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RESEARCH ARTICLE

Hepatoprotective effects of *Ficus racemosa* stem bark against carbon tetrachloride-induced hepatic damage in albino rats

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Abstract

In the present study, the hepatoprotective effects of petroleum ether (FRPE) and methanol (FRME) extract of *Ficus racemosa* Linn. (Moraceae) stem bark were studied using the model of hepatotoxicity induced by carbon tetrachloride (CCl_4) in rats. CCl_4 administration induced a significant decrease in serum total protein, albumin, urea and a significant increase ($P \leq 0.01$) in total bilirubin associated with a marked elevation in the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) as compared to control rats. Further, CCl_4 intoxication caused significant increase in the TBARS and decrease in glutathione (GSH) levels in serum, liver and kidney. Pretreatment with FRPE and FRME restored total protein and albumin to near normal levels. Both the extracts resulted in significant decreases in the activities of AST, ALT and ALP, compared to CCl_4-treated rats. However, a greater degree of reduction was observed in FRME pretreated group (FRPE 43%, 38%, and 33%; FRME 55%, 73%, and 38%). Total bilirubin content decreased from 2.1 mg/dL in CCl_4-treated rats to 0.8 and 0.3 mg/dL in FRPE and FRME pretreated rats, respectively. The extracts improved the antioxidant status considerably as reflected by low TBARS and high GSH values. FRME exhibited higher hepatoprotective activity than a standard liver tonic (Liv52), while the protective effect of FRPE was similar to that of Liv52. The protective effect of *F. racemosa* was confirmed by histopathological profiles of the liver. The results indicate that *F. racemosa* possesses potent hepatoprotective effects against CCl_4-induced hepatic damage in rats.

Keywords: Ficus racemosa*; hepatoprotective; CCl4; oxidative stress; liver damage; hepatic enzymes*

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Introduction

Ficus racemosa Linn. (Moraceae), commonly known as "gular", is widely distributed all over India and other parts of Asia (CSIR, 1952; Kulkarni & Ansari, 2004). All parts of this plant are medicinally important in the traditional system of medicine in India and have been used extensively in biliary disorders, jaundice, dysentery, diabetes, diarrhea, and as an anti-inflammatory agent (Kirtikar & Basu, 1975; Nadkarni et al., 1976; Chopra et al., 1958). The stem bark of *F. racemosa* is used in folklore medicine for treatment of coughs and colds (Chopra et al., 1958). An infusion of bark is employed as a mouth wash for spongy gum condition and the decoction is used in treating various skin diseases and ulcers. It is used as a poultice in inflammatory swelling and boils. It is reported to be effective in the treatment of hemorrhoids, dysentery, asthma, gonorrhea, gleet, menorrhagia, leucorrhea, hemoptysis, and urinary diseases (CSIR, 1952; Kirtikar & Basu, 1975; Nadkarni et al., 1976). *F. racemosa* is reported to possess various biological effects such as hepatoprotective, chemopreventive, antidiabetic, anti-inflammatory, antipyretic, antitussive, antidiarrheal and antidiuretic (Mandal et al., 2003; Khan & Sultana, 2005; Rao et al., 2002a, 2002b, 2003; Mandal et al., 2000; Mukherjee et al., 1998; Ratnasooriya et al., 2003).

Carbon tetrachloride (CCl_4), an industrial solvent, is a well-established hepatotoxin. Various studies have demonstrated that the liver is not the only target organ

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of CCl_4 and it causes free radical generation in other tissues also such as kidneys, heart, lung, testis, brain and blood (Ahmad et al., 1987; Ohta et al., 1997; Ozturk et al., 2003). It has also been reported that exposure to CCl_4 induces acute and chronic renal injuries (Perez et al., 1987; Churchill et al., 1983). In view of this, the present study evaluated the protective effects of *F. racemosa* bark on liver damage caused by CCl_4 in Wistar rats and observed the changes in the antioxidant defenses.

Materials and methods

Chemicals and reagents

Total protein, albumin assay kits (Span Diagnostics, Surat, India), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, urea, creatinine (Agappe Diagnostics, Ernakulam, India) assay kits and Liv52 (Himalaya Healthcare, Bangalore, India), a standard liver tonic, were used. 5,5-dithio (bis) nitro benzoic acid (DTNB) was purchased from Sigma Aldrich (Bangalore, India). All the chemicals and reagents used in the study were of analytical grade.

