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HEPATOPROTECTIVE ACTIVITY OF FRUIT AND LEAF EXTRACTS OF *FICUS CARICA* AND *FICUS BENGHALENSIS* IN EXPERIMENTAL RATS

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ABSTRACT

Ficus plants have traditionally been used as potential remedies for treating various diseases. Hepatotoxicity is one of the severe threats to human health which must be adequately cured. The study was planned to investigate the hepato-protective potential of methanolic extracts of fruit and leaves of *Ficus carica* and *Ficus benghalensis* against carbon tetrachloride (CCl_4)-induced hepatotoxicity in an experimental rat model. The study was planned using a randomized control design (RCD). The study included 6 groups of animals (n= 5 per group) having average body weight (230±20 g), out of which 5 groups were treated with CCl_4 (15 µL kg^{-1} body weight), and the remaining one was left as healthy control. Four of the five CCl_4-treated groups were administered individually with fruit and leaf extracts (25 mg kg^{-1} body weight) of F. carica and F. benghalensis, while the fifth was left as CCl_4-treated control. The total serum bilirubin (TSB), total serum protein (TSP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) levels of the control group during the treatment period ranged from 0.54±0.16 to 0.59±0.15 $mgdL^{-1,}$ 8.56±0.73 to 8.66±0.75 gdL^{-1}, 46.00±21.41 to 49.41±22.68 UL^{-1}, 41.6±13.99 to 44.41±13.16 UL^{-1}, and 139.80±28.72 to 145.62±28.82 UL^{-1}, respectively. CCl_4 administration significantly (p<0.05) increased the TSB, ALT, AST, and ALP levels in the range of 1.48±0.30-2.30±0.19 $mgdL^{-1}$, 147.6±34.22 to 233.81±14.94 UL^{-1}, 118.8±15.88 to 167.8±16.4143 UL^{-1}, and 213.8±21.46 to 260±26.664 UL^{-1}, respectively. The elevated TSB, ALT, AST, and ALP levels were significantly (p<0.05) decreased after *F. carica* and *F. benghalens* extract treatment to 1.06±0.15-1.70±0.21 $mgdL^{-1}$, 115.00±28.19-190.21±25.68 UL^{-1}, 89.8±16.29-111.8±23.81 UL^{-1}, and 195.38±42.29-218.4±35.02 UL^{-1} respectively. Moreover, TSP level was significantly decreased after CCl_4 administration and improved after extract treatment. It was concluded that methanolic extract from the leaf and fruit of both *F. benghalensis* and *F. carica* protects against CCl_4-induced hepatotoxicity in rats.

Keywords: Hepatoprotective potential, *Ficus carica*, *Ficus benghalensis,* Hepatic damage, Experimental rat model

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INTRODUCTION

Hepatic damage adversely impacts human health, resulting in a high morbidity rate worldwide (Fontana *et al.*, 2014). Viral infections, drug ingestion, alcohol abuse, metabolic disorders, portal hypertension, autoimmunity, and reactive oxygen species are the etiologies responsible for hepatic damage (Gopal *et al.*, 2015; Török, 2008). Hepatocyte damage leads to many liver function complications, including liver cirrhosis, portal hypertension, and liver failure (Bataller and Brenner, 2005). There are many proposed treatments for hepatic damage, including herbal treatment. Treating liver disorders using natural remedies has a long-standing history, such as Ayurvedic medicines and earlier Chinese and European medicine systems. In the 21st century, there is again an exceptional shift towards evaluating herbal products for therapeutic purposes in liver disorders. The natural healing processes of the liver are accelerated by most herbal drugs (Mani Senthilkumar *et al.*, 2005). Medicinal plants and their constituents have significantly been used to promote health effects because of their potential to modulate biological and physiological activities and have a confirmed role in treating and preventing different diseases (Rahmani *et al.*, 2015, 2014).

