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Preclinical Safety Assessment of Hydro-Alcoholic Extract of Cycas Pectinata Buch.-Ham.

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ABSTRACT:

Objectives

To assess the acute oral toxicity and safety profile of hydroalcoholic extract of Cycas pectinata (Cycadaceae) in female mice according to OECD Guideline.

Methods

The hydroalcoholic extract of C. pectinata (CPE) was administered orally to female mice at graded doses up to 2000 mg/kg body weight. Clinical signs of toxicity, behavioral changes, morbidity and mortality were observed for 14 days. Body weight, food intake and water consumption were recorded throughout the study. At the end of the experimental period, blood samples were collected for hematological and biochemical analysis and vital organs were examined histopathologically for systemic toxicity.

Results

No mortality or significant behavioral abnormalities were observed at any tested dose. Food and water intake and body weight gain were comparable to the control group. The hematological parameters were within the normal physiological range showing no deleterious effect to the blood components. Biochemical analysis revealed mild, dose-dependent fluctuations in creatinine and ALT at the highest dose (2000 mg/kg), but all values were within reference limits. Histopathological examination of the kidney, spleen and liver revealed preserved organ architecture with mild, non-specific changes.

Conclusions

The hydroalcoholic extract of Cycas pectinata did not show any significant acute toxicity in mice even at doses up to 2000 mg/kg. The results indicate a large safety margin and support the safe oral use of the extract and provide a basis for further pharmacological investigation.

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INTRODUCTION

Toxicology investigates the properties and biological effects of potentially harmful substances, highlighting dose-response relationships in the assessment of safety and therapeutic potential. It is an important part of drug development in identifying adverse effects and establishing appropriate safety margins [1]. Preclinical toxicity studies are important to characterize safety profiles of therapeutic agents and to evaluate absorption, distribution, metabolism and excretion (ADME). These evaluations, mostly using validated animal models, include acute oral toxicity testing to assess initial tolerability, to detect obvious toxic effects, and to guide dose selection for subsequent studies [2]. Hence, new therapeutic agents must undergo systematic toxicological evaluation for safety assessment.

Cycas pectinata Buch.-Ham. (Family: Cycadaceae), commonly known as *moniraj* or *nagmoni*, is medicinally important species of the genus *Cycas* [3]. Numerous ethnopharmacological uses have been documented across *Cycas* species, and indigenous communities throughout Northeast India traditionally utilized the leaves, seeds, and bark of *C. pectinata* for several medicinal purposes. The plant has traditionally been used to promote hair growth and to treat stomach ailments and ulcers [4,5]. Previous studies have shown that secondary metabolites extracted from *C. pectinata* possess a broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, thrombolytic, anxiolytic, sedative, antinociceptive, and antidiarrheal properties [4,6]. Phytochemical analysis of the plant has further revealed the presence of diverse classes of bioactive constituents, including alkaloids, glycosides, flavonoids, terpenoids, and steroids [7].

Despite its extensive traditional use and emerging pharmacological evidence, systematic toxicological investigations of *C. pectinata* remain limited. Establishing an adequate safety profile is therefore an essential prerequisite for its further pharmacological development and potential therapeutic application. Accordingly, the present study was undertaken to evaluate the acute oral toxicity of a hydroalcoholic extract of *C. pectinata* in mice, with the aim of establishing a preliminary safety profile to guide its further pharmacological and therapeutic development.

MATERIALS AND METHODS

Collection and Identification of plant material

Fresh female cones of *Cycus pectinata* were collected from village Chachal, Kamrup Metro district, Assam, India. The plant specimen was identified and authenticated by Taxonomist, TERI Guwahati, India and voucher specimen was deposited in departmental herbarium section for future reference.

2.3. Preparation of extract

Plant Material and Preparation of Extract.

The collected fresh female cones of *C. pectinata* were cut into small pieces and dried under shade. The air-dried plant material was subsequently ground to the powdered before extraction. The powdered material (200 g) was macerated with 70% ethanol (1.5 L× 3 Times) for 72 h with occasional shaking and stirring. The extract was then filtered through muslin cloth and Whatman No. 1 filter paper simultaneously. The combined filtrate was concentrated in a rotary evaporator (Buchi, New castle, DE, USA) (40°C) under reduced pressure to obtain hydroalcoholic extract of *C. pectinata* (CPE) with a yield of 5.6% w/v.

