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Toxicological study of the ethanolic extract of *Cleome viscosa* leaves in Wistar rats

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ABSTRACT

Cleome viscosa is traditionally used to cure various pathologies, especially malaria, hemorrhoids, fever and headaches. However, there are few experimental data on its possible toxicity. The present study investigated the toxicity of the extract of *Cleome viscosa* in Wistar rats. In acute toxicity, a single administration of the extract of *Cleome viscosa* at 5000 mg/kg was administered orally to rats. General behavior, adverse effects and mortality were recorded up to 14 days after treatment. For subchronic toxicity, the extract at 500 mg/kg/day and 1000 mg/kg/day were administered orally to rats for 28 days. The body weight of rats was recorded daily, while hematological and biochemical parameters and relative organ weights were assessed on day 29. Neither was mortality nor induction of intoxication recorded in the treated. Subchronic administration of *Cleome viscosa* did not result in any significant changes in weight gain or feeding in the rats. Macroscopic observation of the organs of treated rats showed no significant change in color and texture. Also, hematological and biochemical parameters showed no significant changes. Oral administration of extract of *Cleome viscosa* can be considered relatively free of toxicity.

Keywords : Toxicity, acute, subchronic, *Cleome viscosa*.

INTRODUCTION

Medicinal plants have been considered for centuries as a remedy for various diseases. Although the development and mass production of synthetic drugs have revolutionized health therapeutics worldwide, studies reveal that more than 80% of people in Africa use medicinal plants for therapeutic and prophylactic purposes (Sobiecki et al., 2014). Medicinal plants are primarily used to promote health and treat chronic and acute diseases. In addition, the use of traditional remedies is ative when conventional medicine is not effective.

Medicinal plants contain secondary metabolites which constitute an important source of molecules which are useful in the field of pharmacology. These medicinal plants still remain the primary reservoir of new drugs; they are considered an essential source of raw material for the discovery of new molecules needed for future drug development

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(Mohamed, 2018). Despite the profound therapeutic benefits imbedded in by medicinal plants, some of these plants are potentially toxic, carcinogenic and teratogenic (Teixeira et al., 2003; Oaes-Leme et al., 2005). In fact, using medicinal plants without evaluating their efficiency and safety may result in unexpected or toxic effects on the liver and kidneys in humans (Mapanga and Musabayane, 2010). The lack of standardization constitutes therefore a major concern for the use of natural medicine from medicinal plants (Evenamede et al., 2019). Therefore, it is important to evaluate the toxicity of medicinal plants widely used in traditional pharmacopoeia (Zeggwagh et al., 2013). *Cleome viscosa* (capparidaceae) a plant of the Togolese flora is worth to be studied particularly in the case of treatment of several diseases. Indeed, this plant is widely used by traditional practitioners to cure malaria, hemorrhoids, fever, headaches, abscess, vomiting, sinusitis and wounds (Adanlemegbe et al., 2020). However, despite the widespread use of this plant throughout Africa, and particularly in Togo, less research has focused on its toxicity. Consequently, this study evalutes the toxicity of the ethanolic extract of *Cleome viscosa* leaves in Wistar rats. In this way, we need to identify the nature and magnitude of the effects of extracts or molecules at appropriate doses, in order to prevent humans from any possible risk.

MATERIALS AND METHODS

Plant material

The leaves of *Cleome viscosa* were harvested in Kpetsou in South-East Togo in April 2017. This plant has been identified and registered under TOGO 15758 by the National Herbarium of the University of Lomé.

Extraction

The powder of the *C. viscosa* (100 g) was poured into a liter of the ethanol for 72 H, stirring at regular intervals. The resulting mixture was filtered, and the filtrate was concentrated by evaporation of the ethanol-water mixture at 40°C under reduced pressure using a rotary evaporator (BUCHI, Switzerland).

Animals

Wistar rats (female) aged 2 to 3 months, weighing between 140 g and 170 g, were used to study limit of toxicity and the oral subchronic toxicity. These rats were provided by the animal house of the Physiology/Pharmacology laboratory of the University of Lomé. They were raised in rooms at ambient temperature with a photoperiod of 12 hours. The rats had free access to water and food. Experimental protocols were based on World Health Organization Guidelines for care and use of laboratory animals, and the use of animals was approved by the Ethics Committee of the University of Lomé, a branch of the National Ethics Committee for control and supervision of experiments on animals (N° SBM/UL/14/NS0004).