Ficus is a genus of tropical deciduous trees with above 800 species. The phytochemical studies showed that different parts of *F. carica* and *F. benghalensis* contain numerous bioactive compounds, including phenols, flavonols, flavonoids, glycosides, steroid, pentacyclic triterpenes, triterpenoids, inulin, lignin, cellulose, alkaloids, chloride, protein, organic acids, phytosterols, anthocyanins, coumarins, saponins, tannins, phlobatannins, gallic acid, anthraquinone, rhein,

gallocatechin, vitamin C and different volatile organic compounds including aliphatic alcohols, hydrocarbons, and some other secondary metabolites (Jeong and Lachance, 2001; Vinson *et al.*, 2005, 2001; Ahmad *et al.*, 2011; Slatnar *et al.*, 2011; Vallejo *et al.*, 2012; Bhaskara Rao *et al.*, 2014; Gopukumar *et al.*, 2016; Ambi and Idrees, 2017; Nawaz *et al.*, 2019). Based on the presence of these phytochemical compounds, various parts of *F. carica* and *F. benghalensis* possess anticancer, antimutagenic, antidiarrheal, anti-diabetic, anti-bacterial, anti-fungal, antipyretic, anti-inflammatory, hepatoprotective, hypoglycemic, hypolipidemic, hypocholesterolemic, anti-tuberculosis, nematicidal, anti-spasmodic, anti-platelet, anthelmintic, anti-allergic, anti-hepatotoxic, and antioxidant activities (Lansky *et al.*, 2008; Sirisha *et al.*, 2010; Mawa *et al.*, Ahmad *et al.*, 2011; 2013; Satish *et al.*, 2013).

Previously, studies have shown that the Ficus plants are a significant source of various phytochemicals, possess various biological activities, and are effective against different ailments such as hepatic, cardiovascular, and neurodegenerative disorders (Sirisha *et al.*, 2010). In the present study, the hepato-protective potential of the leaf and fruit of two species of Ficus was investigated against carbon tetrachloride (CCl_4)-induced hepatic damage in a rat model. The study would significantly contribute to the literature exploring the reliable and effective sources of hepatoprotective agents.

MATERIALS AND METHODS

Experimental Protocols: The study was approved by the Advanced Studies and Research Board and Departmental Ethical Committee (No. Biochem./06/2019 dated: 20.06.2019) for the care and use of the animals in the study. Strict adherence to the protocols recommended by the Committee was ensured, and the animals were treated humanely. All the experiments were performed in research laboratories at the Department of Biochemistry, Bahauddin Zakariya University, Multan, Pakistan, from June 2019-May 2020. The study was planned using a randomized control design (RCD). Overall, 6 groups of animals, each consisting of 5 animals (n=30; w=230±20 g, age=40±5 days), were included in the study, out of which 5 groups were treated with CCl_4 (15 µLkg^{-1} bodyweights provided in typical chick's diet). At the same time, the 6^{th} one was left as healthy control. Four out of five CCl_4-treated groups were treated individually with fruit and leaf extracts (25 mg kg^{-1} bodyweights) of *F. carica* and *F. benghalensis* by oral administration. At the same time, the 5^{th} one was left untreated as a positive control. Blood samples of the control, CCl_4-treated, and extract-treated groups of animals were collected. The sera were analyzed for hepatic biomarkers, including total bilirubin, total protein, and some liver function enzymes. The dose selection and treatment protocols are presented in Table 1.

Preparation of plant extracts: The fresh leaves and ripened fruit (500 g each) of *F. carica* and *F. benghalensis* were collected from the local gardens in the urban areas of Multan City, Punjab, Pakistan. A Botanist identified the plants at the Department of Botany (Voucher No. *F. carica*: BZBOT0001567 and *F. benghalensis*: BZBOT0001565), and the samples were brought to the Biochemistry laboratory at Bahauddin Zakariya University, Multan, cleaned from dust, and dried under shade until constant weight. The dried leaves and fruits (10 g each) were ground to a fine powder and extracted in 80% methanol (Solid: solvent 1:10) for 24 h. The solvent was evaporated to dryness in a water bath at 50°C, and the extracts were stored in airtight glass bottles in the dark at 4°C.