Experimental Animals

Healthy female Swiss albino mice were procured from Laboratory Animal House Facility, CSIR-Indian Institute of Toxicology Research, Lucknow, India. All the animals were acclimatized for at least one week in animal house under standard conditions of temperature of (25 ± 2°C), relative humidity 45-55% and 12 h light/dark cycle. The animals fed with standard rodent feed (Ashirwad, India) and water. The mice were randomly assigned to different experimental groups, each containing five albino mice. All the animal experiments were conducted in compliance with the CCSEA guidelines for the care and use of experimental animals and with the prior permission from Institutional Animal Ethics Committee of University Institute of Pharmacy, Chhatrapati Shahu Ji Maharaj University (CSJMU), Kanpur.

Acute toxicity Studies

Acute oral toxicity testing was conducted in accordance with OECD Test Guideline No. 420 [8]. Four groups of mice were used to evaluate any potential adverse effects or deviations from normal behavior. The acute toxicity of the *C. pectinata* was

assessed by orally administering three different doses (500, 1000, and 2000 mg/kg body weight) via gavage needle to three separate groups (group 2, 3 and 4) of animals, while a group first served as the negative control and received the vehicle alone (1% CMC in distilled water). Prior to dosing, all animals were fasted for 24 h, with water provided ad libitum. On the day of the experiment, the animals were weighed and, following the 24-h fasting period, administered the test substance; food was withheld for a further 3–4 h after dosing.

Clinical sign and bodyweight measurement

Each animals were closely observed after the drug administration and special attention was given for the first 4-6 hours after the dosing. The animals were closely observed daily twice (morning & evening) for a total of 14 days for overt signs of toxicity, morbidity and mortality. In addition, each animal was removed from its cage and a physical examination of each animal were systematically recorded daily for any changes in skin, fur, eyes, respiratory function, autonomic effects such as salivation, diarrhea, urination and central nerve effects including tremors and convulsions, and general behavior [9]. The body weights of all the animals were measured at regular interval throughout the study period by using calibrated balance. Subsequent weight changes were calculated and documented.

Relative and absolute organ weight

All organs of experimental animals were collected using standardised surgical procedures at the end of the acute toxicity trial (14 days). Organs such as the liver, spleen and kidney, were removed, cleansed with saline, weighed, and kept in 10% formalin for histopathological investigations.

Consumption of food and water

The amount of food and water consumption of each animal of both control and test groups were calculated daily from the amount of food and water delivered and the amount left after 24 hours during the study period [10].

Hematological examination

At the end of toxicity study, the blood sample were collected in the heparinized centrifuge tubes for analyzing hematological parmeters using an automated vet hematology analyzer. Parameters evaluated include hemoglobin (HGB), erythrocyte count (RBC), hemat-ocrit(HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet count and leucocyte count(WBC) [11,12].

Biochemical examination

For serum separation, the blood samples were collected (after 14 days) in centrifuge tubes and immediately the serum was separated by centrifugation at 3000 rpm for 15 min. The separated serum sample were transferred into serum tubes and stored in freezer until analyzed for biochemical parameters. The biochemical parameters analyzed included total protein, urea, creatinine (CREA), glucose, total cholesterol, aspartate aminotransferase (AST), albumin (ALB), bilirubin (BIL), and lactate dehydrogenase (LDH) [13,14].

Histopathological observation

The collected vital organs (liver, kidney, spleen) were microscopically examined. The morphology of the internal organs were visually observed for any signs of toxicity. These organs were stained with hematoxylin and eosin (H&E) stain. Abnormalities were categorized as mild, moderate, and severe [15,16].

RESULTS

Clinical sign observation

Oral administration of CPE at doses upto of 2000 mg/kg body weight did not produce any significant changes in behavior, skin, breathing, faeces, postural irregularities, impairment in water consumption and food intake and hair loss in experimental animals. No animal mortality occurred in the groups treated with CPE throught the observation period.

Body weight measurement

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The mean body weight of mice was recorded daily for a period of 14 consecutive days and results are shown in table 1. The 1% CMC (negative control) group exhibited slight gain in body weight relative to the other three groups treated with CPE. The % increase of body weight of different groups 2, 3 and 4 were not significantly different (t test, $P \leq 0.10$) from control group 1 at the end of study (14 days).

