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Hepatoprotective response of *Cordia sebestena* L. fruit against simvastatin induced hepatotoxicity

[Respuesta hepatoprotectora de la fruta de *Cordia sebestena* contra la hepatotoxicidad inducida por simvastatina]

Sachin Chaudhary[1*], Ramesh Kumar Gupta[3], Mandeep Kumar Gupta[3], Harish Chandra Verma[3], Hitesh Kumar[3], Amit Kumar[4], Sudhansu Ranjan Swain[3], Abdel-Nasser El-Shorbagi[1,2]

[1]Department of Medicinal Chemistry, College of Pharmacy, University of Sharjah, Sharjah-27272, United Arab Emirates.
[2]Faculty of Pharmacy, University of Assiut, Assiut-71526, Egypt.
[3]Moradabad Educational Trust, Group of Institutions, Faculty of Pharmacy, Moradabad-244001, Uttar Pradesh, India.
[4]School of Pharmaceutical Sciences, IIMT University, Meerut-250002, Uttar Pradesh, India.
*E-mail: schaudhary@sharjah.ac.ae

Abstract

Context: *Cordia sebestena* fruits are traditionally used to treat wounds, boils, tumors, gout, ulcer, flu, fever, asthma, menstrual cramps, dysentery, diarrhea, headache, snakebite and liver disorders. However, information on hepatoprotective potential of *Cordia sebestena* fruit has not been reported in the research.

Aims: To evaluate the hepatoprotective effect of the ethanolic extract of *Cordia sebestena* fruit (CSFE) against simvastatin-induced hepatotoxicity in rats.

Methods: After authentication of fruit, its ethanolic extract was collected. Hepatotoxicity was induced by simvastatin in rodents. Hepatoprotective potential of CSFE was evaluated at 200 and 400 mg/kg, body weight by determining the altered levels of biochemical parameters like serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), cholesterol, bilirubin, urea, albumin, total protein and hematological indices including red blood cells (RBC), white blood cells (WBC), hemoglobin (Hb), platelets, and lymphocytes along with the impact on body and liver weight of treated rats.

Results: The treatment with CSFE at 200 mg/kg and 400 mg/kg, significantly at ($p<0.05$, $p<0.001$) and dose-dependently reversed simvastatin-induced altered level of SGOT, SGPT, cholesterol, urea, total bilirubin and restored the total protein and albumin level in rodents. Hematological indices also were significantly ameliorated at both the doses of CSFE. Histopathological study revealed the regeneration of hepatocytes.

Conclusions: The *Cordia sebestena* fruit extract (CSFE) at dose of 400 mg/kg reversed liver deteriorations induced by simvastatin in rats, therefore manifesting its traditional use as hepatoprotector. Future studies should be performed for isolating biologically active phytoconstituents.

Keywords: cholesterol; *Cordia sebestena*; hepatotoxicity; serum glutamic oxaloacetic transaminase; serum glutamic pyruvic transaminase; simvastatin.

Resumen

Contexto: Las frutas de *Cordia sebestena* se utilizan tradicionalmente para tratar heridas, forúnculos, tumores, gota, úlcera, gripe, fiebre, asma, calambres menstruales, disentería, diarrea, dolor de cabeza, mordedura de serpiente y trastornos hepáticos. Sin embargo, no se ha investigado sobre el potencial hepatoprotector de esta fruta.

Objetivos: Evaluar el efecto hepatoprotector del extracto etanólico de fruta de *Cordia sebestena* (CSFE) contra la hepatotoxicidad inducida por simvastatina en ratas.

Métodos: Después de la autenticación de la fruta, se realizó su extracto etanólico. La hepatotoxicidad fue inducida por simvastatina en roedores. El potencial hepatoprotector de CSFE se evaluó a 200 y 400 mg/kg, peso corporal determinando los niveles alterados de parámetros bioquímicos como transaminasa oxaloacética glutámica sérica (SGOT), transaminasa piruvica glutámica sérica (SGPT), colesterol, bilirrubina, urea, albúmina, proteína total e índices hematológicos, incluidos los glóbulos rojos (RBC), glóbulos blancos (WBC), hemoglobina (Hb), plaquetas y linfocitos, junto con el impacto en el peso corporal y hepático de las ratas tratadas.

Resultados: El tratamiento con CSFE a 200 mg/kg y 400 mg/kg, revertió significativamente, y de manera dependiente de la dosis, los niveles alterados de SGOT, SGPT, colesterol, urea, bilirrubina total inducidos por simvastatina, restaurado los niveles totales de proteína y albúmina en roedores. Los índices hematológicos también mejoraron significativamente ($p<0.05$, $p<0.001$) en ambas dosis de CSFE. El estudio histopatológico reveló la regeneración de los hepatocitos.

Conclusiones: El extracto de fruta de *Cordia sebestena* (CSFE) a una dosis de 400 mg/kg protegió del deterioro hepático inducido por simvastatina en ratas, manifestando así su uso tradicional como hepatoprotector. Se deben realizar estudios futuros para aislar fitoconstituyentes biológicamente activos.

