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Preclinical Evaluation of Ferulic Acid Isolated from Acacia arabica for Hepatoprotection in Chemically Induced Liver Damage in Rats

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ABSTRACT

Background: Hepatic injury induced by drugs and chemicals is a significant health problem and global issue, which in part can be explained by the low accessibility of hepatoprotective drugs with a favourable safety profile. The natural phenolic compounds have aroused a lot of scholarly interest due to their properties of antioxidants. Acacia arabica having long-standing historical use in the therapy of hepatic diseases is a rich source of phenolic compounds.

Aim: The current study aimed at isolating, characterizing, and investigating the hepatoprotective activity of ferulic acid attained out of Acacia arabica in the form of an extract of the Acacia arabica bark generated against chemically induced hepatotoxicity in rodent models.

Materials and Methods: Ferulic acid was obtained using the activity-guided fractionation and identified using infrared spectroscopy, 1H NMR, 13C NMR, high resolution mass spectrometry. The hepatoprotective effect was tested on rats, which were exposed to carbon tetrachloride (CCl4), thioacetamide, and chloroform induced hepatotoxicity. Biochemical parameters and histopathological changes of serum were measured.

Result: When hepatotoxic agents were administered, the contents of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin were seriously increased, and hepatic architecture was disrupted significantly. Ferulic acid treatment produced significant corrections of liver enzymes, and alleviations of histopathological abscess in all models and showed as effective as the reference drug.

Conclusion: Ferulic acid extracted in Acacia arabica has holistic hepatoprotective effects on chemically induced liver injury which is mainly attributed to their antioxidant and membrane stabilizing effect.

KEYWORDS: Acacia arabica; Ferulic acid; Hepatoprotection; CCl_4; Thioacetamide; Chloroform; Oxidative stress

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INTRODUCTION

Liver disease incidence is one of the primary causes of morbidity and mortality in the world, which can be largely attributed to contact with pharmaceuticals, alcohol, environmental toxins and infection with disease-causing agents. The hepatic organ is a kind of metabolic central board with the additional function of detoxification, which makes it particularly susceptible to the damage of the xenobiotics. The hepatotoxicity caused by chemicals is mostly oxidative and lipid peroxidation mediated, as well as interference with antioxidant mechanisms. (Asrani et al., 2023).

Although the modern medicine has made progress, the list of effective hepatoprotective drugs is limited, and currently used treatment options often bear side effects that are also harmful. As a result, the medicinal flora and their bioactive compounds have become a topic of increasing scholarly interest as potential hepatoprotective compounds. (Domitrović et al., 2015).

Acacia arabica (syn Acacia nilotica), native to the Fabaceae family has been widely used in the field of traditional medicine in management of hepatic sinusache, inflammatory diseases and also in infectious diseases. The concentration of phenolic compounds in the bark of this plant is high, the compounds bear high antioxidant activity. (Del WE, 2011). Ferulic acid, a hydroxycinnamic acid derivative, has been reported to possess antioxidant, anti-inflammatory, and cytoprotective activities.

The present study investigates the hepatoprotective efficacy of ferulic acid isolated from Acacia arabica against chemically induced liver injury using carbon tetrachloride, thioacetamide, and chloroform models, which represent free radical– and metabolite-mediated hepatotoxicity.

MATERIALS AND METHODS

Plant Material and Extraction
The bark of Acacia arabica was collected, authenticated, shade-dried, and pulverized. Soxhlet extraction was carried out using ethanol. The extract was concentrated under reduced pressure and subjected to phytochemical screening.

Isolation of Active Fraction by Column Chromatography (CC)
The isolation of the active fraction from the Acacia arabica bark extract was carried out using acid–base fractionation following by column chromatography (CC) in order to enrich phenolic constituents and obtain the bioactive fraction.

Characterization of Ferulic Acid
Activity-guided fractionation was performed using acid–base fractionation and column chromatography. The active fraction (FA2) was further purified and characterized using FT-IR, ^{1}H NMR, ^{13}C NMR, and HR-MS spectroscopy, confirming the structure of ferulic acid.

Experimental Animals
Wistar albino rats (150–200 g) were housed under standard laboratory conditions with free access to food and water. All experimental procedures were approved by the Institutional Animal Ethics Committee and conducted according to CCSEA guidelines.