Collection of plant material

Ficus racemosa stem bark was collected from Mukkadahally, Chamarajanagar district of Karnataka, India, during September 2007, subsequently identified by Shivprasad Hudeda, and the voucher specimen (BOT-001/2008) was deposited at the herbarium of the Department of Studies in Botany, University of Mysore. The bark was cut into small pieces, dried (50°C) and powdered, passed through 60 mesh sieve (BS) and stored in an airtight container at 4°C until further use.

Preparation of the extracts

The bark powder was extracted sequentially with petroleum ether and methanol. Evaporation of respective solvents in a rotary vacuum evaporator yielded petroleum ether extract – a sticky yellow mass (2.5% w/w), and methanol extract – a reddish brown solid mass (5.3% w/w). The extracts were homogenized with olive oil (1:5 w/v) and the rats were force fed using a feeding tube.

Animals

Healthy male Wistar rats between 8 and 9 weeks of age and weighing 140-160 g were obtained from the central animal house, Dept of Zoology, University of Mysore, and divided into 5 groups (n = 6): Control group, normal rats; FRPE group, petroleum ether extract-treated rats (500 mg/kg bw); FRME group, methanol extract-treated rats (500 mg/kg bw); LIV group, Liv52-treated rats (2.5 mL/kg bw); CCl_4 group, untreated rats. All the groups other, than FRPE and FRME, received olive oil (1 mL/kg bw) in order to maintain uniformity. The rats were housed in polyacrylic cages and maintained at 27° ± 2°C, 45-60% relative humidity and 12 h photo period. The rats were provided with a standard pellet diet (Amrut Feeds, Pune, India) and water *ad libitum*. All animal procedures have been approved by the Animal Ethical Committee of the University of Mysore in accordance with animal experimentation and care.

Experimental design

Rats were treated with FRPE and FRME 500 mg/kg orally once a day for 7 days, and then a mixture 0.5 mL/kg (i.p.) of CCl_4 in olive oil (1:1) was injected twice at 12 and 36 h after the final administration of FRPE and FRME. The animals were starved overnight before sacrifice in order to minimize variations in hepatic metabolism. The rats were anesthetized and decapitated 12 h after the final administration of CCl_4 (Lim et al., 2000). Blood was collected by direct cardiac puncture, and liver and kidneys were immediately excised. Portions of the liver and kidneys were homogenized (1:5 w/v) in phosphate-buffered saline (pH 7.4) for estimation of TBARS and GSH, while the other portion of the greater hepatic lobes were excised for histo-pathological studies.

Assays for hepatotoxicity

The activities of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase activities were determined in serum according to the procedures given in the respective assay kits. The contents of glutathione (GSH) and TBARS in serum, liver and kidneys were determined by the methods of Ellman (1959) and Ohkawa et al. (1979) respectively. Total bilirubin, total protein, albumin, urea and creatinine contents in serum were also determined using assay kits.

Histo-pathological procedures

Liver fragments were fixed in a 10% solution of formaldehyde and then dehydrated in graduated ethanol (50-100%), cleared in xylene and embedded in paraffin. The hepatic sections (4–5 μm) were examined with a photomicroscope after staining with hematoxylin and eosin (H-E) dye. Liver morphological changes included cell necrosis, fatty and hydropic degenerative changes. The histopathological studies of liver sections were carried out at Ravi Diagnostic Laboratory, Mysore, India.

Statistical analysis

The values are expressed as mean ± SD. The data was analyzed by ANOVA followed by Tukey's multiple comparisons test for significant differences using SPSS 11.0 software. The values were considered significant at $p \leq 0.05$.

Results

Effect of FRPE and FRME on serum proteins, urea, creatinine and total bilirubin

The data on serum proteins, urea, creatinine and total bilirubin levels of various groups is given in Table 1. A significant decrease ($p \leq 0.05$) in serum total protein (hypoproteinemia) was observed in CCl_4 injected rats. However, the total protein concentration was restored nearer to control levels in FRME-treated rats. A similar trend was observed with respect to serum albumin, where a greater decrease in albumin was observed in CCl_4 injected rats and FRME pretreatment restored albumin levels nearer to control levels, while FRPE and Liv52 restored albumin levels only to a marginal extent.