Toxicity's limit study of the ethanolic extract of *Cleome viscosa*

Acute toxicity test was used here according to the guideline 423 of the OECD (Kouakou et al., 2022), to obtain an idea about the lethal doses of ethanolic extract of *Cleome viscosa* in rats. These rats were divided into two groups of three rats and having body weight between 140 g and 170 g. Prior to oral administration of distilled water for the control group and a single dose of 5000 mg/kg of body weight of the extract, the rats were restrcted from food for 16 hours. The rats were continuously monitored for the first 4 hours, then hourly for 6 hours and, finally daily for 48 hours. Observation of the animals continued once a day for 14 days to record any behavioral changes and deaths. Signs of toxicity included changes (in hair, eyes, and mucous membranes), tremor, convulsion, appearance of feces, lethargy, mobility, restlessness, respiration, asthenia, sleep, and coma. Changes in body weight were also calculated. On day 15, all surviving animals were sacrificed and vital organs such as liver, kidneys, lungs and

heart were removed and subjected to macroscopic observation.

$$Relative\ weight\ = \frac{Weight\ of\ the\ organ}{Weight\ of\ the\ animal} \times 100$$

Subchronic toxicity test

Experimental protocol

To evaluate the subchronic toxicity of the ethanolic extract of *Cleome viscosa* leaves, the repeated dose oral toxicity method was used (Rhiouani et al., 2008). A total of nine rats were used. Before treatment, the rats were examined for any abnormalities and awkward behavioral patterns. The first group (control group) received daily for 28 days hydroethanolic solution by gavage. The second and third groups were treated daily for 28 days by gavage with ethanolic extract of *Cleome viscosa* leaves at doses of 500 mg/kg and 1000 mg/kg of rat body weight respectively. The extract used for the toxicity study was dissolved in a hydroethanolic solution. Every second day, the rats were weighed. Each group of rats was examined daily before and after gavage sessions throughout the experimental period with regard to mortality, morbidity, changes, in behavior, posture, hair and eyes,the presence of lacrimation. On the day 29, the rats were anesthetized with ether and blood was collected via retro-orbital vein puncture using capillary tubes (Warynforth and Frencknell, 1980). The collected blood samples were used for the determination of biochemical and hematological parameters. Blood samples for hematological analysis were collected in tubes containing Ethylene Diamine Tetra Acetic Acid (EDTA) as an anticoagulant, whereas samples for biochemical assays were collected in dry tubes and centrifuged one hour after collection. After blood collection, the rats were sacrificed by cervical dislocation. Organs such as liver, kidney, spleen, lung and heart were removed and washed immediately in fresh 0.9% NaCl solution. These organs were weighed and then macroscopically examinaed each.

Relative organ weight

The excised organs were weighed and the weight of each organ was multiplied by 100 and divided by the weight of the animal before sacrifice to obtain the relative organs weight (%) (Abdullah et al., 2009; Yam et al., 2009).

Hematological parameters

Hematological parameters such as white blood cell (WBC), red blood cell (RBC), hemoglobin level, hematocrit (Ht), mean corpuscular hemoglobin volume (MCV), mean corpuscular hemoglobin content (MCHC), mean corpuscular hemoglobin concentration (MCHC), platelet count (PLT), and mean platelet volume (MPV) were measured using an automated hematology machine (ABX Pentra XL 80, France). Blood smear was performed on each sample. The leukocyte count was performed with a light microscope (Olympus, Italy) after fixation with May Grunwald (Atom Scientific, UK) and staining with Giemsa (Atom Scientific, UK).

Biochemical parameters

Blood samples collected in dry tubes were used to assay biochemical parameters. Blood was centrifuged after coagulation at 3000 rpm (1107 g) for 15 min using an electric centrifuge (Shimadzu Scientific Corporation Tokyo, Japan). The serum was decanted and then frozen at 20°C for subsequent determination of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), creatinine, urea, glucose, cholesterol, triglycerides, total protein, total bilirubin and direct bilirubin.