Acute Toxicity Study
Acute toxicity studies were performed as per OECD guidelines 423 to determine the safe dose of ferulic acid.

Experimental Design
Hepatoprotective activity was evaluated using three chemically induced hepatotoxicity models:

Carbon tetrachloride (CCl_4)-induced hepatotoxicity
Healthy Wistar albino rats of either sex, weighing 200 ± 30 g, were procured from the Animal House Facility of Teerthanker Mahaveer Medical College & Research Centre, Moradabad. After a period of acclimatization under standard laboratory conditions, the animals were randomly divided into 4 groups (n = 6 per group).

Hepatotoxicity was induced using carbon tetrachloride (CCl_4) mixed with olive oil in a 1:1 ratio and administered intraperitoneally at a dose of 1 mL/kg body weight, twice weekly for a duration of 14 days, in accordance with previously reported protocols (Recknagel et al., 1989). The test group received fraction (FA2) orally along with CCl_4 administration. When the experiment time is finished, animals were anesthetized using thiopental sodium. Heart punctures were used to obtain blood samples, and liver tissues were removed for histological analysis and biochemical assessment (Bancroft & Gamble, 2008).

Table 1 Grouping of Animals for CCl_4-Induced Hepatotoxicity Model

S. No.	Groups	Route of Administration	Name of Drug / Dose
1	Control Group	Intraperitoneal	Olive oil (1 mL/kg)
2	Negative Group	Intraperitoneal	Carbon tetrachloride (CCl_4) (1 mL/kg; 1:1 in olive oil)
3	Treated Group	Intraperitoneal + Oral	CCl_4 (1 mL/kg) + (FA2) (100 mg/kg)
4	Standard Group	Intraperitoneal + Oral	CCl_4 (1 mL/kg) + Silymarin (50mg/kg)

Thioacetamide induced hepatotoxicity

Adult Wistar albino rats (200 ± 30 g) were divided into three groups of six animals each after being acclimated for the thioacetamide-induced hepatotoxicity research. The thioacetamide (TAA) was given intraperitoneally twice a week during 21 days and at a dosage of 100 mg/kg body weight to cause the hepatic damage as per the standard experiment protocols (Teck et al., 2004). The course of the trial implied the treatment group being given orally with FA2 by fractionation. Tomorrow, the subjects were euthanized, blood samples were drawn and liver tissue samples were removed to be used in later histological and biochemical studies after the end of the treatment regimen (Bancroft & Gamble, 2008).

Table 2 Grouping of Animals for Thioacetamide-Induced Hepatotoxicity Model

S. No.	Groups	Route of Administration	Name of Drug / Dose
1	Control Group	Intraperitoneal	Normal saline
2	Negative Group	Intraperitoneal	Thioacetamide (100 mg/kg)
3	Treated Group	Intraperitoneal + Oral	Thioacetamide (100 mg/kg) + (FA2) (100 mg/kg)
4	Standard Group	Intraperitoneal + Oral	Thioacetamide (100 mg/kg) + Silymarin (50mg/kg)

Chloroform induced hepatotoxicity

After acclimatization, mature Wistar albino rats with an average body weight of 200 ± 30g were randomly divided into four groups (n = 6). Hepatotoxicity was induced by administering chloroform at a dose of 0.5 mL/kg body weight, diluted in liquid paraffin and given orally once daily for 7 days, following established toxicological protocols (Singh et al., 2001). The therapeutic group received Ferulic acid – rich fraction (FA2) orally along with chloroform administration.

Animals were sacrificed when the treatment time was over under anesthesia. Blood samples were collected, and liver tissues were preserved for biochemical and histological assessments (Bancroft & Gamble, 2008).

Table 3 Grouping of Animals for Chloroform-Induced Hepatotoxicity Model

S. No.	Groups	Route of Administration	Name of Drug / Dose
1	Control Group	Oral	Liquid paraffin
2	Negative Group	Oral	Chloroform (0.5 mL/kg)
3	Treated Group	Oral	Chloroform (0.5 mL/kg) + (FA2) (100 mg/kg)
4	Standard Group	Oral	Chloroform (0.5 mL/kg) + Silymarin (50mg/kg)

Animals were divided into control, negative control, standard, and ferulic acid-treated groups.

Biochemical Parameters

Blood samples were collected, and serum was analyzed for AST, ALT, ALP, GGT, total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, and globulin using standard diagnostic kits.

