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RESEARCH ARTICLE

Evaluation of Safety of *Karnasphota* (*Cardiospermum halicacabum* L.) Leaf through Acute Oral Toxicity Study and Repeated Dose: 28-day Oral Toxicity Study in Wistar Albino Rats

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ABSTRACT

Aim: *Cardiospermum halicacabum* L. is a climbing plant under Sapindaceae family. The plant leaf is used by traditional healers for treatment of various illnesses. Considering the ethno-medicinal value of *C. halicacabum*, the present study was taken up to evaluate single-dose acute toxicity study and repeated dose 28-day oral toxicity study (subacute) in Wistar albino rats.

Materials and methods: The hydroalcoholic extract of *C. halicacabum* leaf was administered orally to Wistar rats as single dose (2000 mg/kg bwt) in acute toxicity study and for continuous 28 days in repeated dose subacute toxicity study at three dose levels (250, 500, and 1000 mg/kg bwt). The study was carried out as per Organisation for Economic Co-operation and Development (OECD) guidelines 423 and 407. Animal mortality and general behavior were observed during the study period.

Results: The study showed that there were no mortality and morbidity in the test groups. The detailed biochemical and hematological investigations evaluated in control and test groups evidenced the safety of the extract as there were no significant differences among control and test groups. Histopathology study in vital organs of test groups showed no significant abnormalities.

Conclusion: The study concluded that the hydroalcoholic extract of *C. halicacabum* was safe at the prescribed dosages in Wistar albino rats.

Clinical significance: As the safety dosage of the hydroalcoholic extract of *C. halicacabum* has been proved in Wistar rats, further studies on biological efficacy or biopotency studies can be taken up using these details.

Keywords: Acute and repeated dose 28-day oral toxicity study, Balloon vine, *Cardiospermum halicacabum.*

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INTRODUCTION

Cardiospermum halicacabum, known as "Balloon vine" or "Love in a puff," is a climbing plant under Sapindaceae family, widely distributed in tropical and subtropical Africa and Asia. It is an annual or sometimes perennial climber, commonly found as a weed in farmland. It is mentioned as one among the "Ten Sacred Flowers" of Kerala State in India, collectively known as "Dasapushpam."[1]

Cardiospermum halicacabum is one of the ethno-medicinal plants of Western Ghats region of India. The plant is used by the local healers for treatment of various illnesses like joint pain, liver disorders, obesity management.[2-5] Even though the plant has been reported for some biological activities, the details of safety and toxicity of the plant had not been reported so far. The present study has been taken up to evaluate safety dose of hydroalcoholic extract of *C. halicacabum* leaf through carrying out the single-dose acute toxicity and repeated dose 28-day oral toxicity study (subacute) in rodents as per OECD guidelines.

MATERIALS AND METHODS

Plant Collection and Extraction

The plant *C. halicacabum* was collected from the Western Ghats region (Palghat and Thrissur) of Kerala, India. The authentication of the plant was done by Taxonomist, Kerala Forest Research Institute (KFRI), Government of Kerala, Thrissur. Voucher specimen is maintained in the Biochemistry Department of National Ayurveda Research Institute for Panchakarma, Cheruthuruthy. The fresh leaves of *C. halicacabum* were collected and used for the present study. The hydroalcoholic extract of leaf (one part alcohol and one part water) was prepared as per Ayurvedic Pharmacopoeia of India Part I Vol. VIII. The extract was stored in refrigerator for the experimental use.

Experimental Animals

Wistar albino rats were procured from College of Veterinary and Animal Sciences, Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur, India. Animals were acclimatized to the laboratory condition before initiating the experiment. The animal studies were carried out as per guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals.

Institutional Animal Ethics Committee Approval for Toxicity Study

Institutional Animal Ethics Committee's (IAEC) approval was obtained for the animal experiments vide Proposal No. IAEC/NRIP/2014-15/03 dated 16.02.2015 in the meeting held at National Research Institute for Panchakarma, Cheruthuruthy, Thrissur, Kerala, India. Toxicity studies were conducted as per OECD guidelines 423 and 407.

Acute Toxicity Study[5]

Single-dose acute toxicity study was carried out as per OECD guidelines 423. The test drug (hydroalcoholic extract of *C. halicacabum*) was administered (2,000 mg/kg bwt) through oral administration to three female rats once as step 1. After an observation period of 14 days, the test was repeated in another three animals as step 2.