Palabras Clave: colesterol; *Cordia sebestena*; hepatotoxicidad; transaminasa glutámica oxaloacética sérica; simvastatina; transaminasa pirúvica glutámica sérica.

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INTRODUCTION

Plant derived drugs have imperative vicinity in both traditional and modern medicine (Mohamed and El-Shorbagi, 1993; Abdel-Moty et al., 1998; Chaudhary and Pal, 2011; Chaudhary et al., 2016a;b; Chaudhary et al., 2018). The World Health Organization (WHO) reported that 80% of the global inhabitants trust primarily on traditional medicines for their primary health care interventions, and significantly traditional therapy is associated with the use of plant extracts or their active phytoconstituents (Akerele, 1993; Aboul-Fadl and El-Shorbagi, 1997; Chaudhary and Kumar, 2014; El-Shorbagi et al., 2018). Relatively, 7000 natural compounds are presently used in novel medicines; predominantly of these had been pre-owned in traditional use. The universal market value of plant derived products exceeds 100 billion dollars annually (Sofowora et al., 2013).

Despite of augmentation in developing bioactive agents to treat protracted illness, the applicability of herbal products for treatment of chronic diseases resumes to flourish (Chaudhary et al., 2010; El-Shorbagi et al., 2015; Chaudhary et al., 2016a;b; El-Shorbagi et al., 2019; Soliman et al., 2019).

Liver is the vivid organ, involved in detoxification of chemicals and metabolism of drugs and food in the body. It secrets bile and enforce protein synthesis essential for blood clotting and other vital functions (Gupta et al., 2012; Chaudhary et al., 2018; El-Toumy et al., 2019). Globally, liver disease is documented for comparatively two million deaths annually, one million due to complexity of cirrhosis and one million due to viral hepatitis and hepatocellular carcinoma. The specific liver diseases accommodate alcohol-associated liver disease (AALD), non-alcoholic fatty liver disease (NAFLD), hepatitis A, B, C, D, and E, autoimmune hepatitis, hepatocellular carcinoma (Eddouks et al., 2014; Farghali et al., 2015; Asrani et al., 2019, Gupta et al., 2019). Extensive research on liver diseases, concluded in development of numerous hepatoprotective drugs. It has been reported that more than one hundred plants with 58 compounds classified into appropriate chemical groups were addressed. Therefore, these plants are attractive targets for future studies, and the identification of their active constituents will probably lead to new therapies for liver disease (Farghali et al., 2015).

Cordia sebestena L., popularly termed as Geiger tree, is a flowering plant belonging to the family *Boraginaceae*. Around 300 species are located broadly in East Africa, Mexico, West Indies, Central America, Sri Lanka, India, and Nigeria. The majority of the species of the genus *Cordia* have been used to treat wounds, boils, tumors, gout, ulcer. Traditionally, the decoction of leaves of several species is used in the treatment of flu, fever, cough, cold, asthma, menstrual cramps, dysentery, diarrhea, headache, snakebite and as tonic. Bark is used as an astringent and liver stimulant. The root decoction is used to treat tuberculosis, bronchitis, and malaria. The fruits of the trees from the same genus are used as demulcent and blood purifier (Oza and Kulkarni, 2017; Chaudhary et al., 2019). The present research determined the hepatoprotective potential of its fruit extract (CSFE) employing simvastatin induced hepatotoxicity in rodents.

MATERIAL AND METHODS

Chemicals

All the chemicals and reagents used were of laboratory reagent grade, purchased from Himedia Laboratories Private Limited, Mumbai, India.

Collection and authentication of fruit

Fresh and matured fruits were collected from the roadside garden of College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates (25°18'18.5"N 55°29'09.9"E). Prof. Sudhansu Ranjan Swain, Director, Department of Pharmacognosy, Moradabad Educational Trust, Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh, India, attained identification and authentication. The voucher specimen number (HGFOP 225) was submitted for future reference.

Extraction

Fresh and matured (500 g) fruits of *Cordia sebestena* were dried and powdered at room temperature (25-28°C). The powdered plant fruit material was macerated in petroleum ether (3 x 1000 mL) at room temperature for 1 days, the marc was exhaustively extracted with ethyl alcohol for 3 days. The extract was dried by rotatory evaporator (Buchi, U.S.A) under reduced pressure and procured in desiccator for further pharmacological investigation. The percentage yield was estimated to be 0.72%.

Animals

Wistar albino rats (150-170 g) of either sex were procured from animal house of Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh, India. They were kept in departmental animal house in well cross ventilated room at 22 ± 2°C with light and dark cycles of 12 h for 1 week before and during the experiments. The experiment was carried out in accordance to the guidelines mentioned in the CPCSEA, and Institutional Animal Ethical Committee, India (Reg. No. 1867/PO/RE/S/16/CPCSEA).

Acute oral toxicity study

The acute toxicity of CSFE was figured out at doses of 5, 50, 300, 500, and 2000 mg/kg, conceding the OECD 423 guidelines (2002) (Chaudhary et al., 2016a;b), and dose of 2000 mg/kg illustrated lethal manifestations. Therefore, in agreement with OECD guideline 423 (2002), it is represented as a LD_{50} cutoff value. Doses 200 and 400 mg/kg, body weight, were preferred for pharmacological investigation by fixed-dose methods (Chaudhary et al, 2018).