RESULTS

Toxicity's limit

The limit of toxicity allows us to know the smallest dose that given in a single dose would lead to the death of 50% of the animals within 24 to 48 hours after treatment, this definition allows us to determine the lethal dose (LD_{50}). Fourteen days after administration of the extract at a single dose of 5000 mg/kg body weight, no induction of intoxication was reported. In addition, no mortality was

recorded in the different batches treated with the ethanolic extract of *Cleome viscosa*. It could be deduced that the LD_{50} is higher than 5000 mg/kg body weight of rats for this extract. On the other hand, the rats treated with the extract showed a clinical map without signs of toxicity. Their behavior was similar to that of control rats. There were no significant differences in the body weight development of control and treated rats. No organ abnormalities were observed at necropsy.

Subchronic Toxicity

Body weight of rats

The evolution of the body weight of the rats during the 28 days of treatment with the ethanolic extract of the leaves of *Cleome viscosa* is presented in Figure 1. It appeared that at all the doses studied the extract did not significantly modify the evolution of the body weight of the treated rats compared to the control rats. No deaths were recorded among either treated or control rats during the entire observation period. No remarkable changes in behavior were observed. Animals in the control and 500 mg/kg and 1000 mg/kg dose groups appeared uniformly well throughout the treatment period. The extracts did not significantly alter the behaviour of the rats with respect to food and water consumption.

Relative organ weights of rats

The effects of ethanolic extract of *Cleome viscosa* leaf on the relative weight of female rats are represented in Table 1. Evaluation of relative organ weights revealed no significant differences between the groups of rats that received the extracts for 28 consecutive days and the control rats. It should be noted that the study focused on the liver, kidney, lung and spleen. Macroscopic observation of the organs of the treated rats showed no significant changes in color and texture compared to the organs of the control rats.

Biochemical examinations of rat sera

The analyses on the chemical parameters allow to determine the effects of the administered substances on the hepatic and renal functions of the rats. The results of these analyses summarized in Table 2 shows that, the oral administration of the ethanolic extract of *Cleome viscosa* leaves showed a slight but not significant ($p>0.05$) decrease in the concentrations of urea, total cholesterol, total bilirubin, direct bilirubin, alkaline phosphate and total protein in female rats compared to the control rats for both doses (500 mg/kg and 1000 mg/kg). As for triglycerides, a slight increase in their levels was noted for the 500 mg/kg and 1000 mg/kg dose of the extract compared to the control group, but this increase was not significant ($p>0.05$) for both doses. On the other hand, the 1000 mg/kg dose significantly ($p<0.05$) reduced the ALT level compared to the control group, this decrease was also observed for the 500 mg/kg dose but this observation was not significant ($p>0.05$). It should also be noted that a non-significant increase in AST was obtained for the 500 mg/kg body weight dose. On the other hand, for the 1000 mg/kg dose, a non-significant decrease of the ASAT level was observed. Both doses of extract (500 mg/kg and 1000 mg/kg) very significantly ($p<0.05$) reduced the glucose concentration. The study revealed that oral administration of the extract (500 and 1000 mg/kg body weight) for 28 days showed no change on creatine concentration.

Hematological analyses

The hematological values of rats treated with ethanolic extract of *Cleome viscosa* leaves are recorded in Table 3. From these results, it can be seen that the dose of 500 mg/kg promoted a non-significant ($p>0.05$) decrease in the number of white blood cells and the dose of 1000 mg/kg slightly but non-significantly increased the number of white blood cells compared to the control rats. In contrast, the 500 mg/kg dose promoted a non-significant ($p>0.05$) increase in red blood cell count and the 1000 mg/ kg dose slightly but non-significantly ($p>0.05$) decreased red blood cell count. On the other hand, the 500 mg/kg and 1000 mg/kg doses caused a non-significant ($p>0.05$) decrease in hemoglobin, hematocrit, mean corpuscular hemoglobin and lymphocyte

content. Also, it could be noted that both doses resulted in a non-significant ($p>0.05$) increase in mean corpuscular hemoglobin concentration (MCHC), platelets (PLT) and neutrophils. It should also be noted that a non-significant ($p>0.05$) decrease in monocytes, lymphocytes, mean platelet volume (MPV) and basophils was observed in rats treated with the 500 mg/kg dose compared to untreated rats. The 1000 mg/kg dose, on the other hand, resulted in a non-significant ($p>0.05$) increase in these levels. Finally, it was also observed that both doses (500 mg/kg and 1000 mg/kg) of the extract caused a slight increase in the eosinophil count in the treated rats. Haemogram results show that the doses of 500 mg/kg and 1000 mg/kg of the ethanolic extract of *Cleome viscosa* did not significantly alter the blood parameters of the treated rats in comparison with the untreated rats.