Table 1: Body weight of mice after 14 days exposure of extracts and control groups

Group	Intial (0 day)	1st weak	2nd weak
Group 1	28.6 ± 2.78	32.6±2.40	35.8±2.28
Group 2	29.0± 2.30	33.8±1.64	34.3±1.60
Group 3	30.6 ± 2.39	37.6±2.02	36.6±2.028
Group 4	30.0 ± 2.98	36.2±2.44	37.8±2.15

Group 1: 1% CMC, Group 2: 500 mg/ kg, Group 3: 1000 mg/ kg, Group 4: 2000 mg/ kg body weight; Number of mice =5 per group

Complete blood count (CBC) test

At the end of 14-day observation period of acute toxicity, hematological parameters were analyzed in mice and results are shown in table 2. Changes in RBC-related parameters (Hb, total RBC count, HCT, MCV, MCHC and MCH) were mild and dose-related, particularly at 2000 mg/kg, where hemoglobin and RBC counts slightly drop. RBC-related parameters were within normal reference ranges and there were no signs of overt anemia or hemolysis. WBC and differential counts were stable at all treatment doses indicative of no significant immunosuppression or immunostimulation. Platelet counts also remained unchanged indicating the absence of any hematopoietic toxicity affecting thrombopoiesis. No significant hematological toxicity was found overall the highest dose (2000 mg/kg).

Table 2: Effect of oral administration of hydroalcoholic extract of *C. pectinata* on haematological parameters of mice.

Biological marker	Unit	Group 1 Normal N=5	Group 2 Dose 500 mg/kg N=5	Group 3 Dose 1000 mg/kg N=5	Group 4 Dose 2000 mg/kg N=5
HB	(g/dl)	14.5	13.91	13.41	14.1
TOTAL RBC	X(10 ^ 6) / µL	8.47	8.21	7.91	8.41
HCT	%	54.1	54.23	53.80	54.2
MCV	FL	63.9	62.9	63.1	63.8

MCHC	(g/dl)	26.8	26.4	26.2	26.5
PLATELET COUNT	X(10 ^ 3) / µL	644	642	641	640
WBC COUNT	X(10 ^ 3) / µL	7.63	7.53	7.62	7.61
NEUTROPHILS	%	53.4	53.2	53.3	53.2
LYMHOCYTES	%	22.0	22.1	22.2	22.0
MONOCYTES	%	0.5	0.5	0.5	0.6
EOSINOPHILS	%	7.4	7.2	7.4	7.3
MCH	Pg	17.9	17.4	17.5	17.7
BASOPHILS	%	16.7	16.1	16.2	16.3

Biochemical analysis

Table 3 indicated the changes in readings for the diverse biochemical indicators across the majority of the CPE treated groups. Mild increase was observed in some parameters such as creatinine, ALT, and cholesterol at highest dose level.

Table 3: Effect of oral administration of hydroalcoholic extract of *C. pectinata* on biochemical parameters of mice.

Parameter	Normal N=5	Dose500mg/kg N=5	1000mg/kg N=5	2000mg/kg N=5
CREAT (mg/dL)	0.56 ± 0.06	0.42 ± 0.12	0.30 ± 0.01	0.76 ± 0.10
Urea (mg/dL)	42.13 ± 4.42	48.70 ± 5.81	46.90 ± 6.48	42.40 ± 2.95
ALT (U/L)	80.00 ± 6.81	61.33 ± 10.17	69.33 ± 8.11	122.7 ± 19.46
AST (U/L)	140.30 ± 22.60	136.70 ± 20.93	124.00 ± 4.16	134.00 ± 6.43

Tot Chol (mg/dL)	50.00 ± 7.37	35.67 ± 0.88	43.33 ± 9.33	71.00 ± 22.27
Na + (mmol/L)	105.00 ± 1.80	124.70 ± 1.07	129.60 ± 0.41	151.00 ± 0.56
K+ (mmol/L)	6.97 ± 0.05	6.53 ± 0.56	6.12 ± 0.15	6.08 ± 0.09
Cl-(mmol/L)	109.60 ± 5.11	151.00 ± 2.56*	159.20 ± 3.63*	106.80 ± 0.84

Data are expressed as Mean ± SEM;*significant *p*-value when control is compared with treatment groups; n (number of mice) =5 per group for treated groups while 5 per group for control for the combined analysis.