Systematizing of animals for hepatoprotective studies

Wistar albino rats (150-170 g) of either sex were divided into five different groups, each group having 6 rats. Group-I rats, termed as normal control received distilled water for 30 days, orally. Group-II rats, termed as toxicant control were administered with simvastatin (20 mg/kg, *p.o.)* alone for 30 days orally. Group-III and IV rats received simvastatin along with CSFE, 200 mg/kg and 400 mg/kg, *p.o.* respectively for 30 day as these doses represented no lethal manifestations and Group-V rats, termed as standard control received simvastatin along with silymarin (20 mg/kg, *p.o.*) for 30 days. On the 31st day, blood samples were collected, and all the animals were sacrificed by cervical dislocation under mild ether anesthesia and liver sample were harvested, rinsed in saline and stored at -80°C for further hematological analysis (Gupta et al., 2018).

Assessment of hepatoprotective activity

The collected blood sample was allowed to clot and serum was separated by centrifugation in a refrigerated table top centrifuge at 2500 rpm for 15 min and the biochemical parameters like serum glutamic oxaloacetic transaminase (SGOT, U/L), serum glutamic-pyruvic transaminase (SGPT, U/L) (Shakeel and Jabeen, 2016), cholesterol (CHL, mg/dL) (Janckila and Yam, 2009), urea (mg/dL), bilirubin (mg/dL) (Malloy and Evelyn, 1937), total protein and albumin were determined (Lowry et al., 1951; Verma et al., 2011).

Assessment of hematological components

Hematological indices like red blood cells (RBC) counts, Hemoglobin (Hb), platelets (PLT) counts, White blood cells (WBC) counts, and % lymphocytes counts were determined using hematology analyzer SB21, New Delhi, India.

Body weight and liver weight in rats

On 31st day of study, all the animals were sacrificed by cervical dislocation under mild ether anesthesia and liver was dissected out and weighed using analytical balance (ME54T, Mettler Toledo India Private Limited, Mumbai, India).

Histopathology

For histopathological studies, the liver tissues were affixed with 10% phosphate buffered neutral formalin, dehydrated in graded (50-100%) alcohol and embedded in paraffin. Fine sections (5 µM)

were cut using rotatory microtome (AMR 400, Amos Scientific, Australia) and stained with routine hematoxylin and eosin (H&E). The liver sections were investigated for photo microscopic analysis (Nikon Eclipse E400 microscope with digital camera, USA).

Statistical analysis

The statistical comparison between the groups were made by one-way ANOVA, followed by Student-Newman-Keul's test using Graph Pad Prism 5.0 Software. The value $p<0.05$ was considered statistically. The values were represented as mean ± SEM for six rats.

RESULTS

Outcome of acute oral toxicity study

The ethanolic CSFE did not show any sign of mortality up to a dose of 400 mg/kg *p.o.* in experimental animals. Hence, doses of 200 mg/kg and 400 mg/kg body weight were used for hepatoprotective studies.

Outcome of CSFE on serum hepatic status

The results (Table 1) narrated that CSFE at dose of 400 mg/kg, body weight treated rats exhibited the significant escalation of liver serum markers like the SGOT, SGPT, cholesterol (CHL), bilirubin (BLB), urea levels while downturn in the total protein (TP) and albumin (ALB) level. The rats treated with CSFE at 200 mg/kg and CSFE at 400 mg/kg demonstrated, the significant depreciation in the SGOT, SGPT, CHL, bilirubin (BLB), urea levels while enhanced the level of total protein and albumin in dose dependent manner. The effect two different doses of CSFE were studied on serum marker enzymes and total bilirubin in simvastatin intoxicated animals. Hepatic injury induced by simvastatin caused significant transformation in marker enzyme as SGOT by 160.75%, SGPT by 95.10%, CHL by 129.06%, BLB by 227.11%, urea by 45.26%, ALB by 33.43%, and total protein by 72.55% as compared to Group-I. The percentage protection in the marker enzyme of treated group at CSFE 200 mg/kg, for SGOT was 9.51 ($p<0.05$), SGPT 20.39 ($p<0.01$), CHL 13.31 ($p<0.001$), BLB 12.95 ($p<0.01$) urea 8.66 ($p<0.001$), ALB 4.52 ($p<0.01$) and for total protein was 79.06 ($p<0.001$) compared to Group-II. The pre-eminent percentage protection in marker enzymes was noticed at the dose of CSFE 400 mg/kg, and silymarin (20 mg/kg) as SGOT 30.29 ($p<0.001$), 40.41 ($p<0.001$), SGPT 29.03 ($p<0.001$), 44.77 ($p<0.001$), CHL 23.22 ($p<0.001$), 47.74 ($p<0.001$), BLB 47.66 ($p<0.001$), 59.06 ($p<0.001$), urea 23.05 ($p<0.001$), 28.68 ($p<0.001$), ALB 34.84 ($p<0.001$), 45.24 ($p<0.001$), and total protein 131 ($p<0.001$), 141.08 ($p<0.001$) respectively, which is almost comparable to the Group-V.