Histopathological Examination

Specimen liver tissues were fixed in 10% neutral buffered formalin solution and then paraffin embedded, dried by performing serial sections and finally stained with hematoxylin and eosin procedure. The resultant parts were observed under a light microscope using 100× magnification.

Statistical Analysis

The results were represented in the form of mean ± standard deviation (n=6). A one-way analysis of variance (ANOVA), preceded by the post hoc of Dunnett, was used to do statistical analyses. The value of statistically significant was determined to be $*p < 0.05$ and the difference was highly significant, which was denoted by the use of the $**p < 0.01$.

RESULTS

CCl_4-Induced Hepatotoxicity Model

Serum Biochemical Parameters

The treatment with CCl4 resulted in a significant increase in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin level compared to the control group, thus it was an indication of extensive hepatocellular damage. Ferulic acid treatment showed hepatoprotective activity through significant reduction in the levels of AST and ALP and bilirubin restoration to normal levels and was, therefore, hepatic protective similarly to a standard therapeutic agent. (Table 4).

Table 4. Biochemical Parameters of CCl_4-Induced Hepatotoxicity Model

Test	Control	Negative	Treated	Standard	Units
AST (SGOT)	58.30 ± 7.92	185.60 ± 15.24**	112.40 ± 10.35*	98.20 ± 8.45*	U/L
ALT (SGPT)	46.10 ± 5.87	96.80 ± 9.42**	48.60 ± 6.11 ns	42.30 ± 5.96 ns	U/L
GGTP	2.60 ± 0.48	1.30 ± 0.41 ns	1.45 ± 0.36 ns	1.50 ± 0.29 ns	U/L
Alkaline Phosphatase	325.40 ± 14.21	182.30 ± 16.42**	128.70 ± 11.64**	110.50 ± 9.38**	U/L
Total Bilirubin	0.18 ± 0.02	0.62 ± 0.04*	0.21 ± 0.02 ns	0.29 ± 0.03*	mg/dL
Direct Bilirubin	0.21 ± 0.02	0.10 ± 0.02 ns	0.07 ± 0.01 ns	0.06 ± 0.01 ns	mg/dL
Indirect Bilirubin	0.19 ± 0.02	0.05 ± 0.01 ns	0.03 ± 0.01 ns	0.03 ± 0.01 ns	mg/dL
Total Protein	6.40 ± 0.31	4.10 ± 0.28 ns	6.55 ± 0.22 ns	5.80 ± 0.34 ns	g/dL
Albumin	3.85 ± 0.52	2.75 ± 0.33 ns	3.40 ± 0.26 ns	2.65 ± 0.21 ns	g/dL
Globulin	2.05 ± 0.74	3.10 ± 0.62 ns	3.15 ± 0.48 ns	2.20 ± 0.19 ns	g/dL
A : G Ratio	1.88 ± 0.02	0.89 ± 0.02 ns	1.08 ± 0.03 ns	1.20 ± 0.02 ns	—

All values are expressed as Mean ± SD (Standard deviation); n=6; One-Way ANOVA followed by Tukey's test v/s Control. *p<0.05; **p<0.01; ns=Not significant.

Histopathological Findings

The treatment with CCl4 resulted in a significant increase in serum aspartate aminotransferase (AST), alanine aminotransferase

(ALT), alkaline phosphatase (ALP) and total bilirubin level compared to the control group, thus it was an indication of extensive hepatocellular damage. Ferulic acid treatment showed hepatoprotective activity through significant reduction in the levels of AST and ALP and bilirubin restoration to normal levels and was, therefore, hepatic protective similarly to a standard therapeutic agent. (Figure 1).