Hematological and Biochemical Parameters Evaluation Result

The effect of CPE at doses of 500, 1000 and 2000 mg/kg were evaluated across hematological, renal, hepatic, lipid and electrolyte parameters in treated animals compared to control (n=5 per group). The results are summarized as follows:

Hemoglobin (HB) levels remained relatively stable across all treated groups (13.91-14.1 g/dl) compared to the control (14.5 g/dl), suggesting no significant impact on hemoglobin concentration. Total RBC count showed a slight, non-significant decrease in a dose-dependent manner, from 8.47×10^{6}/ µL in control to 8.41×10^{6}/ µL at the highest dose (2000 mg/kg), but remained within the normal range throughout. Hematocrit (HCT) values were consistent across all groups (54.2–54.23%), and red cell indices (MCV, MCH, MCHC) showed minimal variation (MCV: 62.9–63.8 fL; MCH: 17.4–17.7 pg; MCHC: 26.4–26.5 g/dL), indicating stable red blood cell morphology. Platelet counts remained comparable across all groups (~642–640×10^{3}/ µL), indicating no evidence of thrombocytopenic or thrombocytosis effects due to treatment. Total WBC count (7.53–7.61×10^{3}/µL) and differential leukocyte counts (neutrophils ~53%, lymphocytes ~22%, monocytes 0.5–0.6%, eosinophils 7.2–7.3%, basophils 16.1–16.3%) likewise showed no significant differences between treated and control groups. Overall, none of the hematological parameters evaluated differed meaningfully from control at any dose tested.

Renal function

Both serum creatinine and urea levels, which are indicators of renal function, remained within normal physiological ranges across all treatment group and did not differ significantly from control ($p > 0.05$), suggesting that renal and glomerular filtration were not impared by the CPE.

Liver enzyme

No significant differences in ALT or AST were observed between 500 and 1000 mg/kg groups and control ($p > 0.05$) showing no hepatocellular damage at these doses. However, at the highest dose (2000 mg/kg) ALT was significantly increased indicating mild hepatic stress. Elevated ALT is usually associated with hepatocyte membrane leakage and may indicate early cellular irritation at high doses. Conversely, at this dose AST was unchanged suggesting that any hepatic effect was mild and not indicative of significant liver injury.

Lipid profile

Total serum cholesterol levels were decreased at the doses of 500 and 1000 mg/kg suggesting a probable hypolipidemic activity of the CPE which could be attributed to phytosterols or flavonoids that could have an effect on lipid metabolism. However, at 2000 mg/kg there was an increase in cholesterol levels, which may be a stress-related or dose-dependent biochemical response rather than a direct lipid modulating effect.

Electrolytes

Serum Na^{+} and K^{+} concentrations were within normal physiological ranges in all treatment groups indicating the balance of electrolytes was maintained ($p > 0.05$). But at the 500 and 1000 mg/kg doses, Cl^{-} levels were noticeably higher ($p < 0.05$), which might be related to a small acid-base adjustment but did not result in any toxicity symptoms.

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Histopathology.

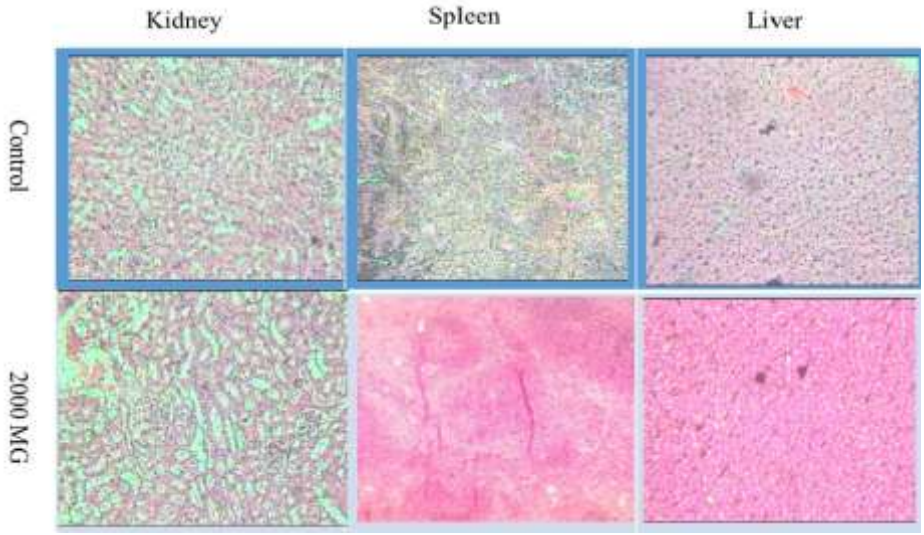

Fig.1. Representative Histopathological Photomicrographs of the Kidney, Spleen, and Liver from Control and 2000 mg/kg CPE Following Acute Oral Toxicity Study (H&E Staining, ×100).

