated with CCl₄, confirming the induction of liver fibrosis. After induction, the rats were divided into four groups (i.e., G2 to G5) with 6 rats in each group. Group 3 was treated with silymarin standard drug, groups 4 and 5 were treated with (+)-catechin gallate low dose (50 mg/kg) and high dose (100 mg/kg) for four weeks. After treatment, the levels of ALP, AST, and ALT revealed highly significant results compared to the standard drug. Histopathological study after treatment with (+)-catechin gallate revealed a reduction in inflammation, nuclear damage, necrosis, and hemorrhage. The study clearly shows the anti-liver fibrosis potential of (+)-catechin gallate which could be used as a potential drug candidate in the treatment of liver fibrosis in future.

Keywords: Liver fibrosis; (+)-catechin gallate; carbon tetrachloride; liver function test; histopathology

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INTRODUCTION

Liver fibrosis resulting from chronic liver disorder is a significant worldwide health challenge. Fibrosis is a vital component for the progress of liver disorder(s) and hepatocellular carcinoma (HCC), as it is correlated with liver illness. The pathway of liver fibrosis disorder is similar in all major liver disease etiologies despite the differences in the mechanisms of original liver injury and illness (Hussain *et al.*, 2023). Fibrosis is a persistent state that commences a cascade of biophysical and biochemical changes in the liver and it is also responsible for apoptosis and necrosis of highly specialized endothelial cells of liver, across the release of inflammatory arbiters and start the activation of liver stellate cells. Extracellular matrix protein turnover is reduced and excess is deposited as a result of further aggravating this chronic wound healing response. Recent studies show that the high stiffness of the matrix is caused by a higher density of extracellular matrix and it is correlated with the enhancement of liver fibrosis (Akkız *et al.*, 2024).

Liver disease is responsible for two million deaths annually on a global scale, with one million caused by viral hepatitis and hepatocellular cancer and another reason is the complications of cirrhosis. Cirrhosis is currently the 11th leading cause of death worldwide, and liver cancer is the 16th leading cause of death. Together they account for 3.5% of global deaths. Cirrhosis is one of the top 20 causes of disability-adjusted life years and years lost, accounting for

1% and 2% of the global burden, respectively (Liu and Chen, 2022). The reaction of hepatocytes against inflammation has an important role in the process of physiopathology of hepatic fibrosis, which concerns the recovery of both pro- and anti-inflammatory cells including macrophages and monocytes. This process enhances counteract across the yield of various chemo and cytokines, which accelerate the impetus of liver stellate cells by inducing pro-inflammatory cells. Stellate cells can easily mold into myofibroblasts when the macrophages trigger the growth transforming factors (Miyazaki *et al.*, 2025).

These pathways have different clinical associations such as the growth of curative alternatives that allow us to stop liver fibrosis and enhance liver function (Bi *et al.*, 2025). However, there is no approved medication that can effectively treat fibrosis, and it is still unknown when fibrosis becomes incurable. Irreversible changes comprise the development of portal hypertension, the development of regenerative nodules, and the data show early hepatic failure as irreversible changes (Dezső *et al.*, 2022). Recent research has however provided data for the reversibility of the process in the event when the injury-causing stimulus has been removed. This argument has been shown in both clinical samples of a cirrhotic human liver and laboratory models of hepatic fibrosis (Zhang *et al.*, 2022). The initial steps in the recovery of liver fibrosis include a decrease in cytokines level, the elimination of fibrous scars and myofibroblasts by senescence and apoptosis, and a rise in collagenase activities (Koda *et al.*, 2022). Phytochemicals are biologically active substances derived from plants and

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provide protection to them. There are many different phytochemicals derived from various sources including vegetables, fruits, grains, nuts, and herbs. In addition to having powerful antioxidant effects, phytochemicals have antibacterial, antiviral, antidiarrheal, and antiallergic characteristics (Ali *et al.*, 2021). Keeping in view the importance of plant phytochemicals, the anti-fibrotic characteristics of the plant phytochemical (+)-catechin gallate have been investigated in the current study.

MATERIAL AND METHODS

Animals and chemicals used

In the *in vivo* validation, a total of 30 adult male albino rats (weighed 150-200 g) were used. Rats were kept in a room at 22±2°C with a relative humidity of 55–60% and subjected to 12 h/12 h light/dark cycles. The chemicals (+)-catechin gallate, and CCl₄ were purchased from Sigma-Aldrich Chemie (Steinheim, Germany). The CCl₄ (used to induce liver fibrosis) was mixed in olive oil, which acts as an emulsifier, allowing CCl₄ to dissociate sufficiently to cause liver damage. Furthermore, olive oil exhibits no toxicity or any biological or pharmacological activities in terms of hepatotoxicity. Silymarin was used as a standard drug and purchased from Abbott Laboratories Chicago, Illinois, US.

