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Hepatoprotective and Anti-inflammatory Activities of Hydro-alcoholic Extract of *Oxalis debilis* Kunth. Leaves

Julfikar Ali Junejo [1], Kamaruz Zaman [1,*], Mithun Rudrapal [2,*]

[1] Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India; jalijunejo@gmail.com (J.A.J.); kzaman71@dibru.ac.in (K.Z.);
[2] Department of Pharmaceutical Chemistry, Rasiklal M. Dhariwal Institute of Pharmaceutical Education and Research, Chinchwad, Pune, Maharashtra, India; rsmrpal@gmail.com (M.R.);
* Correspondence: kzaman71@dibru.ac.in (K.Z.); rsmrpal@gmail.com (M.R.);

Scopus Author ID 36524068400

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Abstract: This study aimed to investigate hepatoprotective and anti-inflammatory activities of the hydro-alcoholic extract of *Oxalis debilis* (ODHE) leaves. Acute oral toxicity evaluated ODHE in graded oral doses (100, 500, 1000, 3000, and 5000 mg/kg body weight) in rats. The hepatoprotective activity was evaluated in CCl_4 intoxicated rats at 200 and 400 mg/kg body weight doses of ODHE, while anti-inflammatory activity was determined by carrageenan-induced paw edema in rats at 200, 400, 800 mg/kg body weight doses of ODHE. The ODHE was safe at the highest dose of 5000 mg/kg in experimental rats. In hepatoprotective activity, ODHE significantly reduced the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TB) levels as compared to the CCl_4control group. On the other hand, ODHE showed an anti-inflammatory effect similar to that of the control group in the carrageenan-induced paw edema model. The histopathological findings showed a significant difference between the ODHE (400 mg/kg) and CCl_4 groups. The present experiment showed that ODHE has significant hepatoprotective and anti-inflammatory activities. Results confirm the use of *O. debilis* in folk medicine in the treatment of hepatotoxicity and inflammation.

Keywords: hepatoprotective; anti-inflammatory; ethnomedicine; hydro-alcoholic; *Oxalis debilis.*

1. Introduction

Although still an unwritten science, herbal therapy is still an unwritten science. Herbal therapy is well established in some countries and traditions and has become a way of life in almost 80% of the population in rural areas. Chronic anti-inflammatory diseases, including rheumatoid arthritis, are still one of the main health problems of the world's population [1, 2]. Although synthetic drugs dominate the market, the element of toxicity that these drugs entail cannot be ruled out. Their prolonged use may cause severe adverse effects on chronic administration, the most common being gastrointestinal bleeding and peptic ulcers [3].

Consequently, there is a need to develop a new anti-inflammatory agent with minimum side effects. Search for safe and effective anti-inflammatory agents have been given priority in scientific research in the herbal system of medicine. The liver plays a major role in regulating various physiochemical functions of the body, including synthesis, secretion, and metabolism of xenobiotics. Damage to the hepatic parenchyma may prove harmful to these physiochemical functions [4]. Many etiological factors may induce such damage, including infectious agents

and hepatotoxic chemicals. In experimental animal studies, carbon tetrachloride (CCl4) is one of the most commonly used hepatotoxins for inducing liver injury [5, 6]. The lack of effective modern medications for treating acute and chronic liver injury has led to research into the hepatoprotective activity of numerous medicinal plants using various experimental models.

Oxalis debilis Kunth. (Oxalidaceae) is a tristylous species native to Southern America and is a member of the bulb-forming shrub and distributed widely throughout the world. It is abundantly found in the Brahmaputra valley region of India [1]. The traditional uses of herbs and their extracts have been to cure human ailments since ancient times. It has been used traditionally for the treatment of dysentery and diarrhea [7]. A wide range of phytochemical constituents such as fatty acids, flavonoids, glycoglycerolipid, glycosides, phenol, phytosterols, tannins, and volatile oil has been reported from the leaves of the plant [8]. In modern literature, this plant species' antioxidant, anticancer, analgesic, antimicrobial, antiamoebic, antifungal, astringent, diuretic, and febrifuge activities have also been reported [9].