A significant decrease ($p \leq 0.05$) in serum urea concentration was observed in CCl_4-treated rats, while no significant differences were observed with respect to the serum creatinine levels among various groups. FRPE and FRME treatment did not cause any significant change in serum urea and creatinine levels as compared to those in CCl_4-treated rats. The total bilirubin content in FRME pretreated rats was comparable with that of control rats. The bilirubin content in FRPE pretreated rats was comparable with that of Liv52 pretreated rats and was significantly lower ($p \leq 0.05$) then that of CCl_4-treated rats.

Effect of FRPE and FRME on serum transaminases, alkaline phosphatase (ALP)

Pretreatment with FRPE and FRME attenuated the increase in the activities of AST, ALT and ALP indicating their protective effect against CCl_4-induced hepatic damage/injury (Figure 1). FRME exhibited maximum inhibition of the activities of AST, ALT and ALP nearer to those of control levels. FRPE and Liv52 exhibited similar but significant hepatoprotective effect.

Effect of FRPE and FRME on serum, hepatic, renal TBARS and GSH

The effect of FRPE, FRME and Liv52 on antioxidant status is shown in Figure 2. Pretreatment with FRPE and FRME significantly decreased ($p \leq 0.05$) the lipid peroxidation induced by CCl_4 as reflected by lower TBARS values in serum, liver and kidneys. Liv52 also decreased the oxidative stress significantly ($p \leq 0.05$) and it was comparable with that of FRPE. However, none of the extracts resulted in complete reversal of the oxidative stress to normal levels. FRME significantly restored the depleted GSH levels similar to that of control rats. FRPE also restored the GSH but it did not reach the control levels. The Liv52 also exhibited GSH restoration effect which was similar to that of FRPE (Figure 3).

Effect of FRPE and FRME on the histopathology of liver

The protective effects of FRPE and FRME were confirmed by histopathological examination of the liver

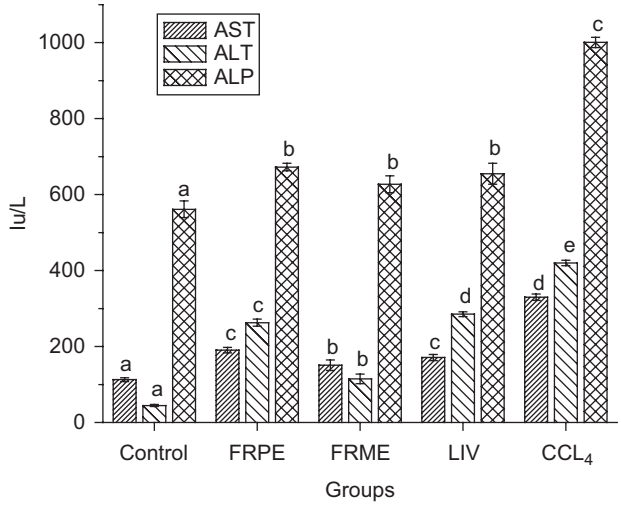

Figure 1. Effect of FRPE and FRME on serum hepatic enzymes.

Table 1. Effect of FRPE and FRME on serum proteins, urea, creatinine and total bilirubin.

Groups	Total protein (g/dL)	Serum albumin (g/dL)	Total bilirubin (mg/dL)	Creatinine (mg/dL)	Urea (mg/dL)
Control	5.9 ± 0.16^{d}	3.4 ± 0.05^{d}	$0.2^{a} \pm 0.02$	$0.5^{a} \pm 0.01$	$45.1^{d} \pm 0.37$
FRPE	5.20 ± 0.15^{b}	2.50 ± 0.08^{b}	$0.8^{b} \pm 0.03$	$0.6^{a} \pm 0.01$	$40.9^{b} \pm 0.63$
FRME	5.47 ± 0.11^{c}	2.86 ± 0.04^{c}	$0.3^{a} \pm 0.01$	$0.5^{a} \pm 0.02$	$42.8^{c} \pm 0.94$
LIV	5.25 ± 0.22^{bc}	2.53 ± 0.07^{b}	$0.7^{b} \pm 0.03$	$0.5^{a} \pm 0.03$	$40.9^{b} \pm 0.86$
CCL_4	4.5 ± 0.06^{a}	2.1 ± 0.04^{a}	$2.1^{c} \pm 0.05$	$0.7^{a} \pm 0.03$	$37.9^{a} \pm 0.76$

*Values are mean ± SD (n = 6).