Experimental Design

The animal study was evaluated and approved by the Ethics Committee of Government College University Faisalabad with approval number: GCUF/ERC/331. A study of the potential effects of standard drug and (+)-catechin gallate on CCl₄-induced liver fibrosis in rats was conducted as mentioned by Hafez *et al.*, (2017). The animals were divided into the following groups: Group 1: Healthy group of normal non-infected rats (n=6). The remaining 24 rats were intoxicated with CCl₄. For intoxication, the rats received CCl₄ (0.7 mL/kg) with olive oil (1:1) for the induction of liver fibrosis for six weeks. After intoxication, the rats were divided into four groups (i.e., G2 to G5) with six rats in each group. Group 2: intoxicated group with no treatment. Group 3: standard drug group, Group 4: (+)-catechin gallate (low dose (LD) of 50 mg/kg) and Group 5: (+)-catechin gallate (high dose (HD) of 100 mg/kg).

Biochemical parameters and histological examination

Sodium thiopental as anesthesia was given to rats and blood samples from each group were taken and centrifuged. The serum was maintained at –20°C to assess liver enzyme functioning including alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT), serum proteins and kidney function test (urea and creatinine). Rats were sacrificed to collect liver fragments for histological investigation and preserved in a 10% formalin solution. Alcohol dehydrated the samples after the liver sections were set for one or two days

in 10% formalin. For this, the samples were placed in ethanol to increase concentrations (from 70% to 96%) and then left at each concentration for twelve hours. After that, the samples were placed in xylene for one to three hours, and then they were left in 57°C liquid paraffin for another two to three hours. Hematoxylin-eosin was used to stain the materials after Semithin sections had been formed on a microtome (Bozhkov *et al.*, 2024).

STATISTICAL ANALYSIS

The results were presented as means ± standard error of mean (SEM). All statistical analyses have been carried out using the one-way analysis of variance (ANOVA) test in Graph Pad Prism software version 6 (CA, USA). The significance level has been selected at $p < 0.05$.

RESULTS

Cytotoxicity was induced by injecting CCl₄ in male rats for a period of six weeks and twice a week. The CCl₄ dose was prepared in olive oil with a 1:1 ratio and administered to the intoxicated group except the healthy group (control). Liver biomarkers (i.e., ALT, AST, and ALP), serum proteins and kidney biomarkers were found to be increased in the intoxicated group compared to the healthy group and significantly recovered in the treatment groups.

Effect of (+)-catechin gallate on liver biomarkers

Silymarin was used as a standard drug for the *in vivo* study of liver fibrosis. The phytochemical (+)-catechin gallate was used for the treatment of liver fibrosis in rats which showed significant results for different liver function, serum proteins, and kidney function parameters compared to the standard drug. The level of ALT was increased in the intoxicated group (i.e., 81.33±6.5) compared to the healthy group (i.e., 39.66±7.5). After treatment with daily doses of (+)-catechin gallate low dose (i.e., 50 mg/kg) and high dose (i.e., 100 mg/kg) for four weeks, the level of ALT was found to be decreased significantly (fig. 1a). In case of AST, the level was increased in the intoxicated group (i.e., 123.66±8.02) compared to the healthy group (i.e., 33.33±6.5). After treatment with low and high doses of (+)-catechin gallate, the level of AST was significantly recovered (fig. 1b). The ALP level was also increased significantly in the intoxicated group and recovered highly significantly in low and high doses of (+)-catechin gallate compared to the standard drug group (Fig. 1c). Similarly, the levels of total proteins (TP), bilirubin, A/G, and albumin were decreased significantly while the levels of urea and creatinine were increased significantly in the intoxicated group which were recovered very significantly in the treatment groups (table 1).