Animals: White albino male rats (n=30, w=230±20 g, age=40±5 days) were purchased from the Institute of Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan. The animals were housed in steel cages and acclimated for one week at 30±2°C temperature, 40-45% humidity and: 13/11 h light/dark duration). The animals were allowed to drink tap water *ad labium* and feed on a regular chick diet throughout the study.

Induction of liver damage and extract treatment: The animals were administered CCL_4 (15 µL kg^{-1} body weight) in a routine chicks' diet per the experimental protocol to induce hepatotoxicity. The CCL_4 treatment was repeated after an interval of 24 h for one week. The CCL_4-treated animals were orally administered with leaves and fruit extract of *F. carica* and *F. benghalensis* (25 mg kg^{-1} body weight) 24 h after the last dose of CCL_4. The extract dose was repeated thrice after an interval of 24 h. The overall treatment plan is given in Table 1.

Blood sampling: The blood sample (1 mL) was collected individually from each animal in each group in gel sample tubes from the coccygeal vein of the animals before CCL_4 treatment and 24 h after CCL_4 and extract treatment. The sera were obtained by centrifugation at 4000 × g for 20 min and stored at -20°C.

Hepatic parameters: The hepatic parameters, including total serum bilirubin (TSB), total serum protein (TSP), and liver function enzymes such as alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), were estimated as a response of CCL_4-induced hepatocellular injury and extract treatment.

The TSB level was determined by the previously reported diazo sulfanilic acid assay (Ichida and Nobuka, 1968) following the protocols provided along with the commercially available bilirubin kit (Cat. No. BR3859, Randox, UK).

The results were reported in terms of TSB $mgdL^{-1}$. The Biuret method determined the TSP level (Johnson *et al.*, 2007) according to the protocols described in the commercially available protein kit. The TSP level was calculated as gdL^{-1} using Bovine serum albumin as standard. The ALT, AST, and ALP levels were determined following the method recommended by the International Federation of Clinical Chemistry (IFCC 2002) using commercially available kits (Cobas, Roche Diagnostics, Germany) Cat. No. 10851132 216, 10851124 216, and 12173107 122, respectively (Siekmann *et al.*, 2002; Schumann *et al.*, 2011, 2002). The activity of ALT and AST (UL^{-1}) was measured in terms of change in absorbance of NADH, and that of ALP (UL^{-1}) was determined proportionally to the absorbance of *p*-nitrophenol at 340 nm using Micro-lab 300 following the test protocols provided in the assay kits.

Statistical analysis: The experimental results were presented as mean ± standard deviation of five replicates. The significance of variance in the means at different levels of the study was analyzed by one-way analysis of variance (ANOVA) using Tukey's multiple range tests at a 95% confidence level.

RESULTS

The experimental values of the studied parameters of the study groups are presented in Table 2.

Total serum bilirubin: The TSB level of the control group during the treatment period ranged from 0.54±0.16 to 0.59±0.15 $mgdL^{-1}$. The CCl_4 treatment resulted in a statically significant ($p<0.05$) increase in the TSB level of the animals ranging from 1.48±0.30 to 2.30±0.19 $mgdL^{-1}$. The TSB level of the CCl_4-treated study groups was significantly decreased ($p<0.05$) after extract administration. The *F. carica* fruit and leaf extract administration significantly reduced ($p<0.05$) the TSB level to 1.40±0.17 and 1.06±0.15 $mgdL^{-1}$, respectively. The *F. benghalensis* fruit and leaf extract administration also showed a significant decrease ($p<0.05$) in TSB level to 1.70.21 and 1.58±0.30 $mgdL^{-1}$, respectively. However, the TSB level of the healthy and CCl_4-treated control groups remained statistically unchanged ($p>0.05$) during extract treatment (Figure 1a, b).