Ethnobotanical study indicates that leaf decoction of *O. debilis* has been used by tribal people of the North-eastern states of India for the management of liver disorders and inflammatory diseases [10]. There are no scientific reports in modern literature on the hepatoprotective and anti-inflammatory efficacy of *O. debilis* leaves. The objective of our present study was to ascertain the scientific basis of using this particular plant species traditionally in the management of liver disorder and inflammatory diseases and isolate phytoconstituents. According to WHO guidelines, the extract of *O. debilis* leaves was prepared using hydro-alcoholic solvent and evaluated for hepatoprotective and anti-inflammatory efficacy.

2. Materials and Methods

2.1. Chemicals and reagents.

All chemicals and reagents were of analytical grade and were procured from Rankem, Mumbai, and Himedia Laboratories Ltd., Mumbai. Commercial reagent kits used for the determination of biochemical parameters and enzymatic assays were purchased from SPAN Diagnostics Ltd., Surat (India). Silymarin was obtained from Quality Pharma Products Pvt. Ltd. Dibrugarh (India).

2.2. Plant material.

Fresh leaves of *Oxalis debilis* Kunth. were collected from forest areas of Dibrugarh district, Assam (India) during December 2014. The plant species were identified and authenticated (BSI/ERC/2014/Plant identification/360, dt. 26.08.2014) by Dr A. A. Mao, Scientist E, BSI, Eastern Regional Centre, Botanical Survey of India, Eastern Regional Centre, Shillong (India). A voucher specimen (DU/PSC/HRB/B-11/2014) of the identified plant species was deposited in the Herbarium of the Department.

2.3. Preparation of hydro-alcoholic extract (ODHE).

The air-dried leaves were coarsely powdered (Sieve no. 40) using a cutter mill, and 80 g of powdered leaves were used to prepare extract. Powdered leaves were extracted using sufficient quantity (600 ml) of the ethanol-water mixture (7:3) by cold maceration for 24 h.

The extraction was carried out successively greatly, and the combined extract was then concentrated under reduced pressure to dryness in a rotary vacuum evaporator to obtain a thick semisolid-like paste. The crude extract was dried at -40 °C in a lyophilizer, and the dried extract (dark brown color) so obtained was stored in a desiccator until further use. The percentage yield of the dried hydro-alcoholic extract (ODHE) was calculated per dry weight of powdered leaves.

2.4. Test animals.

Healthy Wistar male albino rats (240–260 g) were maintained under standard environmental conditions (temperature 25±2 ^{o}C, relative humidity 50 ± 5%) with a 12 h light/dark cycle. They were fed on a normal laboratory chow pellet diet, and drinking water was given *ad libitum*. Animals were allowed to acclimatize for 7 days before the commencement of the experiment. The animals were used with the approval of the Institutional Animal Ethics Committee (Approval no. IAEC/DU/50 dt. 24.9.13) under guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (India).

2.5. Phytochemical screening.

Preliminary phytochemical screening [11-13] of the ODHE was carried out to detect the presence of various phytoconstituents like alkaloids, glycosides, flavonoids, phenolic compounds, tannins, saponins, proteins, amino acids, and steroids.

2.6. Acute toxicity test.

Health adult rats that were starved overnight were divided into six groups (n = 6). The rats were orally administered with increasing levels of dose concentration (100, 500, 1000, 3000, and 5000 mg/kg) of the plant hydro-alcoholic extract, and one group was kept as control. The animals were continuously observed for 4 h at an interval of 30 min under behavioral, neurological, and autonomic profile including toxicity and mortality, and then periodically after 6 h and then 24 h for any signs of acute toxicity up to 14 days [14].