Observation

The animals were observed individually after dosing, at least once during the first 30 minutes periodically during the first 24 hours, with special attention given during the first 4 hours, and daily thereafter for a total of 14 days. The animals were observed for morbidity, mortality, and clinical signs of toxicity (changes in skin and fur, eyes and mucous membrane, behavior pattern, tremors, convulsions, salivation, diarrhea, lethargy, sleep, and coma) for a period of 14 days. Body weight and feed consumption were recorded weekly.

Repeated Dose 28-day Oral Toxicity Study[6]

Repeated dose 28-day oral toxicity study (subacute toxicity study) was carried out as per OECD guidelines 407. A total of 48 Wistar albino rats (12 weeks old) were randomized and equally divided into four groups (6 males and 6 females). Based on the findings of the acute study, the subacute study was carried out at three different doses. The animals in control group received distilled water. The animals of other three groups received the test compound dissolved in distilled water at the dose of 250, 500, and 1000 mg/kg bwt, for 28 days. Biochemical and hematological investigations had been carried out at the end of the study.[7-10] This was followed by euthanization and organ necropsy as well as histopathological examination of various organs that included heart, lung, liver, spleen, stomach, kidney, testis/ovary, sciatic nerve, brain and pancreas.

Observation

The animals were observed individually after dosing at least once during the first 30 minutes periodically during the first 24 hours, with special attention given during the first 4 hours, and daily thereafter for a total of 28 days. The animals were observed for morbidity, mortality, and clinical signs of toxicity (changes in skin and fur, eyes and mucous membrane, behavior pattern, tremors, convulsions, salivation, diarrhea, lethargy, sleep, and coma) for a period of 28 days. Body weight and feed consumption were recorded weekly.

Statistical Analysis

The data were expressed as mean ± standard error of mean (SEM). Statistical significance was analyzed using one-way analysis of variance with posttest.

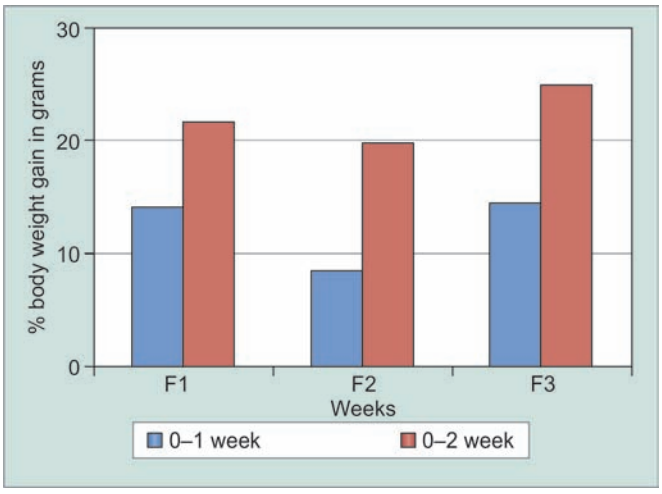
RESULTS AND DISCUSSION

Single-dose Acute Toxicity Study

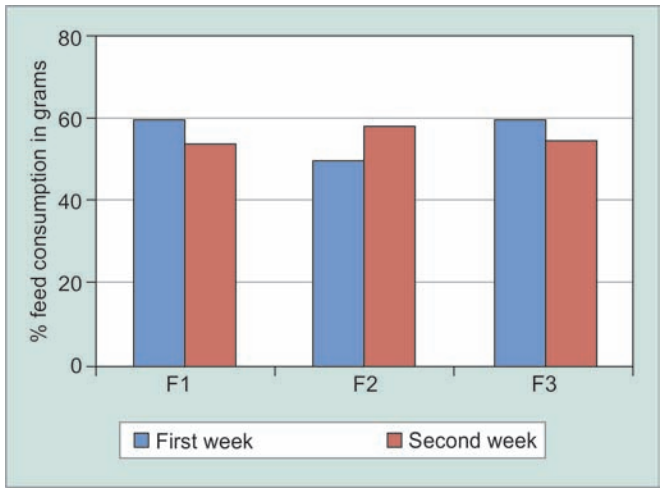
The acute study with single exposure of test extract at 2,000 mg/kg bwt showed that there were no preterminal deaths, no clinical signs of toxicity, and no abnormal behavior in the animals. Feed intake of the animals and weekly body weight gain were found to be adequate. The % body weight gain and % feed consumption in experimental animals for a period of 14 days in experimental steps 1 and 2 are recorded in Graphs 1 to 4.