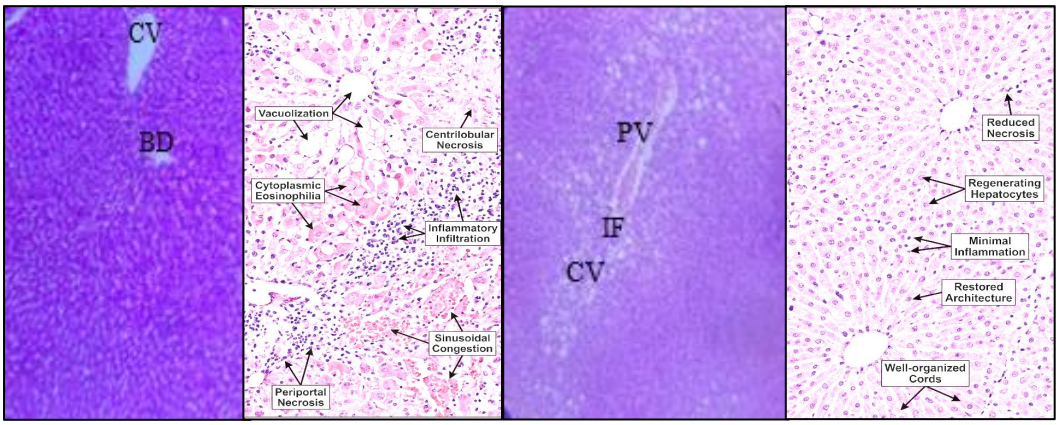

Figure 1. Histopathology of Liver Tissue in CCl4 Induced Hepatotoxicity Model (A) Control group, (B) Negative group, (C) Standard group, (D) Treated group. (CV) Central vein. (PV) Portal vein. (IF) Inflammatory infiltrate. (BD) Bile duct.

Thioacetamide-Induced Hepatotoxicity Model

Serum Biochemical Parameters

Thioacetamide exposure caused significant increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin levels. The treatment of ferulic acid resulted in substantial decrease of the AST and ALP level and normalization of bilirubin and protein parameters (Table 5).

Table 5. Biochemical Parameters of Thioacetamide-Induced Hepatotoxicity Model

Test	Control	Negative	Treated	Standard	Units
AST (SGOT)	55.90 ± 8.12	210.40 ± 18.60**	124.60 ± 12.34*	102.80 ± 9.56*	U/L
ALT (SGPT)	43.80 ± 6.05	110.70 ± 10.22**	52.40 ± 6.98 ns	44.10 ± 5.84 ns	U/L
GGTP	2.45 ± 0.50	1.20 ± 0.35 ns	1.35 ± 0.28 ns	1.42 ± 0.30 ns	U/L
Alkaline Phosphatase	310.20 ± 13.60	198.90 ± 17.21**	140.30 ± 12.18**	118.40 ± 10.46**	U/L
Total Bilirubin	0.19 ± 0.02	0.68 ± 0.05*	0.24 ± 0.03 ns	0.31 ± 0.04*	mg/dL

Direct Bilirubin	0.22 ± 0.03	0.11 ± 0.02 ns	0.09 ± 0.02 ns	0.07 ± 0.01 ns	mg/dL
Indirect Bilirubin	0.21 ± 0.02	0.06 ± 0.01 ns	0.04 ± 0.01 ns	0.03 ± 0.01 ns	mg/dL
Total Protein	6.35 ± 0.27	3.95 ± 0.30 ns	6.20 ± 0.25 ns	5.75 ± 0.32 ns	g/dL
Albumin	3.88 ± 0.60	2.60 ± 0.40 ns	3.30 ± 0.29 ns	2.70 ± 0.20 ns	g/dL
Globulin	2.00 ± 0.80	3.25 ± 0.58 ns	2.90 ± 0.50 ns	2.10 ± 0.18 ns	g/dL
A : G Ratio	1.94 ± 0.02	0.80 ± 0.02 ns	1.14 ± 0.03 ns	1.28 ± 0.02 ns	—

All values are expressed as Mean ± SD (Standard deviation); n=6; One-Way ANOVA followed by Tukey's test v/s Control. *p<0.05; **p<0.01; ns=Not significant.

Histopathological Findings

Thioacetamide-treated cohort liver sections were examined histologically and showed severe client degeneration, necrosis and inflammatory infiltration. These pathological changes were significantly and significantly prevented by administration of ferulic acid and therefore restored normal hepatic architecture (Figure 2).