**FRPE, petroleum ether extract-treated rats; FRME, methanol extract-treated rats; LIV, Liv52-treated rats; CCl_4, untreated rats.

#Values carrying different superscript letters a, b, c, d in columns differ significantly ($p \leq 0.05$).

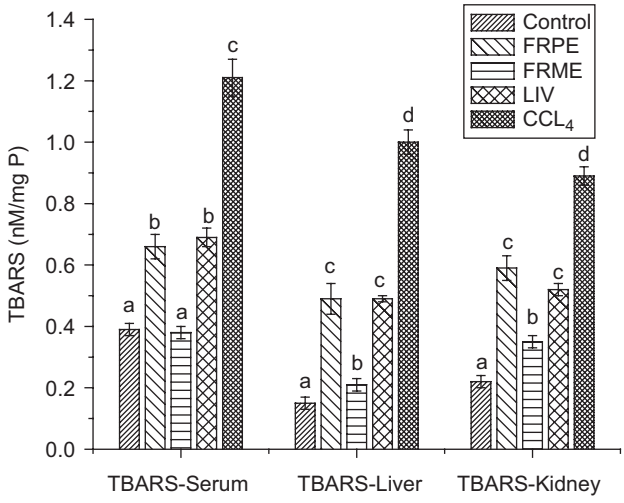

Figure 2. Effect of FRPE and FRME on serum, hepatic, renal TBARS.

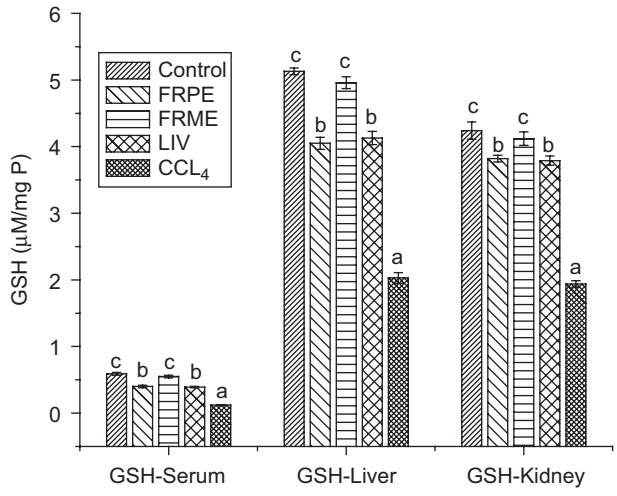

Figure 3. Effect of FRPE and FRME on serum, hepatic, renal GSH.