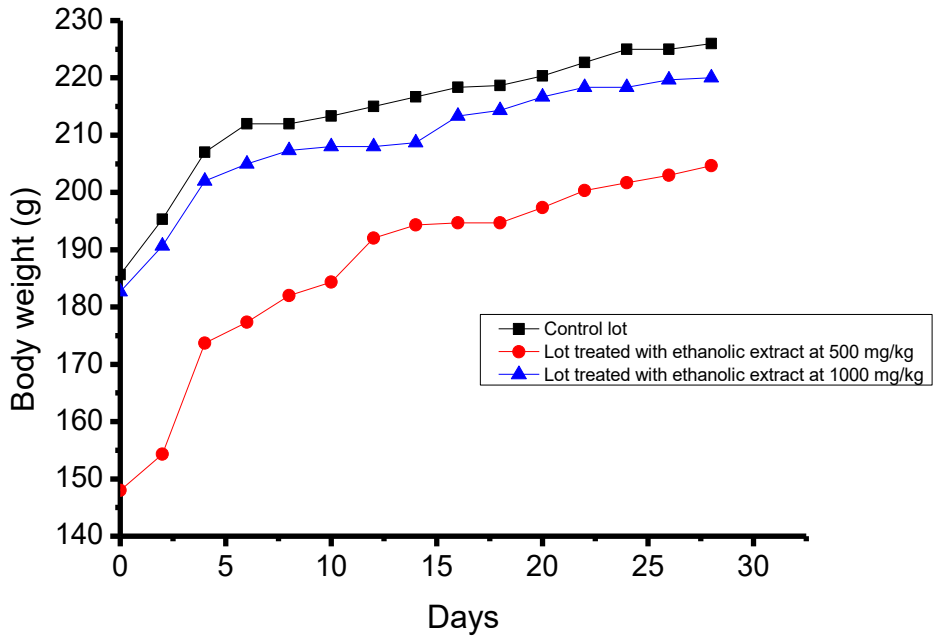

Figure 1 : Evolution of the body weight of rats

Table 1 : Relative organ weights of rats.

Organs	Control	Doses of ethanolic extract of *Cleome viscosa* leaves	
		500 mg/kg	1000 mg/kg
Liver	3.55±0.1	3.72±0.43	3.52±0.08
kidneys	0.65±0.4	0.67±0.12	0.67±0.04
Heart	0.33±0.02	0.36±0.01	0.34±0.03
Lungs	0.80±0.1	1.06±0.11	0.93±0.06
Spleen	0.36±0.05	0.32±0,01	0.32±0.01

Values are expressed as mean ± MSE, n = 3; *P < 0.05, significant difference **P < 0.05 highly significant difference from Controls (ANOVA one way followed by Tukey's multiple comparison test).

Table 2 : Effect of the extract on biochemical parameters of rats.

Biochemical parameters	Control	Doses of ethanolic extract of *Cleome viscosa* leaves	
		500 mg/kg	1000 mg/kg
ASAT (UI/I)	159±17	175.67±13.33	152.67±8.33
ALAT (UI/I)	85±5	82.67±7.33	65±3*
PAL (UI/I)	222.67±11.33	221.67±18.33	160±10
Urea (g/L)	0.3±0.03	0.3±0.09	0.29±0.04
Glucose (g/dL)	1.3±0.2	1.02±0.09**	0.94±0.1**
Creatinine (mg/L)	4.67±0.67	4.67±0.67	4.67±0.67
Total Cholesterol (g/L)	0.63±0.08	0.59±0.2	0.53±0.19
Triglycerides (g/L)	0.91±0.02	1.07±0.17	1.07±0.21
Total Bilirubins (mg/dL)	0.89±0.03	0.81±0.04	0.83±0.37
Direct Bilirubines (mg/dL)	0.69±0.05	0.67±0.03	0.67±0.14
Total Protein(g/L)	71.67±5.33	74±5	68.33±3.67

Values are expressed as mean ± SEM (n= 3 rats); p > 0.05 no significant difference from Controls; (one-way ANOVA followed by Tukey's multiple comparison test); ASAT : Aspartate Aminotransférase ; ALAT : Alanine aminotransférase ; PAL : Phosphatase Alcaline ; UI/l=unité internationale par litre

Table 3 : Effect of the extract on hematological parameters.