Repeated Dose 28-day Oral Toxicity Study

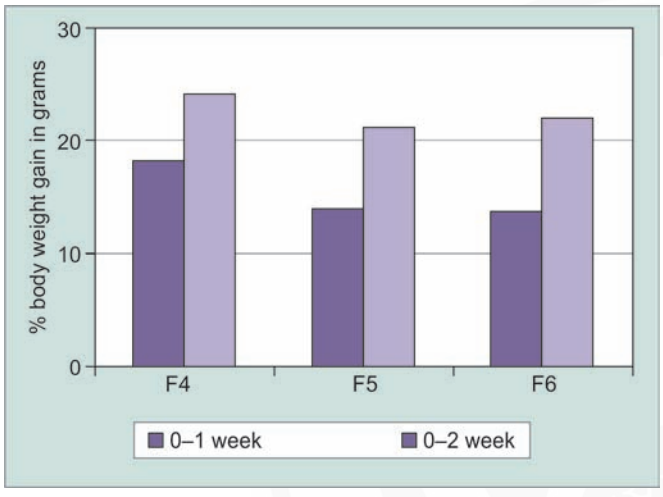
There were no preterminal deaths, no toxic signs, and no abnormal behavior in the animals exposed to the test



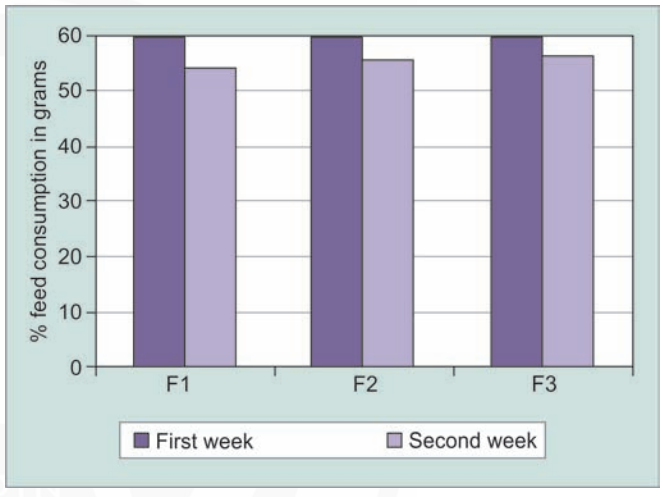
Graph 1: Percentage body weight gain of female Wistar albino rats during acute toxicity study: step 1



Graph 2: Percentage feed consumption in female Wistar albino rats during acute toxicity study: step 1



Graph 3: Percentage body weight gain of female Wistar albino rats during acute toxicity study: step 2



Graph 4: Percentage feed consumption in female Wistar albino rats during acute toxicity study: step 2

Table 1: Percentage body weight gain as compared with initial weight in Wistar albino rats during subacute toxicity study

	% Body weight gain (in grams)			
Groups	*0–1 weeks*	*0–2 weeks*	*0–3 weeks*	*0–4 weeks*
Control	26.82 ± 3.27	41.43 ± 5.22	51.19 ± 7.41	59.74 ± 8.57
Low dose	24.19 ± 2.01	38.85 ± 2.65	50.99 ± 3.11	60.18 ±3.42
Average dose	25.19 ± 1.54	38.98 ± 1.93	50.01 ± 2.53	58.88 ± 4.75
High dose	24.56 ± 3.46	37.09 ± 5.33	48.43 ± 7.33	56.01 ± 8.71

Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

compound in various dose levels, viz., low dose (250 mg/kg bwt), average dose (500 mg/kg bwt), and high dose (1,000 mg/kg bwt). No clinical signs of toxicity were observed in any of the animals. The % body weight gain and % feed consumption in experimental animals for a period of 28 days had been recorded (Tables 1 and 2). It showed that feed intake of the animals and weekly body weight gain were found to be adequate.