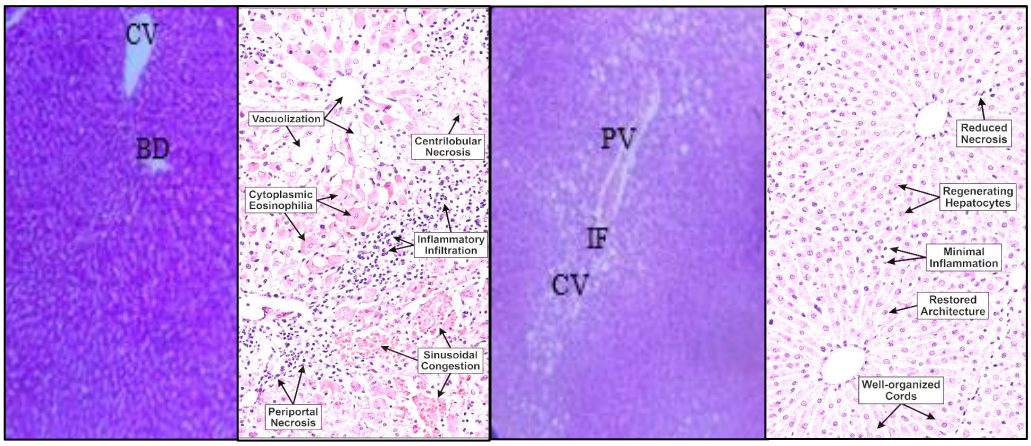

Figure 2. Histopathology of Liver Tissue in Chloroform-Induced Hepatotoxicity Model (A) Control group, (B) Negative group, (C) Standard group, (D) Treated group. (CV) Central vein. (PV) Portal vein. (IF) Inflammatory infiltrate. (BD) Bile duct.

Chloroform-Induced Hepatotoxicity Model

Serum Biochemical Parameters

Chloroform administration significantly elevated AST, ALT, ALP, and bilirubin levels. Ferulic acid treatment significantly normalized these biochemical markers, indicating hepatoprotection (Table 6).

Table 6. Biochemical Parameters of Chloroform-Induced Hepatotoxicity Model

Test	Control	Negative	Treated	Standard	Units
AST (SGOT)	57.40 ± 7.85	172.30 ± 14.60**	108.50 ± 9.92*	96.70 ± 8.31*	U/L
ALT (SGPT)	45.30 ± 6.14	88.90 ± 8.56*	46.20 ± 5.90 ns	41.80 ± 5.21 ns	U/L
GGTP	2.55 ± 0.46	1.35 ± 0.40 ns	1.40 ± 0.33 ns	1.48 ± 0.25 ns	U/L
Alkaline Phosphatase	320.80 ± 13.90	168.50 ± 15.88**	122.40 ± 10.65**	105.30 ± 9.70**	U/L
Total Bilirubin	0.18 ± 0.02	0.60 ± 0.04*	0.22 ± 0.02 ns	0.28 ± 0.03*	mg/dL
Direct Bilirubin	0.20 ± 0.02	0.09 ± 0.02 ns	0.08 ± 0.01 ns	0.06 ± 0.01 ns	mg/dL
Indirect Bilirubin	0.19 ± 0.02	0.05 ± 0.01 ns	0.03 ± 0.01 ns	0.03 ± 0.01 ns	mg/dL
Total Protein	6.38 ± 0.30	4.15 ± 0.29 ns	6.48 ± 0.26 ns	5.78 ± 0.31 ns	g/dL
Albumin	3.92 ± 0.58	2.72 ± 0.38 ns	3.42 ± 0.24 ns	2.62 ± 0.22 ns	g/dL
Globulin	2.03 ± 0.79	3.05 ± 0.60 ns	3.06 ± 0.46 ns	2.15 ± 0.17 ns	g/dL
A : G Ratio	1.93 ± 0.02	0.89 ± 0.02 ns	1.12 ± 0.03 ns	1.22 ± 0.02 ns	—

All values are expressed as Mean ± SD (Standard deviation); n=6; One-Way ANOVA followed by Tukey's test v/s Control. *p<0.05; **p<0.01; ns=Not significant.

Histopathological Findings

The hepatic tissue microscopic studies revealed centrilobular necrosis, sinusoidal dilation and inflammatory cell infiltration in the cohort which was exposed to chloroform. There was almost normal hepatic architecture in the rats which were exposed to ferulic acid, and cellular damage was slight. (Figure 3).