Total serum protein: The TSP level of the control group during the treatment period ranged from 8.56±0.73 to 8.66±0.75 gdL^{-1} that was found to be significantly ($p<0.05$) decreased to 3.56±0.42 to 4.52±0.63 gdL^{-1} after CCl_4 treatment. The administration of *F. carica* fruit and leaf extract increased the TSP level of the CCl_4-treated study groups up to 5.74±0.85 and 6.72±0.41 $gdL^{-1,}$ respectively. The TSP level was also increased to 4.94±0.44 and 5.52±0.90 after the *F. benghalensis* fruit and leaf extract administration, respectively. However, statistically, no significant variation ($p>0.05$) was observed in the TSP level of the healthy and CCl_4-treated control groups during extract treatment (Figure 2a, b).

Liver function enzymes

Alanine transaminase: The ALT levels of the control group during the treatment period ranged from 46.00±21.41 to 49.41±22.68 $UL^{-1,}$ which remained statistically similar throughout the study period. The CCl_4 administration resulted in a significant ($p<0.05$) increase in the ALT level of the study groups ranging from 147.6±34.22 to 233.81±14.94 UL^{-1}. The administration of *F. carica* fruit and leaf extract decreased the ALT level of the CCl_4-treated animals up to 115.00±28.19-115.6±33.87 UL^{-1}. The ALT level of the CCl_4-treated animals was also found to be reduced to 190.21±25.68 and 153.80±18.26 UL^{-1} after administration of fruit and leaf extract of *F. benghalensis* (Figure 3a, b).

Aspartate transaminase: The AST level of the control group during the treatment period ranged from 41.6±13.99 to 44.41±13.16 UL^{-1}. The CCl_4 administration of the study groups resulted in a significant ($p<0.05$) increase in the level of AST ranging from 118.8±15.88 to 167.8±16.4143 UL^{-1}. The administration of *F. carica* fruit and leaf extract resulted in a significant decrease in the AST level of the CCl_4-treated animals to 89.8±16.29-105.6±12.89 UL^{-1}, respectively. The ALT level of the CCl_4-treated animals was also found to be decreased to 91.6±21.60 and 111.8±23.81 UL^{-1} after administration of fruit and leaf extract of *F. benghalensis,* respectively (Figure 4a, b).

Alkaline phosphatase: The ALP levels of the control group during the treatment period ranged from 139.80±28.72 to 145.62±28.82 UL^{-1}. The CCl_4 administration resulted in a significant ($p<0.05$) increase in the level of ALP, ranging from 213.8±21.46 to 260±26.664 UL^{-1}. The administration of *F. carica* fruit and leaf extract decreased the ALP level of the CCl_4-treated animals to 207.68±40.70 and 195.38±42.29 UL^{-1}, respectively. The fruit and leaf extract of *F. benghalensis* also decreased the ALT level of CCl_4-treated animals to 218.4±35.02 and 215.6±25.94 UL^{-1}, respectively (Figure 5a, b).

However, statistically, no significant decrease ($p>0.05$) was noted in the level of the TSB, TSP and the studied liver function enzymes of the healthy control group during the CCl_4 and extracts treatments.

Table 1. Study groups, diet plan, and treatment protocols .

Sr. No	Study group	Diet	CCl_4 treatment	Extract treatment
1	Healthy control	Normal chick's diet	Untreated	Untreated
2	*CCl_4-treated control	Normal chick's diet	CCL_4 (15 µL /kg bodyweight)	Untreated
3	FCF-treated	Normal chick's diet	CCL_4 (15 µL/kg bodyweight)	*F. carica* fruit extract (25 mg/kg body weight)
4	FCL-treated	Normal chick's diet	CCL_4 (15 µL/kg bodyweight)	*F. carica* leaf extract (25 mg/kg body weight)
5	FBF-treated	Normal chick's diet	CCL_4 (15 µL/kg bodyweight)	*F. benghalensis* fruit extract (25 mg/kg body weight)
6	FBL-treated	Normal chick's diet	CCL_4 (15 µL/kg bodyweight)	*F. benghalensis* leaf extract (25 mg/kg body weight)

*CCl_4: Carbon tetrachloride, FCF: *F. carica* fruit, FCL: *F. carica* leaf, FBF: *F. benghalensis* fruit, FBL: *F. benghalensis* leaf

Table 2. Experimental values of the hepatic parameters of the control, CCl_4-treated, and extract-treated animals.