2.7. Hepatoprotective activity.

Protocol previously described by Hussain et al. (2020) [15] was employed to determine the hepatoprotective activity. 200 mg/kg and 400 mg/kg of ODHE and standard drug silymarin (100 mg/kg) with saline and olive oil (1 mL/kg) were administered 48, 24, and 2 h before induction of hepatic injury by 1 ml/kg CCl_4 (i.p) solution. Rats were divided into five groups;, each group consisting of six animals.

Group I : Control
Group II : CCl_4 1 ml/kg (i.p.)
Group III : ODHE 200 mg/kg + CCl_4
Group IV : ODHE 400 mg/kg + CCl_4
Group V : Silymarinstandard 100 mg/kg + CCl_4

After 7 days the blood samples were collected from the rats, and biochemical analysis was done. Reitman and Frankel's [18] method was employed to determine serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) colorimetrically. Serum

total bilirubin (TB) was determined by Jendrassik and Grof method, and serum alkaline phosphatase (ALP) activity was determined by King and Kings Method.

2.8. Anti-inflammatory activity.

Carrageenan induced paw edema model Paw edema was induced [16] by injecting 0.1 ml of 1% w/v carrageenan suspended in 1% CMC into subplantar tissues of the left hind paw of each rat. Rats were divided into four groups;, each group consisting of six animals.

Group I : Carrageenan control
Group II : ODHE 200 mg/kg)
Group III : ODHE 400 mg/kg)
Group IV : ODHE 800 mg/kg)
Group V : Indomethacin standard (10 mg/kg)

The paw thickness was measured before injecting the carrageenan and after 60, 120, 180, 240, 300 min. using a vernier caliper. The anti-inflammatory activity was calculated as percentage inhibition of edema in the animals treated with extract under test compared to the carrageenan control group.

The percentage (%) inhibition of edema is calculated using the formula:

$$\% \text{ inhibition} = T_o - T_t/T_o \times 100$$

where T_t is the thickness of paw of rats given test extract at the corresponding time, and T_o is the paw thickness of rats of the control group at the same time.

2.9. Statistical analysis.

Data were expressed as Mean ± S.E.M (standard error of mean). Statistical analysis as performed by one-way analysis of variance (ANOVA) followed by Dunnett's comparison test to determine the degree of significance with a single normal and experimental control group. Plotting and normalization of the non-linear concentration-inhibition curve were done using GraphPad Prism 6.07 (GraphPad Software, Inc. version 5.0). The value of IC_{50} was calculated from the normalized curves. The *p*-value less than 0.05 was considered statistically significant.

3. Results and Discussion

3.1. Acute toxicity.

Intensive observations on the animals treated with various doses of ODHE show no lethality or behavioral changes [17]. The experimented highest dose of 5000 mg/kg showed no toxicity and lethality at the end of the experiment.

3.2. Hepatoprotective activity.

A significant reduction in the production of the serum marker enzymes ($p \leq 0.001$) was observed in CCl_4 treated animals pre-treated with ODHE compared to the CCl_4 treated control group. CCl_4 treatment had no significant affect on the increase of ALP in the group pre-treated with 200 mg/kg ODHE and ALP and TB in the group pre-treated with 400 mg/kg ODHE. Further, the administration of 400 mg/kg ODHE reduces the serum marker enzyme activity almost close to the level observed in the group treated with silymarin (100 mg/kg) (Table 1).

The CCl_4 treated animals also showed an elevated level of AST, ALT, and ALP Hepatic injury was sufficiently protected by ODHE. The normalization of the serum marker level may

be due to the conditioning of hepatocytes by reverting the accumulation of the toxic bile salt in the liver cell, thereby maintaining the integrity of the membrane to check the leakage of the serum marker to the circulation [18]. AST is accompanied by an increase in ALT, which has a pivotal role in converting amino acids to keto acids. Biliary pressure increases the ALP synthesis, which increases its level [19]. The decrease in the serum marker enzyme in the study was found to be dose-dependent.