Histological examination

Histological observations supported the biochemical findings. Hepatic portions from normal rats revealed an average-sized central vein encircled by regular liver cells

Table 1: Liver biomarkers, blood serum and renal kidney parameters

Parameter	G1	G2	G3	G4	G5
Total Proteins	65.33±3.05	47.33±5.5	64.66±4.5	64.0*±5.0	74***±5
Bilirubin	2.06±0.35	1.69±0.31	2.86±0.2	2.11*±0.09	2.01**±0.14
A/G	1.3±0.2	0.43±0.04	1.77±0.11	1.25±0.06***	1.1±0.1***
Albumin	36.3±1.65	23±4	31±4	33.66±4.5	30.33±3.51
Urea	33.0±5.0	72.0±5.0	57.33±4.50	41.33±4.50**	34.66±3.51***
Creatinine	0.84±0.06	1.27±0.07	1.2±0.1	0.61±0.1***	0.6±0.1***

G1: Healthy group, G2: Intoxicated group, G3: Standard drug group, G4: (+)-catechin gallate low dose group, G5: (+)-catechin gallate high dose group. *Significant results ($p<0.05$), **Very significant results ($p<0.01$), *** Highly significant results ($p<0.001$)

organized in strands and divided by normal-sized blood sinusoids. Furthermore, portal pathways exist inside thin fibrous tissue without development or fibrosis. In contrast, the CCl₄-intoxicated group displayed portal tract inflammation, nuclear damage, necrosis, and bleeding, resulting in a significant increase in both inflammation and fibrosis when compared to the control group. CCl₄-intoxicated rats treated simultaneously with silymarin and (+)-catechin gallate showed reduced hepatic damage and fibrosis (fig. 2), as evidenced by a significant decrease in both inflammation and fibrosis compared to CCl₄-intoxicated rats. Finally, when compared to the CCl₄-intoxicated and silymarin-treated groups, (+)-catechin gallate treatment therapy revealed relatively small portal tract inflammation with focal patchy necrosis and a small number of portal tracts with fibrous expansion but no fibrous septa. This resulted in considerable reductions in inflammation and fibrosis.

DISCUSSION

Increased fibrillar collagen synthesis and its buildup in the liver stroma, along with irregular cellular rearrangement, are the causes of liver fibrosis. Cirrhosis, which is characterized by abnormal hepatocyte structural distortion, nodule formation, reduced blood flow, portal hypertension, hepatocellular cancer, and liver failure, can develop from liver fibrosis (Peugnet-González *et al.*, 2023). Liver fibrosis was previously believed to be irreversible. An increasing amount of clinical and experimental data, however, points to the contrary. Histological evaluation of biopsies from animal models of fibrosis and humans with chronic liver disease of different etiologies that have received successful treatment showed that fibrosis is a dynamic, bidirectional process where treatment with remodeling of scar tissue is feasible. As a result, over the last ten years, the mechanism behind liver fibrosis has gone through a major change in consideration, and it is no longer seen to be an inert or continuous condition (Roehlen *et al.*, 2020).

(+)-Catechin gallate is primarily found in green tea and is a polyphenolic compound with anti-fibrotic properties. Although there are limited mechanistic studies of (+)-catechin gallate but the studies related to its structural

analog, epigallocatechin-3-gallate (EGCG) provides valuable insights into potential mechanisms by which (+)-catechin gallate may exert its anti-fibrotic effects. Recent studies have shown EGCG is involved in several important pathways such as it blocks Smad2/3 phosphorylation in hepatic stellate cells (Sekar *et al.*, 2024), reduces TGF- β 1 expression in bile duct-ligated rats (Salhab *et al.*, 2022), directs inhibition of PI3K/Akt phosphorylation in liver fibrosis models (Yang *et al.*, 2024), reduces Akt activation in cardiac fibroblasts (Li *et al.*, 2022). EGCG also exerts anti-inflammatory effects through prevention of nuclear translocation of NF- κ B (Li *et al.*, 2022), downregulation of TNF- α and IL-1 β in pulmonary fibrosis (Mokra *et al.*, 2022). In a fibrosis model induced by irradiation, EGCG reduced the number of histological alterations in the lungs, reduced serum levels of TGF- β 1, IL-6, IL-10, and TNF α , activated Nrf2 and related antioxidant enzymes HO-1 and NQO-1, increased SOD activity, and decreased collagen deposition and (myo)fibroblast growth (You *et al.*, 2014).