The hematological parameters, such as white blood count (WBC) count, lymphocyte count, granulocyte count, monocyte count, red blood cell (RBC) count, and hemoglobin showed that there were no significant differences between control and experimental groups (Tables 3 to 6). Serum biochemical investigations including glucose, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), liver function

Table 2: Percentage feed consumption in Wistar albino rats during subacute toxicity study

	% Feed consumption (in grams)			
Groups	I week	II week	III week	IV week
Control	77.70 ± 4.30	59.58 ± 1.93	51.97 ± 2.34	41.70 ± 2.06
Low dose	73.95 ± 2.79	60.06 ± 1.66	49.27 ± 1.84	43.61 ± 1.47
Average dose	75.00 ± 2.99	61.77 ± 2.63	50.55 ± 2.26	41.03 ± 1.78
High dose	74.53 ± 4.5	58.75 ± 2.38	51.41 ± 1.95	41.04 ± 1.70

Values are expressed as mean ± SEM, N = 12 per group, p > 0.05, not significant

Table 3: Hematological parameters of Wistar albino rats during subacute toxicity study

	Hematological parameters			
Groups	WBC count (cells/cmm)	Lymphocyte (cells/cmm)	Monocyte (cells/cmm)	Granulocyte (cells/cmm)
Control	8925.00 ± 734.03	6766.67 ± 593.57	291.66 ± 19.30	1866.66 ± 166.21
Low dose	7941.60 ± 822.73	5575.00 ± 563.02	233.33 ± 25.62	2133.00 ± 262.08
Average dose	7833.33 ± 666.44	5958.30 ± 566.82	216.66 ± 34.45	1658.33 ± 154.46
High dose	8566.60 ± 742.47	6525.00 ± 631.75	275.00 ± 25.00	1766.66 ± 164.38

Values are expressed as mean ± SEM, N = 12 per group, p > 0.05, not significant

Table 4: Hematological parameters of Wistar albino rats during subacute toxicity study

	Hematological parameters				
Groups	Lymphocyte (%)	Monocyte (%)	Granulocyte (%)	RBC count (million cells/cmm)	Hemoglobin (gm%)
Control	74.42 ± 1.74	3.58 ± 0.28	22.00 ± 1.67	6.58 ± 0.09	13.69 ± 0.14
Low dose	70.16 ± 1.52	3.25 ± 0.17	26.58 ± 1.25	6.65 ± 0.10	13.88 ± 0.10
Average dose	71.91 ± 1.99	3.16 ± 0.27	24.91 ± 1.95	6.38 ±0.09	13.57 ± 0.24
High dose	75.66 ± 1.60	3.16 ± 0.24	21.17 ± 1.46	6.75 ± 0.10	13.86 ± 0.16

Values are expressed as mean ± SEM, N = 12 per group, p > 0.05, not significant

Table 5: Hematological parameters of Wistar albino rats during subacute toxicity study

	Hematological parameters				
Groups	Packed cell volume (%)	Mean cell volume (fL)	Mean cell hemoglobin (pg)	Mean cell hemoglobin concentration (%)	Red cell distribution width (%)
Control	37.11 ± 0.44	56.33 ± 0.47	20.69 ± 0.18	36.75 ± 0.16	10.52 ± 0.17
Low dose	37.39 ± 0.36	56.18 ± 0.41	20.78 ± 0.21	36.88 ± 0.18	11.35 ± 0.26
Average dose	37.04 ± 0.68	56.10 ± 0.27	20.72 ± 0.12	36.79 ± 0.27	10.91 ± 0.37
High dose	37.88 ± 0.42	56.18 ± 0.50	20.50 ± 0.17	36.58 ± 0.13	10.74 ± 0.18

Values are expressed as mean ± SEM, N = 12 per group, p > 0.05, not significant

Table 6: Hematological parameters of Wistar albino rats during subacute toxicity study

	Hematological parameters				
Groups	Platelet count (lakh cells/cmm)	Mean platelet volume (fL)	Platelet distribution width (%)	Plateletcrit (%)	Prothrombin time (sec)
Control	9.87 ± 1.39	5.34 ± 0.11	16.60 ± 0.20	0.45 ± 0.04	9.56 ± 0.12
Low dose	8.71 ± 0.51	5.34 ± 0.09	16.40 ± 0.07	0.46 ± 0.02	9.67 ± 0.20
Average dose	9.19 ± 0.38	5.19 ± 0.09	16.35 ± 0.07	0.47 ± 0.01	9.71 ± 0.16
High dose	8.17 ± 0.74	5.36 ± 0.12	16.41 ± 0.12	0.46 ± 0.02	9.80 ± 0.31

Values are expressed as mean ± SEM, N = 12 per group, p > 0.05, not significant

parameters, such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), bilirubin, and renal function test parameters, such as creatinine and urea were carried out. The metabolic biochemical parameters showed that there were no significant differences between control and experimental groups (Tables 6 to 10). The urine analysis also evidenced that there were no abnormalities in the experimental group. The postmortem analysis showed that there was no significant difference in organ weight with respect to body weight among control and test groups (Tables 11 and 12).