Table 1. Effects of ODHE on serum biochemical parameters in CCl_4-intoxicated rats

Group	Treatment	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (mg/Dl)
Group-I	Control	142.16 ± 7.78$^{\#\#}$	77.33 ± 6.05$^{\#\#}$	225.16 ± 9.02$^{\#\#}$	0.14 ± 0.01$^{\#\#}$
Group-II	CCl_4 1ml/kg (i.p.)	602 ± 19.19**	492.16 ± 18.65**	426.16 ± 7.91**	0.32 ± 0.01$^{**\#\#}$
Group-III	ODHE 200 mg/kg + CCl_4	322.66 ±13.96$^{**\#\#}$	253.36 ±10.39$^{**\#\#}$	259.33 ± 6.46$^{\#\#}$	0.24 ± 0.04$^{\#\#}$
Group-IV	ODHE 400 mg/kg + CCl_4	227.5 ± 7.37$^{**\#\#}$	149.38 ± 8.91$^{**\#\#}$	234.61 ± 9.96$^{\#\#}$	0.20 ± 0.03$^{\#\#}$
Group-V	Silymarin 100 mg/kg + CCl_4	193.5 ± 34.19$^{**\#\#}$	82.16 ± 30.94$^{\#\#}$	229.83 ± 15.81$^{\#\#}$	0.17 ± 0.02$^{\#\#}$

** $p \leq 0.01$ vs. control (Group I)

$^{\#\#}$ $p \leq 0.001$ vs. toxic control (Group II)

3.3. Anti-inflammatory activity.

Table 2 shows the effect of aqueous extract of leaves and standard drug compared to carrageenan control at different hours in a carrageenan-induced paw edema model using a vernier caliper. ODHE administered at a dose of 200 mg/kg p.o prevented carrageenan-induced paw edema with a percentage inhibition of 9.26%, 26.17%,35.15%, 40.54 and 46.90% at 1, 2, 3,4 and 5 hour, respectively, while 13.10%, 30.15%, 42.55%, 50.00% and 53.39%, at a dose of 400 mg/kg p.o. at 1, 2, 3, 4 and 5 hour, respectively, while 17.06%, 31.95%, 45.68%, 58.44% and 64.83 %, at a dose of 800 mg/kg p.o. at 1, 2, 3, 4and 5 hour, respectively, Indomethacin at a dose of 10 mg/kg p.o. prevented carrageenan-induced paw edema with a percentage inhibition of 29.80%, 41.40%, 57.67%, 62.91%, and 68.68% at 1, 2, 3, 4, and 5 hours, respectively.

Carrageenan-induced acute inflammation is one of the most suitable test procedures to screen anti-inflammatory agents. A biphasic curve generally represents the time course of edema development in the carrageenan-induced paw edema model in rats. The first phase of inflammation occurs within an hour of carrageenan injection and is partly due to the trauma of injection and also due to histamine and serotonin components [20, 21].

Table 2. Anti-inflammatory activity of ODHE on carrageenan-induced paw edema in rats.

Group	0 min	60 min	120 min	180 min	240 min	300 min
Group I: Control	0.563± 0.016	1.641 ± 0.070	1.884 ±0.047	1.852 ±0.052	1.766 ±0.039	1.74 ±0.052
Group II: ODHE 200	0.572± 0.016	1.489 ±0.027*	1.391±0.018*	1.201 ±0.016*	1.05 ± 0.014*	0.924 ± 0.047*
Group III: ODHE 400	0.555± 0.019	1.426 ±0.018*	1.316± 0.027*	1.064 ± 0.036*	0.883 ± 0.012*	0.811 ± 0.047*
Group IV: ODHE800	0.560± 0.082	1.361 ±0.021*	1.282 ±0.018*	1.006 ± 0.016*	0.734 ± 0.019*	0.612 ± 0.012*
Group V: Indomethacin	0.541± 0.006	1.152 ±0.048*	1.104 ±0.023*	0.784 ± 0.033*	0.655 ± 0.035*	0.545 ± 0.021*