Outcome of CSFE on hematological parameters in rats

Table 2 enclosed the outcome of CSFE at 200 mg/kg and 400 mg/kg, along with standard drug on hematological parameters of simvastatin induced hepatotoxicity in rodents. The significant devaluation in the levels of RBC, Hb, PLT and elevation in the levels of WBC and % lymphocytes was discovered in Group-II. CSFE at both doses significantly intensified the levels of RBC, Hb, PLT and the level of WBC's and % lymphocytes was significantly maintained to normal range.

Outcome of CSFE on body weight and liver weight in rats

The outcome of CSFE at 200 mg/kg and 400 mg/kg, was inspected on body weight and liver weight of experimental rats. The results in Table 3, demonstrated that in Group-II, the body weight was depreciated by 2.81% while liver weight was enhanced by 39.42% compared to Group-I. Rats treated with CSFE at the doses of 200 mg/kg and 400 mg/kg significantly boost the body weight by 1.07% ($p<0.05$), 2.02% ($p<0.05$) and liver weight was declined by 5.14% ($P<0.01$) and 22.62% ($p<0.001$), respectively compared to Group-II. The results also expressed that % ratio of liver weight to body weight was elevated in toxicant control (Group-II) as compared to normal control (Group-I), However, pretreatment with CSFE at 200 mg/kg and 400 mg/kg, offered significant protec-

tion against simvastatin induced hepatic damage by reversing the % ratio of liver to body weight.

Histopathological studies

The liver section of Group-I (Fig. 1A) exhibited normal histology with conventional hepatocytes. The liver section of Group-II (Fig. 1B) presented hydropic degeneration, necrosis and cellular infiltration around central vein. The liver section of Group-III (Fig. 1C) displayed less fatty degeneration of hepatocytes and modest dilation of sinusoids. The liver section of Group-III (Fig. 1D) demonstrated relatively normal histoarchitecture, infinitesimal cellular infiltration around central vein and regeneration of hepatocytes. The liver section of Group-IV (Fig. IE) showed natural cellular architecture of hepatocytes.

Table 1. Consequence of CSFE on serum enzymes and biochemical indices against simvastatin induced liver toxicity in rats.

Groups	SGOT (U/L)	SGPT (U/L)	CHL (mg/dL)	BLB (mg/dL)	UREA (mg/dL)	ALB (mg/dL)	TP (mg/dL)
Group-I	34.20 ± 1.8	26.34 ± 1.3	101.50 ± 3.4	0.59 ± 0.03	6.12 ± 0.01	3.32 ± 0.01	4.70 ± 0.02
Group-II	89.23 ± 3.1†	51.39 ± 1.7†	232.50 ± 4.2†	1.93 ± 0.09†	8.89 ± 0.05†	2.21 ± 0.04†	1.29 ± 0.03†
Group-III	80.74 ± 2.5[a]	40.91 ± 2.1[b]	201.50 ± 5.6[c]	1.68 ± 0.06[b]	8.12 ± 0.08[c]	2.31 ± 0.08[b]	2.31 ± 0.04[c]
Group-IV	62.20 ± 3.1[c]	36.47 ± 2.3[c]	178.50 ± 4.6[c]	1.01 ± 0.03[c]	6.85 ± 0.07[c]	2.98 ± 0.04[c]	2.98 ± 0.01[c]
Group-V	49.60 ± 2.4[c]	28.38 ± 2.4[c]	121.50 ± 3.6[c]	0.79 ± 0.04[c]	6.34 ± 0.04[c]	3.21 ± 0.03[c]	3.11 ± 0.03[c]

Values are mean ± S.E.M. of 6 rats in each group, n: non-significant. P values: †<0.001 compared with respective control group (Group-I). P values: [a]<0.05, [b]<0.01, [c]<0.001 compared with (Group-II). SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; CHL: cholesterol; BLB: bilirubin; ALB: albumin; TP: total protein; Group-I: normal control received distilled water; Group-II: simvastatin 20 mg/kg; Group-III: simvastatin plus CSFE 200 mg/kg; Group-IV: simvastatin plus CSFE 400 mg/kg; Group-V: simvastatin plus silymarin 20 mg/kg. All treatments were administered p.o. for 30 days.

Table 2. Consequence of CSFE on the hematological indices in rats.