Table 7: Glucose and lipid profiles estimation in serum samples of Wistar albino rats during subacute toxicity study

	Biochemical parameters					
Groups	*Glucose (mg/dL)*	*Cholesterol (mg/dL)*	*HDL (mg/dL)*	*LDL (mg/dL)*	*VLDL (mg/dL)*	*Triglyceride (mg/dL)*
Control	89.25 ± 3.18	75.08 ± 3.48	22.83 ± 1.49	36.08 ± 3.24	16.17 ± 1.15	80.58 ± 5.61
Low dose	84.91 ± 3.57	76.58 ± 2.31	25.33 ± 0.66	34.16 ± 2.42	17.08 ± 0.73	85.16 ± 3.73
Average dose	87.41 ± 3.21	78.75 ± 3.43	24.08 ± 0.94	38.08 ± 2.62	16.58 ± 0.82	81.91 ± 4.02
High dose	91.33 ± 3.45	74.50 ± 5.17	21.58 ± 3.09	36.75 ± 3.74	16.17 ± 1.17	80.92 ± 5.88

VLDL: Very-low-density lipoprotein; Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

Table 8: Serum protein estimation in serum samples of Wistar albino rats during subacute toxicity study

	Biochemical parameters			
Groups	*Total protein (gm/dL)*	*Albumin (gm/dL)*	*Globulin (gm/dL)*	*A/G ratio*
Control	6.55 ± 0.09	2.93 ± 0.07	3.61 ± 0.12	0.81 ± 0.04
Low dose	6.62 ± 0.09	3.13 ± 0.05	3.47 ± 0.05	0.89 ± 0.01
Average dose	6.45 ± 0.06	3.02 ± 0.02	3.42 ± 0.07	0.89 ± 0.02
High dose	6.64 ± 0.16	2.94 ± 0.05	3.70 ± 0.15	0.80 ± 0.03

Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

Table 9: Renal function test and electrolyte estimation in serum samples of Wistar albino rats during subacute toxicity study

	Biochemical parameters						
Groups	*Urea (mg/dL)*	*Creatinine (mg/dL)*	*Uric acid (mg/dL)*	*Sodium (mmol/L)*	*Potassium (mmol/L)*	*Chloride (mmol/L)*	*Calcium (mg/dL)*
Control	34.17 ± 1.04	0.47 ± 0.03	1.96 ± 0.19	143.00 ± 0.46	5.58 ± 0.21	97.25 ± 1.00	9.50 ± 0.19
Low dose	32.58 ± 1.78	0.48 ± 0.02	1.76 ± 0.18	142.16 ± 0.70	5.26 ± 0.18	97.66 ± 0.41	9.65 ± 0.06
Average dose	34.00 ± 1.30	0.48 ± 0.01	2.34 ± 0.08	143.00 ± 0.38	5.45 ± 0.15	97.16 ± 0.45	9.48 ± 0.04
High dose	35.67 ± 1.49	0.50 ± 0.02	2.28 ± 0.25	143.83 ±0.59	5.73 ± 0.18	96.83 ± 0.66	9.59 ± 0.25

Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

Table 10: Liver function parameters of Wistar albino rats during subacute toxicity study

	Biochemical parameters			
Groups	*Total bilirubin (mg/dL)*	*SGOT (U/L)*	*SGPT (U/L)*	*ALP (U/L)*
Control	0.29 ± 0.01	166.50 ± 11.18	45.25 ± 1.79	130.17 ± 17.29
Low dose	0.29 ± 0.02	149.41 ± 7.22	52.33 ± 3.01	120.08 ± 13.91
Average dose	0.34 ± 0.01	151.91 ± 7.32	52.16 ± 3.03	123.66 ± 14.64
High dose	0.33 ± 0.01	143.00 ± 11.61	48.91 ± 3.24	124.33 ± 19.34

ALP: Alkaline phosphatase; Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

Table 11: Organ weight in % body weight of Wistar albino rats during subacute toxicity study