Sample	Untreated	CCl_4 treated	Extract treated	p-value
Total serum bilirubin (mg/dL)				
Healthy control	0.58±0.17	0.59±0.15	0.54±0.16	0.31
*CCl_4-control	0.68±0.15	1.48±0.30	1.60±0.18	0.01
FCF-treatement	0.78±0.13	2.04±0.18	1.40±0.17	0.00
FCL-treatement	0.64±0.21	1.62±0.17	1.06±0.15	0.00
FBF-treatement	0.72±0.18	2.30±0.19	1.71±0.21	0.00
FBL-treatement	0.78±0.19	2.16±0.14	1.58±0.29	0.00
Total serum proteins (g/dL)				
Healthy control	8.63±0.74	8.56±0.73	8.66±0.75	0.46
*CCl_4-control	7.84±1.13	4.32±0.52	4.39±0.51	0.02
FCF-treatement	6.71±1.09	4.52±0.63	5.74±0.86	0.00
FCL-treatement	7.98±1.09	4.18±0.49	6.72±0.41	0.00
FBF-treatement	7.14±1.04	3.86±0.31	4.94±0.44	0.00
FBL-treatement	6.72±1.05	3.56±0.42	5.52±0.90	0.00
Alanine aminotransferase (U/L)				
Healthy control	46.00±21.41	48.41±20.40	49.41±22.68	0.84
*CCl_4-control	54.01±10.54	147.60±34.22	150.50±20.04	0.01
FCF-treatement	66.62±10.09	196.42±12.72	115.00±28.19	0.00
FCL-treatement	54.22±22.64	153.80±18.24	115.61±33.87	0.00
FBF-treatement	62.61±14.40	233.81±14.35	190.22±25.68	0.00
FBL-treatement	69.60±18.82	227.40±14.58	153.81±18.26	0.00
Aspartate aminotransferase (U/L)				
Healthy control	41.61±13.99	43.11±14.12	44.41±13.16	0.50
*CCl_4-control	46.40±8.56	121.80±14.38	125.80±13.65	0.02
FCF-treatement	57.12±9.76	137.00±17.69	89.80±16.29	0.00
FCL-treatement	45.41±17.87	118.81±15.88	105.60±12.89	0.00
FBF-treatement	54.22±13.22	151.42±24.05	91.61±21.60	0.00
FBL-treatement	58.00±16.43	167.82±16.41	111.82±21.80	0.00
Alkaline phosphatase (U/L)				
Healthy control	139.80±28.72	145.62±28.82	143.51±26.32	0.38
*CCl_4-control	157.80±15.88	213.80±31.50	220.81±31.93	0.03
FCF-treatement	171.60±11.04	252.22±24.17	207.68±40.70	0.00
FCL-treatement	149.00±31.40	221.01±36.57	195.38±42.29	0.00
FBF-treatement	166.84±14.46	260.34±26.66	218.41±35.02	0.00
FBL-treatement	167.78±8.27	242.66±15.46	215.59±25.93	0.00

* CCl_4: Carbon tetrachloride, FCF: *Ficus carica* fruit, FCL: *Ficus carica* leaf, FBF: *Ficus benghalensis* fruit, FBL: *Ficus benghalensis*