Parameters	Group-I	Group-II	Group-III	Group-IV	Group-V
RBC (x10^{12})	7.60 ± 0.01	5.98 ± 0.02	6.09 ± 0.03[b]	8.40 ± 0.02[c]	7.90 ± 0.04[c]
Hb (g/dL)	13.01 ± 0.20	10.34 ± 0.01†	10.98 ± 0.02[c]	12.07 ± 0.03[c]	12.78 ± 0.04[c]
PLT (x10^9/L)	613.20 ± 5.60	542.70 ± 4.70†	562.60 ± 3.20[b]	598.70 ± 4.30[c]	601.50 ± 5.10[c]
WBC (x10^9)	8.30 ± 0.10	13.70 ± 0.60†	11.98 ± 0.40[b]	9.20 ± 0.30[c]	9.04 ± 0.20[c]
Lymphocytes (%)	42.60 ± 2.20	68.35 ± 3.20†	61.68 ± 3.40[ns]	54.37 ±2.90[c]	42.26 ± 3.10[c]

Values are mean ± S.E.M. of 6 rats in each group, ns: non-significant. P values: †<0.001 compared with respective control group (Group-I). P values: [a]<0.05, [b]<0.01, [c]<0.001 compared with (Group-II); ns: non-significant. RBC: red blood cells; Hb: hemoglobin; PLT: platelets; WBC: white blood cells counts. Group-I: normal control received distilled water; Group-II: simvastatin 20 mg/kg; Group-III: simvastatin plus CSFE 200 mg/kg; Group-IV: simvastatin plus CSFE 400 mg/kg; Group-V: simvastatin plus silymarin 20 mg/kg. All treatments were administered p.o. for 30 days.

Table 3. Consequence of CSFE on body weight and liver weight against simvastatin induced liver toxicity in rats.

Treatment	Body weight (g)	Liver weight (g)	Liver/body weight ratio (%)
Group-I	152.6 ± 0.03	2.79 ± 0.01	1.82 ± 0.02
Group-II	148.3 ± 0.04†	3.89 ± 0.04†	2.62 ± 0.01†
Group-III	149.9 ± 0.06[a]	3.69 ± 0.06[b]	2.46 ± 0.01[a]
Group-IV	151.3 ± 0.04[b]	3.01 ± 0.03[c]	1.98 ± 0.03[b]
Group-V	151.9 ± 0.06[c]	2.91 ± 0.02[c]	1.91 ± 0.02[c]

Values are mean ± S.E.M. of 6 rats in each group, P values: †<0.001 compared with respective control group (Group-I). P values: [a]<0.05, [b]<0.01, [c]<0.001 compared with (Group-II). Group-I: normal control received distilled water; Group-II: simvastatin 20 mg/kg; Group-III: simvastatin plus CSFE 200 mg/kg; Group-IV: simvastatin plus CSFE 400 mg/kg; Group-V: simvastatin plus silymarin 20 mg/kg. All treatments were administered p.o. for 30 days.