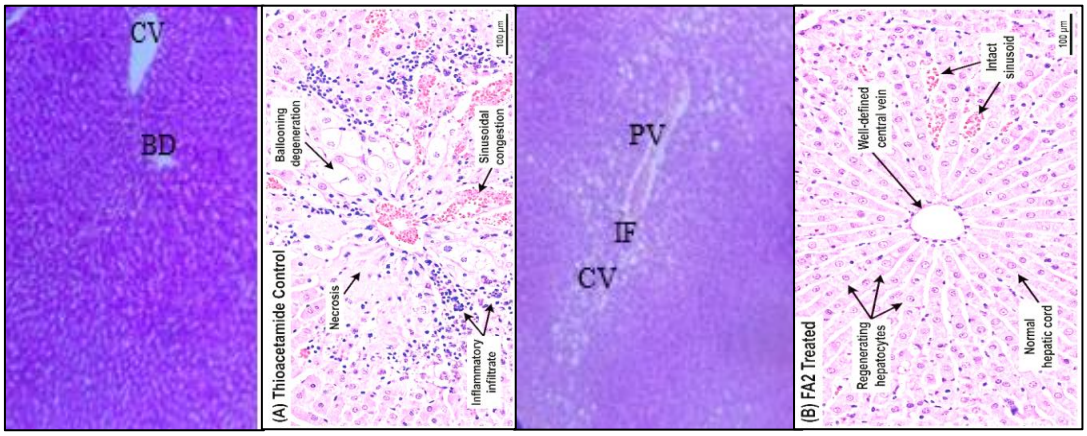

Figure 3. Histopathology of Liver Tissue in Chloroform-Induced Hepatotoxicity Model (A) Control group, (B) Negative group, (C) Standard group, (D) Treated group. (CV) Central vein. (PV) Portal vein. (IF) Inflammatory infiltrate. (BD) Bile duct.

Comparative Evaluation of Hepatotoxic Models

A comparative assessment of ferulic acid showed that hepatoprotective effects were always observed at all the three experimental models with the strongest hepatoprotective effects being observed with the carbon tetrachloride (CCl4) induced model followed by the thioacetamide and the chloroform induced models (Table 7).

Table 7. Comparative Analysis of Biochemical Parameters across Hepatotoxic Models

Models	AST	ALT	Total Bilurubin	Direct Bilirubin	Indirect Bilirubin
Paracetamol	178.4 ± 20.32**	40.12 ± 6.39ns	0.1 ± 0.01ns	0.08 ± 0.02ns	0.02 ± 0ns
Alcohol	191.8 ± 13.36**	40.12 ± 8.99ns	0.5 ± 0.01ns	0.02 ± 0ns	0.48 ± 0ns
CCl4	112.40 ± 10.35*	48.60 ± 6.11 ns	0.21 ± 0.02 ns	0.07 ± 0.01 ns	0.03 ± 0.01 ns
Thioacetamide	124.60 ± 12.34*	52.40 ± 6.98 ns	0.24 ± 0.03 ns	0.09 ± 0.02 ns	0.04 ± 0.01 ns
Chloroform	108.50 ± 9.92*	46.20 ± 5.90 ns	0.22 ± 0.02 ns	0.08 ± 0.01 ns	0.03 ± 0.01 ns

DISCUSSION

Hepatotoxicity models induced by chemicals have found extensive use in evaluation of hepatoprotective agents due to their well established etiological pathogenesis and mainly based on oxidative stress and free radical production. Lipid peroxidation, which results in liver damage, is mainly induced by exposure to carbon tetrachloride (CCl_4) and chloroform, and hepatotoxicity is caused by thioacetamide by generating reactive metabolites and eventually causing malfunction of the mitochondria (Montemayor et al., 2015).

During the current study, ferulic acid significantly reduced increases in hepatic enzymes and improved histopathological parameters in all categories of experimental models. Its antioxidant effects, ability to stabilize cell membrane integrity of the hepatocyte and inhibit lipid peroxidation probably mediate the hepatoprotective effect, which is in concurrence with previous observations of phenolic compounds (Iranshahy et al., 2018).

The hepatoprotective activity of ferulic acid with diverse chemical range of hepatotoxins suggests the potential to have wide spectrum action and supports the fact that it was used traditionally in hepatic diseases.

CONCLUSION

Isolated ferulic acid, which is a product of Acacia arabica berries had great hepatoprotective effects on rats subjected to carbon tetrachloride, thioacetamide and chloroform induced liver damage. Hepatoprotective effects were confirmed by the improvements of biochemical protocols and hepatic architecture was restored. Such results argue in favor of the capability of ferulic acid as a natural hepatoprotective agent and deserve additional molecular and clinical studies.

CONFLICT OF INTEREST

None

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