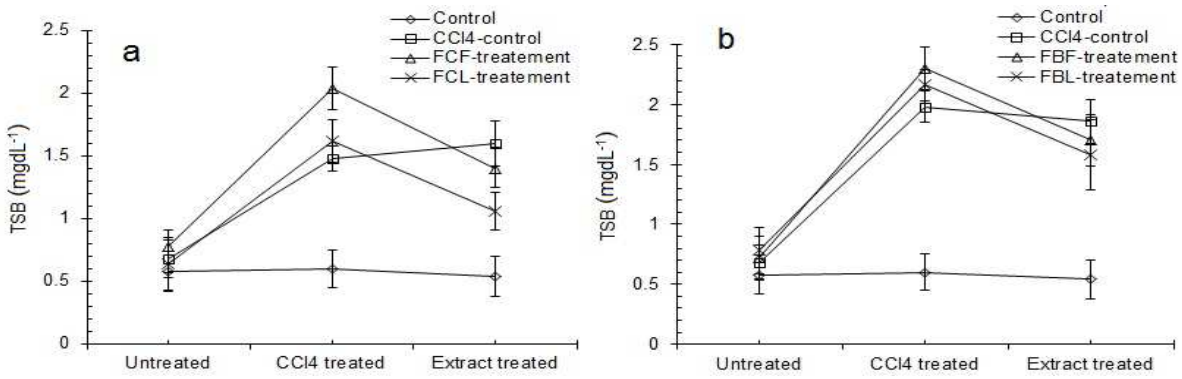

Figure 1 Variation in total serum bilirubin (TSB) level of the control, CCl_4-treated, and extract-treated animals
CCl_4: Carbon tetrachloride, FCF: *Ficus carica* fruit, FCL: *Ficus carica* leaf, FBF: *Ficus benghalensis* fruit, FBL: *Ficus benghalensis*

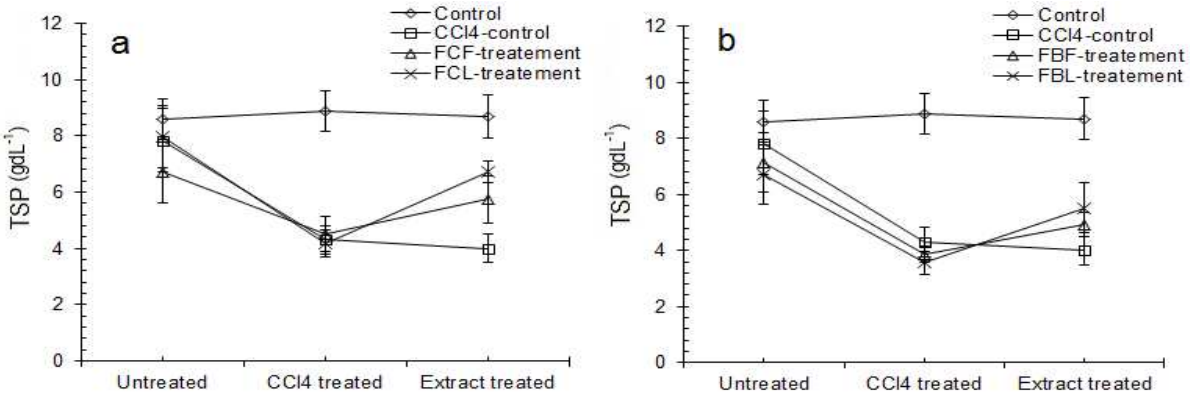

Figure 2 Variation in total serum protein (TSP) level of the control, CCl_4-treated, and extract-treated animals
CCl_4: Carbon tetrachloride, FCF: *Ficus carica* fruit, FCL: *Ficus carica* leaf, FBF: *Ficus benghalensis* fruit, FBL: *Ficus benghalensis*