Kidney

Microscopic examination of the kidney section revealed well-preserved renal architecture with intact glomeruli and renal tubules. The glomeruli appear to have normal morphology with preserved Bowman's spaces, while the tubular epithelium is largely intact. There is no obvious evidence of severe tubular degeneration, glomerular atrophy, crystal deposition, hemorrhage, necrosis, or marked inflammatory cell infiltration in the field examined. The interstitial tissue appears unremarkable without significant edema or fibrosis. Overall, the kidney tissue exhibits near-normal histological features, indicating preservation of renal structure.

Spleen

Both the control and 2000 mg/kg treatment groups' spleens showed normal histological architecture when examined under a microscope. Both the red and white pulp areas had typical splenic sinusoids and lymphoid follicles. It appears that the CPE had no negative effects on splenic tissue because there were no indications of lymphoid depletion, congestion, bleeding, necrosis, inflammatory infiltration, or structural anomalies.

Liver

Hepatic architecture was intact in both the control and 2000 mg/kg CPE treated groups, according to histopathological inspection of the liver sections. Hepatocytes, hepatic sinusoids, central veins, and hepatic lobules all looked normal and on par with the control group. Following acute oral administration of the CPE, no signs of hepatocellular degeneration, lipid alterations, necrosis, inflammatory cell infiltration, sinusoidal congestion, or fibrosis were seen, suggesting the absence of treatment-related hepatotoxicity.

Figure 1 represent photomicrographs of the kidney, spleen, and liver from control and hydroalcoholic extract-treated rats (2000 mg/kg). Histological examination revealed normal tissue architecture in all examined organs with no treatment-related pathological changes, supporting the safety of the hydroalcoholic extract of *Cycas pectinata* following acute oral administration (H&E staining; magnification as indicated).

DISCUSSION

The use of herbs as a natural remedy, has gained widespread popularity in primary healthcare globally. Medicinal plant-derived preparations are often considered as safe and devoid of adverse health effects, leading to their widespread usage in self-medication [13].

However, due to the lack of validated scientific data on the toxicity of many such remedies, further investigation is necessar y, particularly regarding Cycas species. In the present 14-day acute toxicity study, no mortality and no overt signs of toxicity were observed in animals treated with *Cycas pectinata* extract (CPE) at 500, 1000, and 2000 mg/kg. Functional observations, including respiratory effects and signs of autonomic and neurological function, in the high-dose group showed no significant changes in behavior. CPE had no effect on body weight at any dose, and no significant changes in food or water intake were noted, which is indicative of normal metabolic activity and suggests a single oral dose of CPE did not impair growth [17]. There were no significant changes observed in absolute organ weights of liver, kidney, and spleen compared to the negative control group.

Biochemical analysis revealed only minor changes overall. A slight elevation of ALT was seen at the highest dose (2000 mg/kg), but histological examination did not confirm cellular injury in the kidney, which may represent an early, sub-histological stage of renal change [18]. Elevated LDH has been previously associated with lung lesions in mice, but LDH levels in this study were not significantly different among treatment groups, consistent with the absence of corresponding histologic findings.

Hematological analysis after 14 days of the acute toxicity period did not show significant changes in WBC, RBC, hemoglobin, HCT, MCV or MCHC indicating that CPE did not adversely affect blood parameters at any of the doses tested. In the H&E stained liver sections, no abnormal morphological alterations were detected in any of the treatment groups.

CONCLUSION

The safety profile of the hydroalcoholic extract of *Cycas pectinata* was assessed by an acute oral toxicity study according to OECD recommendations. The findings showed that *C. pectinata* extract was well tolerated in mice after oral administration, even at relatively high doses with no signs of any significant acute toxicity. Overall, the extract demonstrated an acceptable acute safety profile at the doses tested, supporting its potential for future therapeutic investigation with appropriate dose selection. However, additional sub-chronic and chronic toxicity studies are warranted to establish its long-term safety and further characterize its toxicological profile.

Acknowledgements

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Ethics statement

All animal experimentations were strictly carried out as per 'CCSEA regulations for Laboratory Animals' with the approval of Institutional Animal Ethics Committee of Chhatrapati Shahu Ji Maharaj University, Kanpur (No. 1589/G0/Re/S/12/CPCSEA)

Conflict of interest disclosure

The authors declare no conflict of interest.

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