	% Organ weight in grams				
Groups	*Heart*	*Lungs*	*Liver*	*Spleen*	*Stomach*
Control	0.365 ± 0.009	0.695 ± 0.023	3.121 ± 0.100	0.295 ± 0.016	0.662 ± 0.020
Low dose	0.387± 0.019	0.704 ± 0.018	3.256 ± 0.187	0.275 ± 0.009	0.693 ± 0.016
Average dose	0.369 ± 0.015	0.708 ± 0.015	3.181 ± 0.068	0.274 ± 0.015	0.695 ± 0.016
High dose	0.362 ± 0.012	0.705 ± 0.031	3.174 ± 0.098	0.310 ± 0.025	0.688 ± 0.016

Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

Table 12: Organ weight in % body weight of Wistar albino rats during subacute toxicity study

	% Organ weight in grams			
Groups	*Kidney*	*Testis*	*Ovary*	*Brain*
Control	0.723 ± 0.019	1.158 ± 0.035	0.050 ± 0.003	0.919 ± 0.020
Low dose	0.771 ± 0.046	1.205 ± 0.056	0.048 ± 0.003	0.940 ± 0.018
Average dose	0.750 ± 0.033	1.221 ± 0.051	0.051 ± 0.004	0.965 ± 0.021
High dose	0.748 ± 0.022	1.108 ± 0.058	0.050 ± 0.005	0.928 ± 0.035

Values are expressed as mean ± SEM, N = 12 per group, $p > 0.05$, not significant

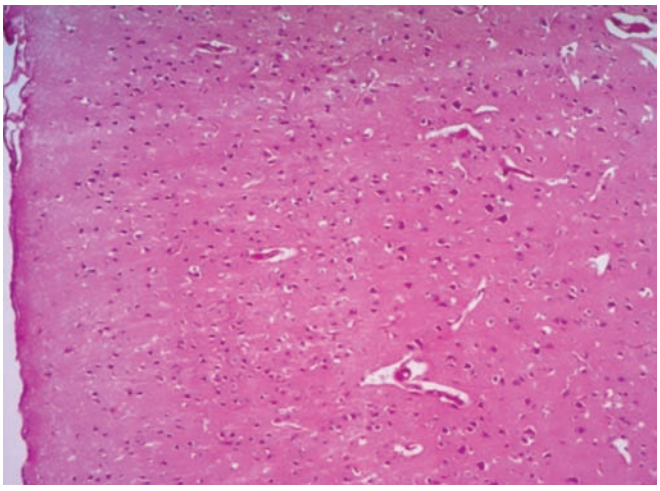


Fig. 1: Histopathology section of brain of a male rat showing normal glial cells and astrocytes (*C. halicacabum* extract at 1,000 mg/kg bwt)

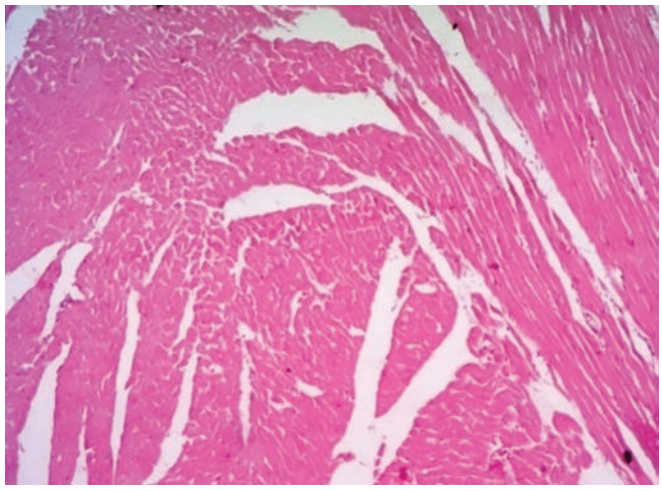


Fig. 2: Histopathology of heart of a male rat showing normal endocardium, myocardium, and pericardium (*C. halicacabum* extract at 1,000 mg/kg bwt)