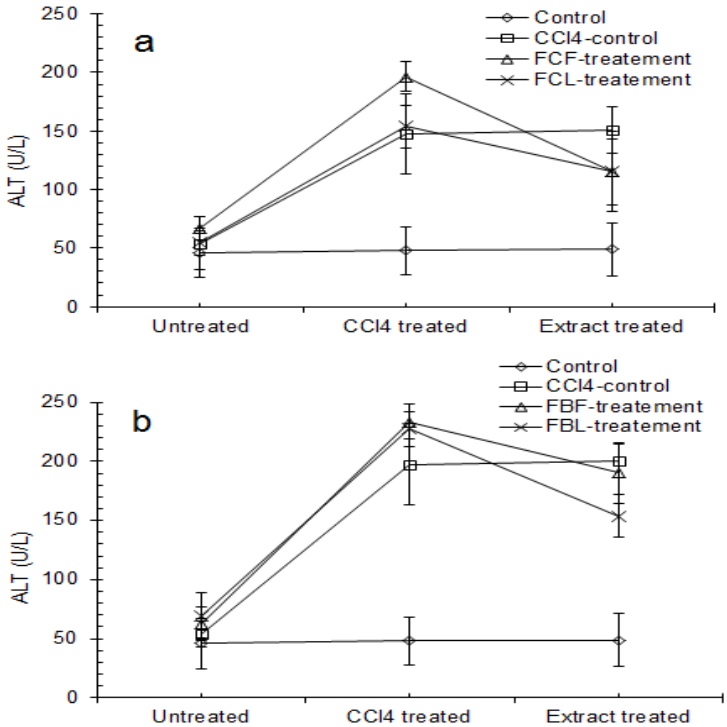

Figure 3 Variation in alanine transaminase (ALT) level of the control, CCl_4-treated, and extract-treated animals
CCl_4: Carbon tetrachloride, FCF: *Ficus carica* fruit, FCL: *Ficus carica* leaf, FBF: *Ficus benghalensis* fruit, FBL: *Ficus benghalensis*

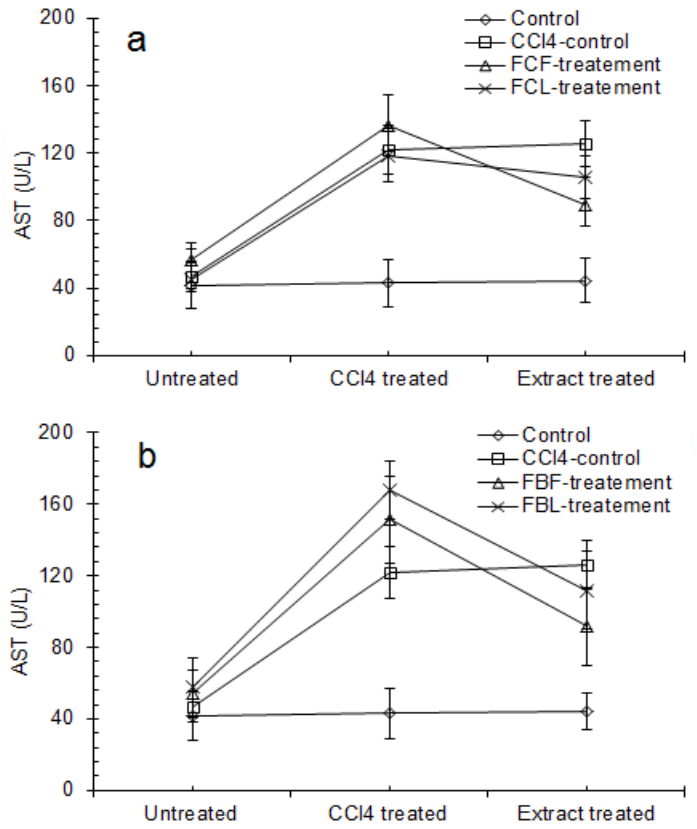

Figure 4 Variation in aspartate transaminase (AST) level of the control, CCl_4-treated, and extract-treated animals
CCl_4: Carbon tetrachloride, FCF: *Ficus carica* fruit, FCL: *Ficus carica* leaf, FBF: *Ficus benghalensis* fruit, FBL: *Ficus benghalensis*