Hematological parameters	Control	Doses of ethanolic extract of *Cleome viscosa* leaves	
		500mg/kg	1000 mg/kg
White blood cells (10^{12}/L)	11.37±1.25	9.76±3.3	11.76±2.3
Red blood cells (10^{12}/L)	7.32±0.6	7.38±0.9	7.14±0.25
Hémoglobin (g/dL)	14.2±0.7	13.77±1.1	13.47±0.47
Hématocrit (%)	41.63±1.2	40.53±2.23	39.07±1.43
VGM (fl)	55.93±2.13	54.73±1.07	54.73±1.07
TCMH	19.03±0.9	18.73±0.9	18.83±0.4
CCMH (%)	34.07±0.2	34.4±0.3	34.1±0.5
PLT (10^9/L)	655.67±20.33	783.5±20.5	762±22
Neutrophils (10^9/L)	25.1±2.15	28.9±3.12	26.9±2.63
Lymphocytes (10^9/L)	62.97±0.8	58.57±9.79	56.23±2.32
Monocytes (10^9/L)	6.6±1.2	5.73±1.1	6.57±0.9
Eosinophils (10^9/L)	8.15±1.5	8.8±1.2	8.06±1.1
VPM (fl)	7.87±0.13	7.57±0.33	7.9±0.5
Basophils (10^9/L)	0.07±0.01	0.0	0.23±0.02

Values are expressed as mean ± SEM (n= 3 rats); p > 0.05 no significant difference from Controls; (one-way ANOVA followed by Tukey's multiple comparison test); MGV: Mean corpuscular volume; MCHT: Mean corpuscular hemoglobin content; MCHC: Mean corpuscular hemoglobin concentration; MPV: Mean platelet volume; PLT: platelet.

DISCUSSION

Medicinal plants are an important source of bioactive compounds and are used worldwide in traditional medicine to cure various sicknesses. Although medicinal plants have beneficial biological properties for humans, the potential toxicity of these bioactive substances has not been well established (Yam et al., 2009). The main purpose of studying the toxicity of plants' toxicity is to know the nature and magnitude of side effects of extracts or molecules at well appropriate doses, in order to prevent any risk to humans. In addition, the identification of the toxic agent, will allow either its elimination to obtain non-toxic active extracts. Despite the widespread use, few scientific studies have been undertaken to verify the safety and effectiveness of the remedies (Graça et al., 2007). Thus, the present study was conducted to evaluate the possible acute toxicity and subchronic toxicity effects on 28 days ethanolic extract of *Cleome viscosa* leave.

For the acute toxicity of the ethanolic extract of *Cleome viscosa* leaves, the single dose of 5000 mg/kg body weight given to rats by the oral route produced no signs of toxicity. There were no obvious signs of delayed toxicity, death, or significant behavioral changes during the 14 days of observation of the rats. Similarly, macroscopic examination of the organs at necropsy on day 15 did not reveal any architectural abnormalities of the organs. These results indicate that the median acute toxicity value or LD_{50} of the ethanolic extract of *Cleome viscosa* leaves is greater than 5000 mg/kg. Any product with an oral LD_{50} greater than 5000 mg/kg can be considered practically non-toxic over a short period of time (Kennedy et al., 1986). The ethanolic extract of *Cleome viscosa* leaves can be practically considered as a non-toxic substance by the oral route and also their safety margin is large. This result was confirmed by Devi who in this work showed that methanolic extract of *Cleome viscosa* is non-toxic and does not cause death in animals at a dose of 3200mg/kg body weight (Devi et al., 2002). Similar results were observed by Silva (2011) and Gomes (2012) with other plants using the same toxicological method.

A correlation was reported between the borderline toxicity in rats and humans, which was however very low (Olson et al., 2000). Therefore, the oral administration of the ethanolic extract of *Cleome viscosa* leaves can be considered as non-toxic over a short period of time.