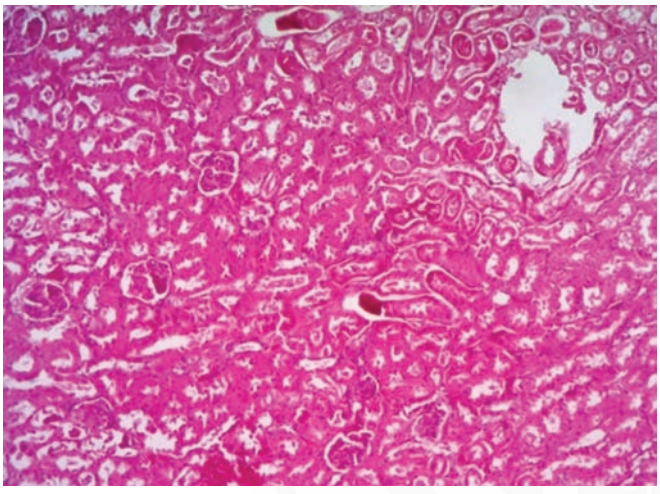


Fig. 3: Histopathology section of kidney a male rat showing normal glomeruli and interstitial tissue (*C. halicacabum* extract at 1,000 mg/kg bwt)

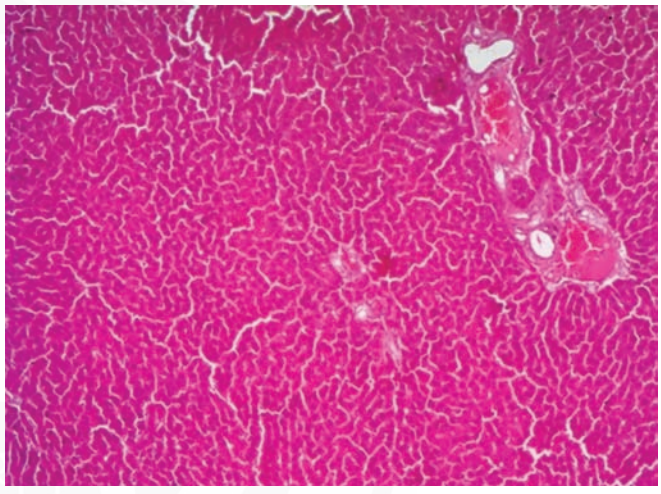


Fig. 4: Histopathology section of liver of a male rat showing normal portal area, central venous system, and hepatocytes (*C. halicacabum* extract at 1,000 mg/kg bwt)

Histopathology

No major histopathological changes were observed in any of the organs from the rats that received high dose of the extract compared with that of control. The histology study evidenced that the test extract was found to be safe at the prescribed dosages (Figs 1 to 6).

CONCLUSION

Single-dose acute oral toxicity study and repeated dose 28-day oral toxicity study exhibited the safety of the hydroalcoholic extract of *C. halicacabum* L. leaf at the selected doses, i.e., up to 1,000 mg/kg bwt, as there was no mortality and morbidity in test group animals. The detailed biochemical, hematological investigations, and histopathology studies also evidenced for the safety of

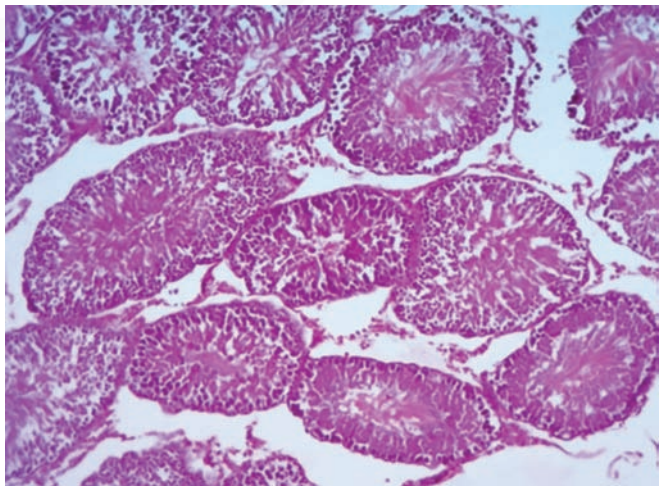


Fig. 5: Histopathology section of testis of a male rat showing seminiferous tubules of varying sizes showing normal spermatogenesis (*C. halicacabum* extract at 1,000 mg/kg bwt)

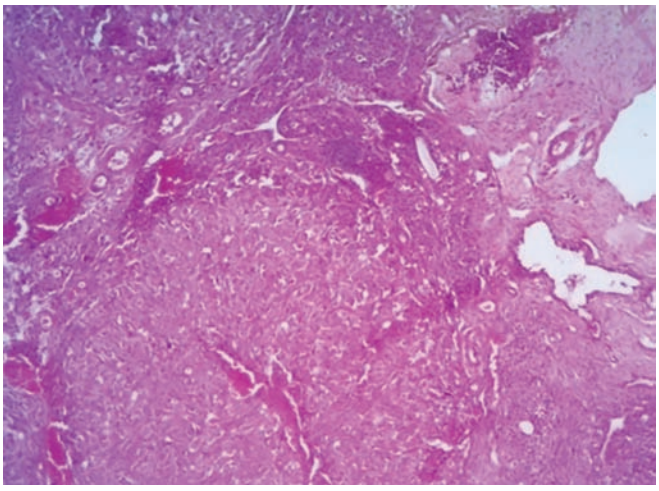


Fig. 6: Histopathology section of ovary of a female rat showing normal stroma and Graafian follicles (*C. halicacabum* extract at 1,000 mg/kg bwt).