Carbon tetrachloride (CCl₄)-induced liver fibrosis animals are commonly used as a model to study the pathophysiology of human liver fibrosis. The current investigation revealed that (+)-catechin gallate therapy treated liver fibrosis caused by CCl₄. The liver fibrosis model in rats was developed by means of intraperitoneal CCl₄ injection. CCl₄ is the most prevalent modeling method to describe liver fibrosis. Its advantages include a high and consistent modeling rate as well as a pathological process in rats which is similar to that of humans (Wu *et al.*, 2023). The toxicant CCl₄ has the potential of liver injury. The fatty acids and intrinsic proteins of the cell membrane are covalently bound by free radicals produced during the enzymatic catalysis of CCl₄ by cytochrome oxidase in the liver. This process starts lipid peroxidation and membrane disintegration, which ultimately results in liver fibrosis and necrosis (Oriakhi and Orumwensodia, 2021). ALT, AST, and ALP are biomarkers used to evaluate hepatic injury, and they are elevated when liver cells are injured. These serum markers with elevated levels suggest a breakdown in the integrity of the liver cell membrane, which may be directly linked to an increase in ROS CCl₄-induced liver injury (Oriakhi, 2020).

The anti-liver fibrotic effect of the (+)-catechin gallate was explored in the current study. (+)-catechin gallate was used

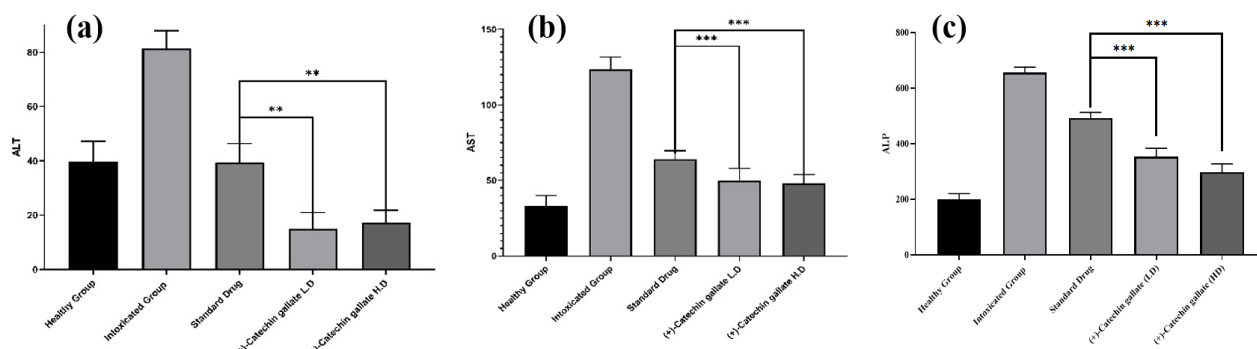


Fig. 1: Effect of standard drug and (+)-catechin gallate on liver biomarkers. (a) Levels of ALT in the healthy, intoxicated, standard drug, and treatment groups. (b) Levels of AST in the healthy, intoxicated, standard drug, and treatment groups. (c) Levels of ALP in the healthy, intoxicated, standard drug, and treatment groups. The results were considered statistically significant, very significant, and highly significant if the p -values were <0.05 , <0.01 , and <0.001 (represented by ‘*’, ‘**’, and ‘***’), respectively.