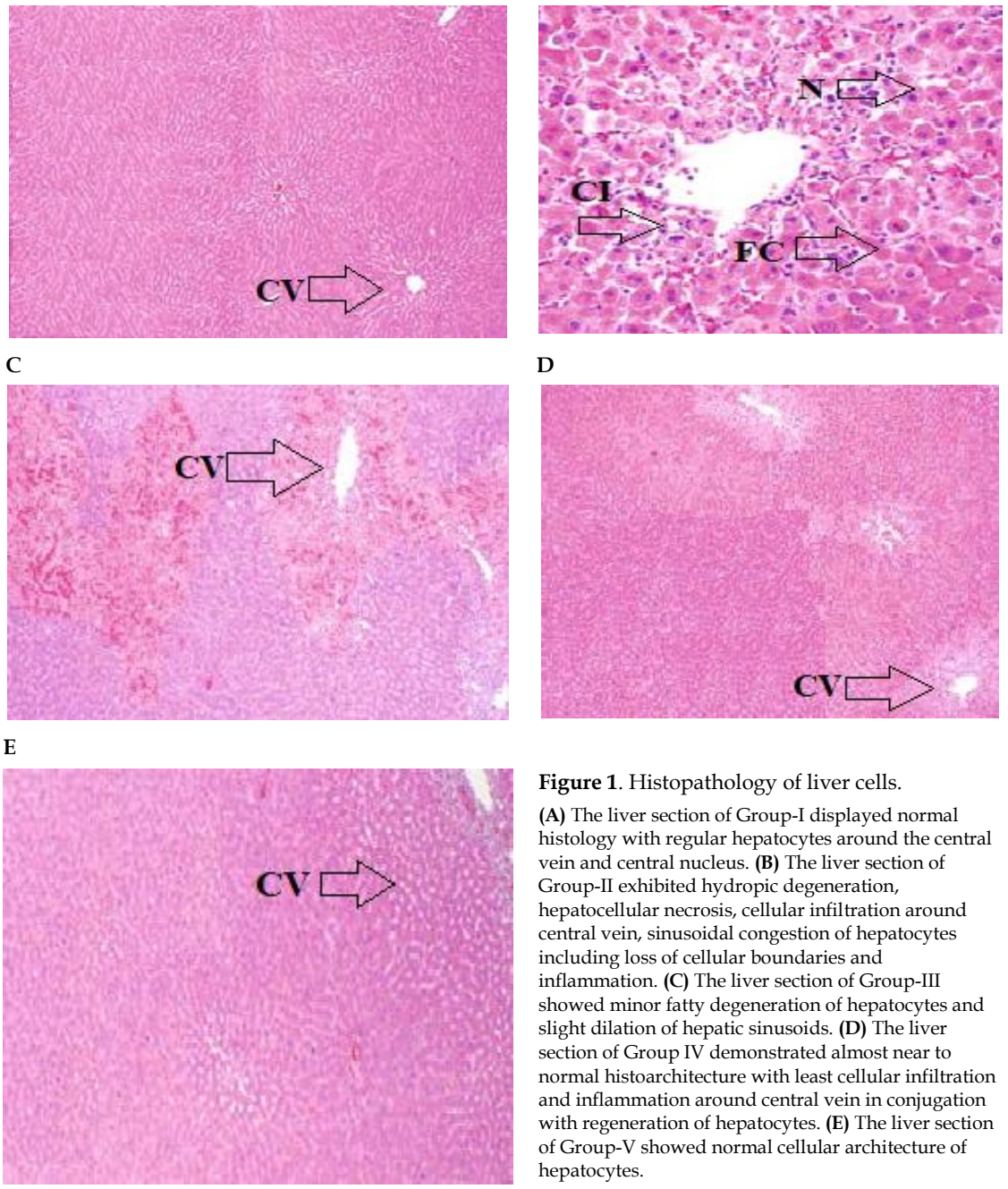

Figure 1. Histopathology of liver cells.

(A) The liver section of Group-I displayed normal histology with regular hepatocytes around the central vein and central nucleus. **(B)** The liver section of Group-II exhibited hydropic degeneration, hepatocellular necrosis, cellular infiltration around central vein, sinusoidal congestion of hepatocytes including loss of cellular boundaries and inflammation. **(C)** The liver section of Group-III showed minor fatty degeneration of hepatocytes and slight dilation of hepatic sinusoids. **(D)** The liver section of Group IV demonstrated almost near to normal histoarchitecture with least cellular infiltration and inflammation around central vein in conjugation with regeneration of hepatocytes. **(E)** The liver section of Group-V showed normal cellular architecture of hepatocytes.

Histopathology was performed by mean of H&E stained sections of liver at 100×. CV: Central vein; CI: Cellular infiltration; N: Necrosis; FC: Fatty changes. Group-I: normal control received distilled water; Group-II: simvastatin 20 mg/kg; Group-III: simvastatin plus CSFE 200 mg/kg; Group-IV: simvastatin plus CSFE 400 mg/kg; Group-V: simvastatin plus silymarin 20 mg/kg. All treatments were administered p.o. for 30 days.

DISCUSSION

Simvastatin (HMG-CoA) reductase inhibitor has been proclaimed to cause acute hepatotoxicity, the projected mechanism for this cause depends on the outcome on cytochrome P-450 system, impairment of bile acid transport process, immune mediated inflammatory response to drug or its metabolites, and oxidative stress caused by intracellular damage (Bharadwaj and Chalasani, 2007; Gupta et al., 2018). The enzymes SGOT and SGPT catalyze the transfer of α-amino group from aspar-

tate and alanine to α-keto group of ketoglutamic acid to generate oxaloacetic and pyruvic acids, that are vital contributors to TCA cycle (citric acid cycle). Liver injury, either acute or chronic, ultimately resulted in an increase in serum concentrations of SGOT and SGPT enzymes that conclusively leads to high serum cholesterol level causing primary biliary cirrhosis (PBC). The maximum inflation occurs in severe viral hepatitis, drug or toxin induced hepatic necrosis and circulatory shock. Therefore, the increased levels of SGOT and SGPT along with serum cholesterol justified the hepatic cellular destruction and liver cirrhosis. Bilirubin is the product of hemoglobin catabolism within the reticuloendothelial system. Heme breakdown determines the formation of unconjugated bilirubin, which is further transported to liver. In the liver, UDP-glucuronyltransferase conjugates the water insoluble unconjugated bilirubin to glucuronic acid, and conjugated bilirubin is further excreted into bile. The level of bilirubin may increase because of augmented bilirubin production or decreased hepatic uptake or conjugation, normally bilirubin level is increased in hepatobiliary disease. Albumin is the most crucial protein in plasma synthesized by the liver and is helpful indicator of liver function. The hepatic synthesis of albumin contributes to decrease during the liver disease (Giannini et al., 2005; Thapa and Walia, 2007). In our study, the results (Table 1) illustrated that the administration of simvastatin in rats resulted in an escalation in levels of SGOT, SGPT, cholesterol, bilirubin, urea in Group-II relative to Group-I animals and the same resulted in depreciation in the levels of albumin and total protein. The animals treated with CSFE at 400 mg/kg, significantly reduced SGOT, SGPT, cholesterol, bilirubin and urea levels while increased the total protein and albumin levels in dose dependent manner as compared to simvastatin along with silymarin treated animals (Group-V).