The results of the subchronic toxicity study showed that daily administration of the ethanolic extract of *Cleome viscosa* at doses of 500 mg/kg and 1000 mg/kg during the 28 days did not cause any death or clinical signs of toxicity in the animals. The body weight of the rats changed normally (Figure 1). These observations suggest that *Cleome viscosa* extract did not alter the overall metabolic processes of the treated rats ; since significant reduction in body weight and significant change in relative weights of internal organs are sensitive indices of toxicity after exposure to toxicants (Ouedraogo et al., 2013). The data obtained in this study showed that no significant changes were observed between the relative organ weights of treated and control rats (Table 1). Macroscopic examination of the organs showed no change in the overall appearance, color, or consistency of the internal organs (Figure 2). This observation suggests that the extract produced no toxic effect on these organs of the rats.

Blood parameters are important in toxicological risk assessment since any changes in the hematological and biochemical systems result in a high risk for toxicity (Olson et al., 2000). The results of these analyses summarized in Table 2 show that, oral administration of ethanolic extract of *Cleome viscosa* leaves showed a slight decrease in urea concentrations, in female rats compared to control rats for both doses (500 mg/kg and 1000 mg/kg). Urea and creatinine concentrations are commonly used in the assessment of renal function (Smith et al., 2006). Thus, urea and creatinine levels above normal levels indicate renal impairment. These results suggest that the renal functions of exposed rats were not impaired. The decrease in urea concentration at the highest dose of *Cleome viscosa* is the further evidence of the safety of this extract on the kidneys.

The results also showed that levels of total cholesterol, total bilirubin, direct bilirubin, alkaline phosphate and total protein were decreased; this allowed us to conclude that the extract is not hepatotoxic but more importantly could have hepatoprotective effects. Transaminases (ASAT and ALAT) are markers of liver and heart damage (Witthawaskul et al., 2003). Salomon also reported that the increase in serum protein levels is an indication of tissue damage and a reflection of liver toxicity (Salomon et al., 1933). The decrease in the levels of these enzymes as a function of the concentration of the extract could indicate that the ethanolic extract of *Cleome viscosa* has hepatoprotective effects. This result confirms that of Mobiya (2010). This result confirms that of Mobiya who in his work showed that the methanolic extract of *Cleome viscosa* has hepatoprotective effects.

Both doses of the extract (500 mg/kg and 1000 mg/kg) reduced very significantly the glucose concentration. The decrease in glucose levels, showed that the ethanolic extract of *Cleome viscosa* has hypoglycemic properties. These effects on the lipid profile would thus constitute an appreciable effect and would justify its use as an antidiabetic agent in traditional medicine.

Hematological values of rats treated with ethanolic extract of *Cleome viscosa* leaves recorded in Table 3 show that the dose of 500 mg/kg promoted a non-significant decrease in the number of white blood cells and the dose of 1000 mg/kg slightly but non-significantly increased the number of white blood cells compared to control rats. In contrast, the 500 mg/kg dose promoted a non-significant increase in red blood cell count and the 1000 mg/kg dose slightly but non-significantly decreased red blood cell count. These indices suggest that *Cleome viscosa* extract is not toxic to hematological parameters. An increase in white blood cells indicates the strengthening of the body's defense. Renal functions were assessed by means of urea, creatinine. Increased blood creatinine is a good indicator of the negative impact on renal function (Smith et al., 2006). These blood count results showed that the 500 mg/kg and 1000 mg/kg doses of *Cleome viscosa* ethanolic extract did not significantly alter the blood parameters of the treated rats compared to the untreated rats.

The results of the present toxicity study demonstrate that *Cleome viscosa* extract is not toxic by the oral route in a single dose of 5000 mg/kg. Administration of this extract at repeated doses of 500 and 1000 mg/kg for 28 days can be considered free of toxicity in rats. This observation suggests that this plant species can be used for therapeutic purposes.

Conclusion

The acute toxicity study of the ethanolic extract of *Cleome viscosa* is highly reassuring with no mortality and no signs of toxicity at the single dose of 5000 mg/kg of body weight. The results of the 28 days subchronic toxicity showed that this extract is not orally toxic in rats. For the biochemical and hematological parameters did not significantly alter considering the control rats. The ethanolic extract of *Cleome viscosa* leaves can be therefore considered free from any toxicity when administered orally.

COMPETING INTERESTS

Authors declare that they have no competing interests concerning this work.

AUTHORS' CONTRIBUTIONS

All authors contributed to this work and to the manuscript preparation.

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