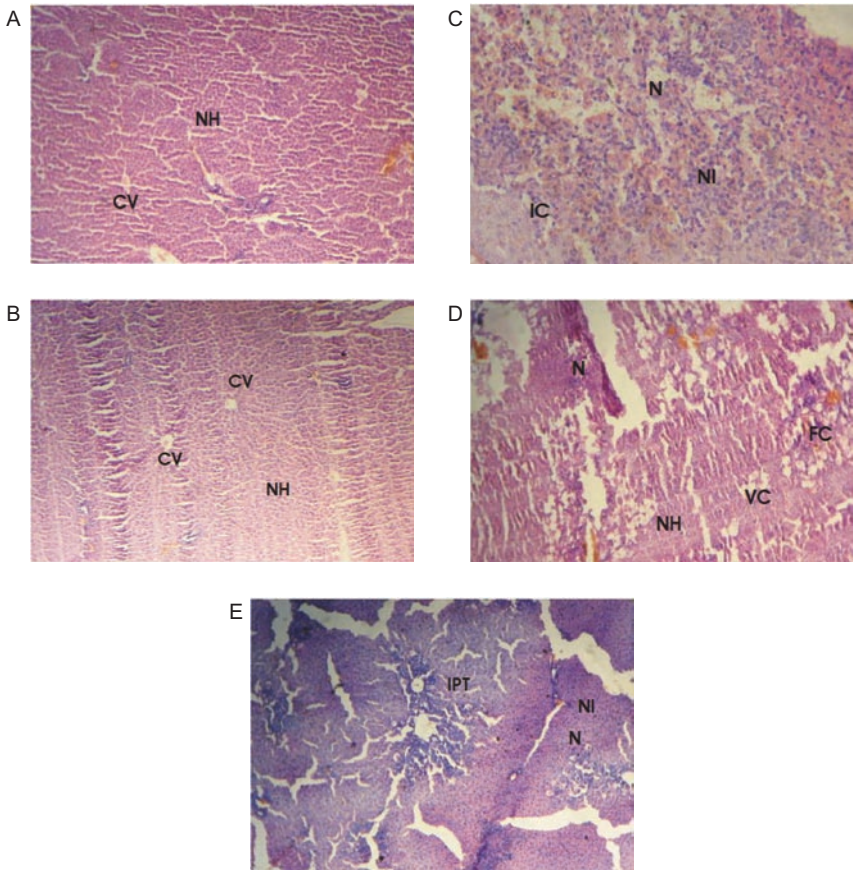

Figure 4. (**A**) Section of the liver tissue of control rats showing normal hepatocytes and central vein. (**C**) Section of the liver tissue of rats treated with CCl_4 showing severe necrosis, neutrophil infiltrate and inflammatory changes. (**D**) Section of the liver tissue of FRPE-pretreated rats showing normal hepatocytes necrosis and fatty changes. (**B**) Section of the liver tissue of FRME-pretreated rats showing normal hepatocytes and central vein. (**E**) Section of the liver tissue of Liv52-pretreated rats showing inflammatory changes and necrosis. NH, normal hepatocytes; CV, central vein; N, necrosis; NI, neutrophil infiltrate; IC, inflammatory cells; FC, fatty changes; VC, vacuolated cells; IPT, inflammatory infiltrate around the portal triad.

sections. In control animals, liver sections showed normal hepatic cells with well-preserved cytoplasm, prominent nucleus, nucleolus and central vein (Figure 4A) similar observations were also found in FRME pretreated rats (Figure 4B). In CCl_4-treated rats the sections showed intense necrosis, steatosis and inflammation with neutrophil infiltration of the hepatic cytoplasm (Figure 4C). Pretreatment with FRPE, and Liv52 showed considerable improvement in the hepatocellular architecture over CCl_4-treated rats, as reflected from a significant reduction in hepatic necrosis (Figure 4D & 4E, respectively), however, fatty cellular changes were seen in both the groups. Vacuolated cells were seen in FRPE rats, and on the other hand, severe inflammation around the portal triad was seen in Liv52 pretreated rats.

Discussion

Carbon tetrachloride is one of the most commonly used hepatotoxins in the experimental study of liver diseases. The hepatotoxic effects of CCl_4 are largely due to its active metabolite, trichloromethyl radical (Johnston & Kroening, 1998; Srivastava et al., 1990). It is well established that CCl_4 administration causes a significant decrease in serum urea, total protein and albumin levels (Ogeturk et al., 2004) and in the present investigation a significant decrease in the levels of total protein, albumin and albumin/globulin ratio was observed. However, pretreatment with the extracts of *F. racemosa* significantly restored the serum protein levels nearer to control levels. The decrease in serum protein content might be ascribed to liver damage caused by CCl_4 as reports indicate that liver damage causes decreased amino acid uptake or hepatic protein synthesis (El-Shenawy & Abdel-Nabi, 2006). As reported in other studies (Ogeturk et al., 2004) CCl_4 administration decreased serum urea levels considerably in comparison with control rats which marginally increased towards normalization in groups pretreated with *F. racemosa* extracts. However, some investigators have reported an increase in serum urea concentrations in CCl_4-treated rats and attributed these changes in urea levels to the reduction in the glomerular filtration rate as a result of CCl_4 intoxication, since the serum concentration of these two parameters depends largely on the glomerular filtration (Moawad, 2007). Such an increase in urea levels may also depend on the CCl_4 intoxication levels. The protective effect exhibited by Liv52 was similar to that of FRPE. FRME exhibited maximum protection and restored serum protein levels effectively. We observed a marginal increase in the serum creatinine levels of CCl_4-treated rats compared to control rats but the difference did not reach statistical significance. The effect of CCl_4 on serum creatinine levels is controversial. Some investigators have reported a decrease in serum creatinine in CCl_4 toxicity, while others have found no significant changes (Ozdogan et al., 2002). In our study, creatinine values in CCl_4 administered rats did not differ from control values.