The abnormalities in hematological indices are frequent in hepatic cirrhosis. Anemia, thrombocytopenia, and leukopenia are affiliated with liver disease. Liver performs a vital role both in hematopoiesis with hemostasis, it is a storage organ for vitamin B_{12} and folic acid, which are essential for the maturation of RBC's and WBC's. It secretes transferrin, which is required for transport of iron from the site of absorption to bone marrow for the synthesis of heme and RBC's production (Qamar and Grace, 2009). CSFE at 400 mg/kg, resulted in significant increase in the RBC's, and hemoglobin levels as compared to control, therefore a patient may consume *Cordia sebestena* fruit in anemic state. This outcome of *Cordia sebestena* fruit may be credited to the initiation of the haemopoietic pathway due to the stimulation of erythropoietin hormone, which is released by the kidney and this hormone stimulate the pluripotent stem cell of red bone marrow. Liver is responsible for synthesis of thrombopoietin, a hematopoietic growth factor that effect platelet count, liver disease contributes to decline thrombopoietin levels that ultimately resulted to cause thrombocytopenia (Marks, 2013). CSFE at dose of 400 mg/kg, significantly increased the platelets counts and it may be due to stimulation of thrombopoietin hormone, which was produced by kidney and liver and is claimed to possess hemostatic aptitude. Hence, *Cordia sebestena* fruit can be practiced to treat dengue as well. Immune system is the defense mechanism of the body against toxic agents facilitated by lymphocytes, during a pathogenic attack its level is increased, the elevated levels of WBC's and lymphocytes suggested that CSFE challenge the immune system of the animals.

In our research, the comparison between body weight and liver weight of treated and untreated rats was performed to figure out the toxicological outcome of the test drugs. The results in (Table 3) revealed that the body and liver weight differed significantly in simvastatin treated group and normal control group. Pre-treatment with CSFE at 200 mg/kg and 400 mg/kg has reversed significantly the increased liver to body weight ratio. Liver histopathological images validated that CSFE declined the hepatocellular necrosis largely and minimized inflammatory cells infiltration; this may be attributed to its liver protective outcome. Nevertheless, additional future investigations are required to conclude the accurate mechanism for hepatoprotective effect of *Cordia sebestena* fruit.

CONCLUSIONS

This research established that CSFE principally at 400 mg/kg dose was competent in reversing liver deteriorations resulted by simvastatin induced hepatotoxicity in rats. Further studies of the extract isolation of the biologically active phyto-constituents is extremely suggested.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

Abdel-Moty SG, Sakai S, Aimi N, Takayama H, Kitajima M, El-Shorbagi A, Ahmed AN, Omar NM (1998) Synthesis of cytotoxic 1-polyhydroxyalkyl-β-carboline derivatives. Eur J Med Chem 32: 1009–1017.

Aboul-Fadl T, El-Shorbagi AN (1997) New carriers for representative peptides and peptide drugs. Arch Pharm 330: 327–332.

Akerele O (1993) Nature's medicinal bounty: don't throw it away. World Health Forum 14: 390–395.

Asrani SK, Devarbhavi H, Eaton J, Kamath PS (2019) Burden of liver diseases in the world. J Hepatol 70: 151–171.

Bharadwaj SS, Chalasani N (2007) Lipid-lowering agents that cause drug-induced hepatotoxicity. Clin Liver Dis 11: 597–613.

Chaudhary S, Gupta RK, Kumar A, Tarazi H (2018) Hepatoprotective and antitubercular potential of *Nyctanthes arbor-tristis* L. leaves against antitubercular drug induced hepatotoxicity. J Pharm Pharmacogn Res 6: 205–215.

Chaudhary S, Hisham H, Mohamed D (2018) A review on phytochemical and pharmacological potential of watercress plant. Asian J Pharm Clin Res 11: 102–107.

Chaudhary S, Kumar A (2014) Phytochemical analysis and assessment of *in-vitro* anthelmintic activity of *Cassia auriculata* linn leaves. Am J Phytomed Clin Ther 2: 161–167.

Chaudhary S, Kumar S, Tarazi H (2016a) Peptide derivatives of 1,2-dihydro-3-methyl-2-oxoquinoxaline-6-carboxilic acid: synthesis and evaluation of antimicrobial, antifungal and antiviral potential. Pharm Chem J 50: 281–288.

Chaudhary S, Negi A, Dahiya V (2010) The study of *in vitro* antimicrobial activity and phytochemical analysis of some medicinal plants in Chamoli Garhwal region. Pharmacogn J 2: 481–485.

Chaudhary S, Pal A (2011) Indian medicinal plants used in liver disease: a short review. Pharmacogn J 3: 91–94.

Chaudhary S, Semwal A, Kumar H, Verma HC, Kumar A (2016b) *In-vivo* study for anti-hyperglycemic potential of aqueous extract of basil seeds (*Ocimum basilicum* Linn) and its influence on biochemical parameters, serum electrolytes and haematological indices. Biomed Pharmacother 84: 2008–2013.

Chaudhary S, Verma HC, Gupta MK, Kumar H, Swain SR, Gupta RK, El-Shorbagi AN (2019) Antidiabetic aptitude of *Cordia sebestena* and its outcome on biochemical parameters, serum electrolytes, and hematological markers. Pharmacogn J 11: 418–423.

Eddouks M, Chattopadhyay D, De Feo V, Cho WC (2014) Medicinal plants in the prevention and treatment of chronic diseases 2013. Evid Based Complement Alternat Med 2014: 1–3.

El-Shorbagi AA, Abdel-Moty S.G, Ahmed AN, Takayama H, Kitajima M, Aimi N, Sakai S (2015) The antiviral (RNA & DNA) profile of some incomplete C-nucleosides inspired from natural β-carboline (pyrido [3,4-b] indole) scaffold; pharmacology of the intermediates in the total synthesis. Der Pharma Chem 7: 87–92.