the test drug. Further studies, such as biological activity, efficacy, or biopotency studies can be carried out using these safety dose details.

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हिन्दी सारंश

विस्टार अल्बिनो रैट्स में एक्यूट ओरल विषाक्तता अध्ययन तथा 28 दिन पुनरावर्तित मात्रा में ओरल विषाक्तता अध्ययन द्वारा *कर्णस्फोट* (*कार्डियोस्पर्मम हेलिकाकाबम* एल.) के पत्र की सुरक्षा का मूल्यांकन

उद्देष्यः *कार्डियोस्पर्मम हेलिकाकाबम* एल. सैपइंडसेई कुल का एक आरोही पादप है। विभिन्न बीमारियों के इलाज के लिए पौधों के पत्तों का पारंपरिक चिकित्सकों द्वारा उपयोग किया जाता है। *सी हेलिकाकाबम* के प्रजातीय औषधीय मूल्य को ध्यान में रखते हुए, वर्तमान अध्ययन को विस्टार एल्बिनों रैट्स में एकल खुराक विषाक्तता अध्ययन एवं 28 दिनों तक पुनरावर्तित मौखिक विषाक्तता अध्ययन उपतीव्र प्रभाव का मूल्यांकन करने के लिए किया गया।

सामग्री एंव विधिः विस्टार रैट्स में तीव्र विषाक्तता अध्ययन के लिए एकल खुराक (200 मि. ग्राम/कि. ग्रा.) के बीच एवं 28 दिनों तक तीन खुराक स्तर (250, 500 एवं 1000 मि. ग्रा. के बीच) पर उपतीव्र विषाक्तता अध्ययन के लिए पुनरावर्तित खुराक के लिए *सी हेलिकाकाबम* पत्तों के हाइड्रोएल्कोहौलिक निस्सार का मौखिक प्रयोग किया गया। उक्त अध्ययन आर्थिक सहयोग एवं विकास संगठन (ओईसीडी) के दिशा निर्देशों यथा 423 एवं 407 के अनुसार किया गया। अध्ययन काल के दौरान पशु संबंधित मृत्युदर एवं सामान्य व्यवहार का भी निरीक्षण किया गया।

परिणामः अध्ययन से पता चला है कि परीक्षण समूहों में कोई मृत्यु दर एंव रुग्ण नहीं थे। नियंत्रण और परीक्षण समूहों में मूल्यांकन किए गए विस्तृत बायोकेमिकल और हेमटोलॉजिकल जांच ने सुरक्षा को प्रमाणित किया क्योंकि नियंत्रण और परीक्षण समूहों के बीच कोई महत्वपूर्ण अंतर नहीं पाया गया। परीक्षण समूहों के महत्वपूर्ण अंगों में हिस्टोपैथोलॉजी अध्ययन सें सम्बंधित कोई महत्वपूर्ण असामान्यताए परिलक्षित नहीं हुईं।

निष्कर्षः *सी हेलिकाकाबम* के हाइड्रोल्ल्कोहलिक निस्सार सम्बंधित अध्ययन से यह प्रमाणित हुआ कि विस्टार अल्बिनो रैट्स में निर्धारित खुराक के स्तर पर सुरक्षित पाया गया।

आतुरीय महत्वः जैसा कि विस्टार रैट्स मे *सी हेलिकाकाबम* का हाइड्रोएल्कोहोलिक निस्सार सम्बंधित सुरक्षात्मक खुराक सही पाया गया अतः आगे इन विवरणों के आधार पर जैविक क्षमता, का अध्ययन आरम्भ किया जा सकता है।

कुंजी शब्दः कार्डियोस्पर्मम हेलिकाकाबम, गुब्बारा बेल, तीव्र और दोहराया खुराक–28 दिन मौखिक विषाक्तता अध्ययन।