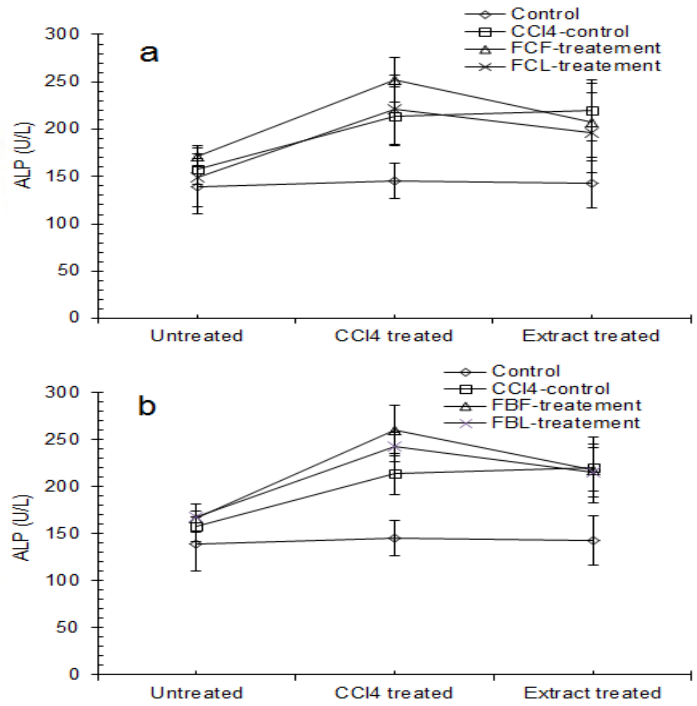

Figure 5 Variation in alkaline phosphatase (ALP) level of the control, CCl_4-treated, and extract-treated animals
CCl_4: Carbon tetrachloride, FCF: *Ficus carica* fruit, FCL: *Ficus carica* leaf, FBF: *Ficus benghalensis* fruit, FBL: *Ficus benghalensis*

DISCUSSION

The present study evaluated the therapeutic effect of leaf and fruit extracts of *F. carica* and *F. benghalensis*, a good source of natural antioxidants, against CCl_4-induced hepatic damage in a rat model. After CCl_4 treatment, the elevation in TSB, ALT, AST, and ALP levels provided evidence of CCl_4-induced free radical production leading to hepatotoxicity and animal cell damage. However, despite the release of liver function enzymes into circulation, the TSP level was surprisingly decreased after CCl_4 treatment which may be attributed to the oxidative degradation of some proteins.

The observed decrease in TSB, ALT, AST, and ALP and increase in the TSP to a significant level after administration of fruit and leaf extracts of *F. carica* and *F. benghalensis* advocates the hepatoprotective and therapeutic potential of these extracts against hepatic damage. The persistence of CCl_4-induced variation in the studied parameters of CCl_4-treated control animals during extract treatment also provides evidence about the hepatoprotective potential of the selected parts of *F. carica* and *F. benghalensis*. The observed hepatoprotective potential of the tested extracts may be attributed to potential bioactive phytochemicals compounds in the fruit and leaf extracts of *F. carica* and *F. benghalensis* (Nawaz *et al.*, 2019).

The fruit and leaves of the selected Ficus species were found to be almost equally effective against hepatotoxicity, with few exceptions where the leaf extracts were found more effective than the fruit extracts. Among the tested extracts, *F. carica* leaf extract showed a comparatively more decrease in TSB level and an increase in TSP level of the CCl_4-treated animals. *F. carica* leaf extract also showed more decline in ALT and ALP levels of the CCl_4-treated animals than other extracts. However, the fruit extracts of both species of Ficus were found to be more effective in lowering the AST levels of the CCl_4-treated animals.

The Ficus extracts showed a relatively higher hepatoprotective potential than those reported earlier (Parameswari *et al.*, 2012). The value of TSP and ALT was comparable, while that of AST and ALP was found to be higher than those reported earlier in the CCl_4-treated animals subjected to Ficus fruit and leaf extract administration (Krishna *et al.*, 2007; Aghel *et al.*, 2011; Mujeeb *et al.*, 2011; Diab *et al.*, 2018).

Conclusions: In conclusion, the CCl_4 treatment of the study groups resulted in a significant elevation in TSB and liver function enzymes and a decline in total protein levels compared to those of the control group. The administration of the methanolic extracts of fruit and leaves of *F. carica* and *F. benghalensis* resulted in a significant decrease in TSB, ALT, AST, and ALP and an increase in the total protein level of the study groups as compared to the CCl_4-treated control. The observed variations in the studied hepatic parameters suggest the hepatoprotective potential of the selected parts of the two Ficus species. However, the chosen plant parts of *F. carica* and *F. benghalensis* showed an almost equal protective effect against CCl_4-induced equal damage. The study would significantly contribute to the literature investigating the effective and reliable sources of anti-hepatotoxic agents.

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