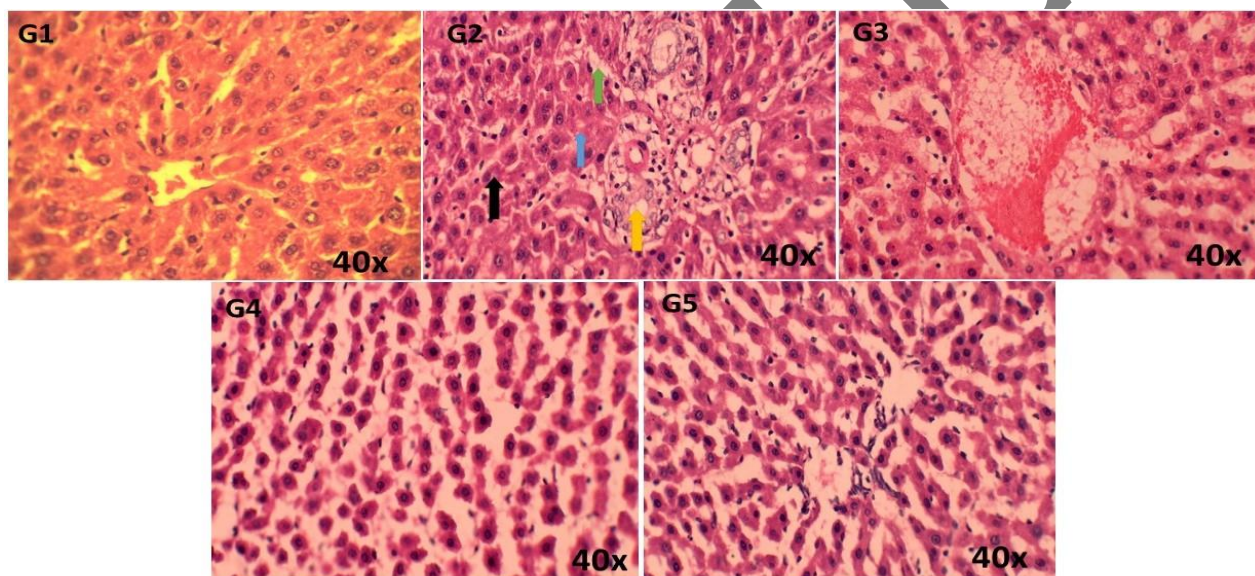


Fig. 2: Histological features of rat liver tissues of healthy, fibrosis, standard drug, and treatment groups. G1: Healthy group G2: Intoxicated group, G3: Standard drug group. Photomicrograph of rat liver in CCl_4 induced liver fibrosis group for six weeks exhibited cellular necrosis, central vein deletion, inflammation, hemorrhage, and nucleus damage. Nucleus (black arrow), hemorrhage (yellow arrow), necrosis (green arrow), Inflammation (blue arrow). G4: Histological features of rat liver fibrosis treated with the phytochemical (+)-catechin gallate low dose, G5: (+)-catechin gallate high dose

in the manners of low and high doses. In the current study, ALP, AST, and ALT levels in the serum of rats were analyzed to assess the liver damage degree. CCl_4 significantly increased serum AST and ALT concentrations, consistent with the previous studies (Mostafa *et al.*, 2019). The treatment with (+)-catechin gallate reduced the levels of ALP, AST, and ALT. The phytochemical (+)-catechin gallate with low and high dose showed very significant results for the recovery of ALT, AST, and ALP levels. In further animal models of lung fibrosis, the beneficial therapeutic activity of epigallocatechin-3-gallate (EGCG) was demonstrated. For example, in bleomycin-induced fibrosis, EGCG inhibited

ROS production, increased antioxidant levels, including Nrf2 activity, decreased lung edema, lowered NF- κ B, TNF α , IL-1 β , and myeloperoxidase activity, lowered hydroxyproline content, lowered TGF- β 1 and α -SMA expression, and reduced lung damage (Adamcakova *et al.*, 2023). In addition to (+)-catechin gallate and its analog, different phytochemicals and plants have been investigated against liver fibrosis. For example, a recent rat study has demonstrated that nanoemulsions of decaffeinated date seed and Arabic coffee extracts significantly improved liver biomarkers, i.e., reduced ALT from 124 to 68 U/L, reduced AST from 318 to 134 U/L, and reduced ALP level from 362 to 129 U/L (Alamri *et al.*, 2024). In a study on

Wistar rats with CCl₄-induced liver injury, *Momordica charantia* extracts significantly reduced ALT, AST, and ALP levels and showed hepatoprotective effects against acute liver damage (Bini *et al.*, 2024). Similarly, in another study, silymarin was shown to improve liver function by reducing ALT, AST, and ALP in rats with diethylnitrosamine-induced liver fibrosis and highlighted its protective role against liver damage (Mansour *et al.*, 2022).

CONCLUSION

Current research was planned to check the potential of a flavonoid (+)-catechin gallate in rat models of liver fibrosis. For this purpose, CCl₄ (1 mL/kg) mixed with olive oil, was used to induce liver fibrosis in male rats for a period of 6 weeks and silymarin was used as a standard drug. Low dose (50 mg/kg) and high dose (100 mg/kg) of (+)-catechin gallate was orally administrated after the confirmation of liver fibrosis. The treatment with (+)-catechin gallate showed significant results comparing with the standard drug. The levels of liver biomarkers (i.e., ALT, AST, and ALP), serum proteins and renal function parameters were improved after treatment with (+)-catechin gallate and exhibited statistically significant results comparing to the standard drug group. Finally, the histopathological studies confirmed significant recovery in the liver tissues compared to the intoxicated group. In the future (+)-catechin gallate could be a potential drug candidate against liver fibrosis. A well-designed clinical trials are needed to evaluate the safety, efficacy, and pharmacokinetics of (+)-catechin gallate in humans with liver fibrosis in future.

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Ethical approval

The animal study was evaluated and approved by the Ethics Committee of Government College University Faisalabad with approval number GCUF/ERC/331.

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