Hepatotoxic compounds such as CCl_4 are known to cause elevation in serum transaminases. As expected, in the present study CCl_4 induced severe hepatic damage as represented by markedly elevated levels of ALT, AST, ALP and total bilirubin. The significant reductions in the activities of serum transaminases (AST and ALT), alkaline phosphatase and total bilirubin content brought about by the pretreatment with FRME could be due to the presence of bergenin, an isocoumarin (Veerapur et al., 2007) reported to exhibit significant hepatoprotective activity (Lim et al., 2000). Liv 52 is reported to exhibit significant hepatoprotective effect and improve liver functionality in CCl_4 intoxicated rats (Dhawan & Goel, 1994).

CCl_4 induces hepatotoxicity by metabolic activation; therefore it selectively causes toxicity in liver cells maintaining semi-normal metabolic function. CCl_4 is metabolically activated by the cytochrome P_{450}-dependent mixed oxidase in the endoplasmic reticulum to form a trichloromethyl free radical ($\cdot CCl_3$) which combines with cellular lipids and proteins in the presence of oxygen to induce lipid peroxidation (Recknagel et al., 1977; De Groot & Noll, 1986). Both FRPE and FRME decreased lipid peroxidation to near normal levels. Similar observations are reported with respect to Liv52 which significantly decreased malonaldialdehyde content in CCl_4 intoxicated rats (Pandey et al., 1994). Reports indicate that some natural extracts containing antioxidants protect against the CCl_4-induced lipid peroxidation and impairment in GSH status (Ko et al., 1995). The reduction in oxidative stress by the extracts of *F. racemosa* could be attributed to the presence of tannins, kaempferol, rutin, bergapten, psoralenes, flavonoids, ficusin, coumarin and phenolic glycosides (Baruah & Gohain, 1992), bergenin and racemosic acid (Li et al., 2004) that are reported to act as strong antioxidant and anti-inflammatory agents (Khan & Sultana, 2005).

In states of oxidative stress, GSH is converted to glutathione disulfide and depleted, leading to lipid peroxidation. Therefore, the role of GSH as a reasonable marker for the evaluation of oxidative stress is important (Recknagel et al., 1977). FRPE, FRME and Liv52 inhibited lipid peroxidation and elevated depleted serum, hepatic and renal GSH levels towards normalization.

Histopathological studies showed that CCl_4 caused severe necrosis, neutrophil infiltration and hydropic degeneration of the liver tissue. Pretreatment with extracts exhibited considerable hepatic protection,

which confirmed the results of biochemical studies. All the effects of the extracts were comparable with those of Liv52, a proven hepatoprotective tonic (Chauhan et al., 1994; Kothari et al., 1990; Kataria & Singh, 1997; Gopumadhavan et al., 1993; Dhawan & Goel, 1994). It is noteworthy to state that FRME exhibited maximum hepatoprotective effect as reflected by both biochemical parameters and histopathology of liver sections. The effect was far superior to Liv52 which can be attributed to the presence of bergenin, a known hepatoprotective agent and racemosic acid, a strong antioxidant (Li et al., 2004; Lim et al., 2000). The hepatoprotective effect of FRPE may be attributed to the presence of lupeol acetate, a triterpenoid (Rahman et al., 1994). The results of our study indicate that simultaneous treatment with *F. racemosa* bark extracts protects the liver against CCl_4-induced hepatotoxicity.

Conclusion

The present study is suggestive of the fact that CCl_4 causes hepatic damage in rats through enhanced lipid peroxidation and alterations in antioxidant defenses. The results demonstrate that *F. racemosa* has potent hepatoprotective action against CCl_4-induced hepatic damage in rats and this effect may be mediated through its antioxidative action. These observations justify the use of *F. racemosa* as traditional medicine in the treatment of jaundice. Further investigations are underway to isolate the phytoconstituents responsible for its hepatoprotective effect.

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