El-Shorbagi AN, Chaudhary S (2019) Monobactams: a unique natural scaffold of four-membered ring skeleton, recent development to clinically overcome infections by multidrug resistant microbes. Lett Drug Des Discov 16: 1305–1320.

El-Shorbagi AN, El-Naggar M, Tarazi H, Chaudhary S, Abdu-Allah H, Hersi F, Omar H (2018) Bis-(5-substituted-2-thiono-1,3,5-thiadiazinan-3-yl) butane as a scaffold of anti-proliferative activity, blended by a multicomponent process. Med Chem Res 27: 1103–1110.

El-Toumy SAH, Salib JY, Shafik NH, Elkarim ASA, Salama A, Omara EAA, Micky J (2019) Evaluation of hepatoprotective activity of *Polygonum equisetiforme* methanolic extract. J Appl Pharm Sci 9: 54–59.

Farghali H, Canova NK, Zakhari S (2015) Hepatoprotective properties of extensively studied medicinal plant active constituents: possible common mechanisms. Pharm Biol 53: 781–791.

Giannini EG, Testa R, Savarino V (2005) Liver enzyme alteration: a guide for clinicians. CMAJ 172: 397–379.

Gupta RK, Chaudhary S, Vaishali, Singh RK (2012) Antihepatotoxic influence of aqueous extract of *Ipomoea carnea* against carbon tetrachloride induced acute liver toxicity in experimental rodents. Asian J Pharm Clin Res 5: 262–265.

Gupta RK, Swain SR, Sahoo J, Chaudhary S, Gupta A (2019) Isolation, characterization and hepatoprotective activity of naturally occurring protopine against simvastatin

induced liver toxicity in experimental rodents. Curr Bioact Comp 15: https://doi.org/10.2174/1573407215666190211151306

Gupta RK, Swain SR, Sahoo J, Gupta A, Chaudhary S (2018) Hepatoprotective potential of *Trichosanthes dioica* Roxb in hepatotoxicity induced by simvastatin and its consequences on biochemical and haematological indices. Pharmacogn J 10: 720–724.

Janckila AJ, Yam LT (2009) Biology and clinical significance of tartrate-resistant acid phosphatases: New perspectives on an old enzyme. Calcif Tissue Int 85: 465–483.

Lowry OH, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. J Biol Chem 193: 265–275.

Malloy HT, Evelyn KA (1937) The determination of bilirubin with the photoelectric colorimeter. J Biol Chem 119: 481–490.

Marks PW (2013) Hematologic manifestations of liver disease. Semin Hematol 50: 216–221.

Mohamed MH, El-Shorbagi AN (1993) (±)-Termisine, a novel lupine alkaloid from the seeds of *Lupinus termis*. J Nat Prod 56: 1999–2002.

OECD - The Organisation for Economic Co-Operation and Development (2002) Guidelines for the testing of chemicals/section 4: Health effects test no. 423: Acute oral toxicity-acute toxic class method, OECD, Paris, France.

Oza MJ, Kulkarni YA (2017) Traditional uses, phytochemistry and pharmacology of the medicinal species of the genus *Cordia* (Boraginaceae). J Pharm Pharmacol 69: 755–789.

Qamar AA, Grace ND (2009) Abnormal hematological indices in cirrhosis. Can J Gastroenetrol 23: 441–445.

Shakeel M, Jabeen F (2016) Toxic effects of titanium dioxide nanoparticles and titanium dioxide bulk salts in the liver and blood of male Sprague-Dawley rats assessed by different assay. Bio Trace Elem Res 173: 405–426.

Sofowora A, Ogunbodede E, Onayade A (2013) The role and place of medicinal plants in the strategies for disease prevention. Afr J Tradit Complement Altern Med 10: 210-229.

Soliman S, Hamoda AM, El-Shorbagi ANA, El-Keblawy AA (2019) Novel betulin derivative is responsible for the anticancer folk use of *Ziziphus spina-christi* from the hot environmental habitat of UAE. J Ethnopharmacol 231: 403–408.

Thapa BR, Walia A (2007) Liver function tests and their interpretation. Ind J Pediat 74: 663–671.

Verma N, Singh AP, Amresh G, Sahu PK, Rao CV (2011) Protective effect of ethyl acetate fraction of *Rhododendron arboreum* flowers against carbon tetrachloride-induced hepatotoxicity in experimental models. Indian J Pharmacol 43: 291–295.

AUTHOR CONTRIBUTION:

Contribution	Chaudhary S	Gupta RK	Gupta MK	Verma HC	Kumar H	Kumar A	Swain SR	El-Shorbagi AN
Concepts or ideas	x							x
Design	x						x	x
Definition of intellectual content	x							x
Literature search	x	x	x	x	x	x	x	x
Experimental studies	x	x						
Data acquisition	x	x	x	x	x	x	x	x
Data analysis	x	x	x	x	x			
Statistical analysis	x	x						
Manuscript preparation	x	x	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x

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