* $p \leq 0.05$

As shown in Table 1, there was no significant inhibition of paw edema, 9.26%, 13.10%, and 17.06% in the early study hours by aqueous extract at 200, 400, and 800 mg/kg, respectively. Hence, it can be concluded that there is no inhibition of histamine and serotonin. Carrageenan induced paw edema model in rats is known to be sensitive to cyclooxygenase

inhibitors. It has been used to evaluate the effect of nonsteroidal anti-inflammatory agents, which primarily inhibit the cyclooxygenase involved in prostaglandin synthesis [22]. It plays a major role in developing the second phase of inflammatory reaction, which is measured at 3 hours. As shown in Table 2, there is a significant ($p < 0.05$) percentage inhibition of paw edema, 46.90%, 53.39%, and 64.83% at 200, 400, and 800 mg/kg doses respectively, at 5 hours by the aqueous extract. Therefore, it can be inferred that the inhibitory effect of aqueous extract on carrageenan-induced inflammation may be due to inhibition of the enzyme cyclooxygenase leading to inhibition of prostaglandin synthesis.

3.4. Histopatological examination.

The liver sections from normal control animals (Group I) showed a classical structure with hepatocyte plates directed from the portal triads toward the central vein. The liver sections from the toxic control rats (Group II) showed massive changes throughout the lobules, with fatty accumulations, cellular vacuolization, and necrosis, as well as dilation of Disse spaces with focal disruption of the sinusoidal endothelium, inflammatory infiltrations of the portal triads, and distortion of the central venules. The pre-and post-treatment of animals with 400 mg/kg hydro-alcoholic *O. debilis* leaves extract (Group IV) and silymarin 100 mg/kg (Group V) revealed milder hepatocellular vacuolation and better preservation of the normal liver architecture, with moderate hepatocyte plate disorganizations and smaller dilations of Disse spaces.

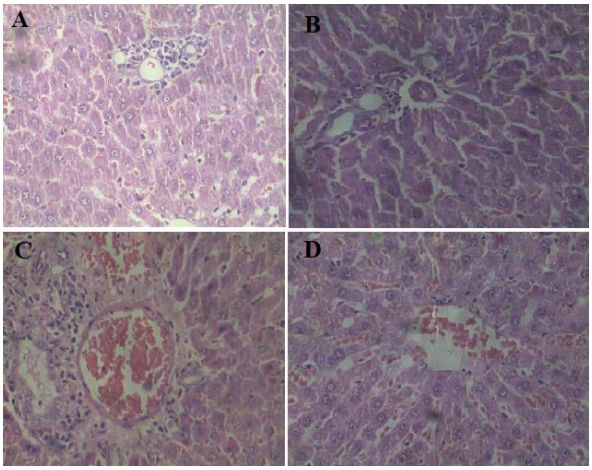

Figure 1. Photomicrographs of liver sections fixed in chilled 10% saline buffer. (A) Group I - normal untreated; (B) Group II - CCl_4 1 ml/kg (i.p.) control; (C) Group IV - ODHE 400 mg/kg + CCl_4; (D) Group V -Silymarin 100 mg/kg as standard reference.

4. Conclusions

In the present study, the hydro-alcoholic leaf extract of *Oxalis debilis* (ODHE) restored the elevated serum enzyme levels. It counteracted the hepatic damage, suggesting that it has hepatoprotective, curative, and protective capacities in CCl_4-intoxicated rats. The extract also showed to have potential anti-inflammatory activity. Results confirm their use in folk medicine in the treatment of hepatotoxicity and inflammation. In conclusion, ODHE needs further experimental approaches to explore its action mechanism and identify the active biomolecules, which will no doubt be a novel approach to treat different diseases.

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Conflicts of Interest

The authors declare no conflict of interest.

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