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A Study of the Toxicity of Cat's Claw Herbal Medicine

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Abstract: Detailed studies on the toxicity of cat's claw capsules were carried out in mice through examination of possible biochemical, hematological and histopathological changes. Acute, subacute and chronic toxicity studies were undertaken by treating mice with a single dose of 150 mg kg^{-1} body weight for acute, 50 mg kg^{-1} body weight administered orally each other day for 7 days for subacute and an oral dose of 10 mg kg^{-1} body weight of the drug daily for 90 days for chronic toxicity studies. Hematological studies revealed a significant reduction in WBC levels ($p<0.05$) upon acute treatment of male and female mice as compared to the control. Biochemical studies showed significant rise in the levels of AST and ALT in acute and subacute treated mice. Hematological studies on the chronically treated male and female mice revealed no appreciable differences as compared to the control, except for a mild increase in platelet count. Biochemical studies revealed a non-significant increase in AST and ALT in the male group. Changes in key hepatic enzymes levels including aspartate aminotransferase, alanine-aminotransferase, alkaline phosphatase, enzyme MB of creatinine kinase, glucose, urea and creatinine and histopathological modifications (heart, liver, kidneys and pancreas) were not observed in mice treated with cat's claw capsules. The low toxicity of cat's claw as evidenced by key hepatic enzymes stability and organ integrity suggests a wide margin of safety for therapeutic doses of cat's claw.

Key words: Cat's claw, acute, subacute and chronic, toxicity, anti-inflammatory, therapeutic doses, peptic ulcers

INTRODUCTION

Cat's claw (*Uncaria tomentosa* (wild) DC) is known with the common names cat's claw, Una de gato, Una de gavilan and hawk's claw. The root, bark and leaves are used medicinally.

The following properties are attributed to cat's claw: antibacterial antimutagenic, antioxidant, anti-inflammatory, antitumorous, antiviral, cytostatic, deputative, diuretic, hypotensive, immunostimulant and vermifuge (Goncalves *et al*., 2005).

Several biologically active natural compounds were isolated from cat's claw: the most attention to date has been on the oxindole alkaloids found in the bark and roots of cat's claw, which have been documented to stimulate the immune system (Kiplinger, 1994). Studies indicated that at least six of these oxindole alkaloids can increase immune function by up to 50% in relatively small amounts (Kiplinger, 1989, 1994; Sheng *et al*., 1998, 2000; Lemaire *et al*., 1999). This has led to its use around the world as an adjunctive treatment for cancer and AIDS as well as other diseases, which negatively impact the immunological system. In addition to its immunostimulating activity for cancer patients, other anti-cancerous properties have been documented on the alkaloids as well as other constituents in cat's claw (Kiplinger, 1989; Stuppner, 1992; Winkler *et al*., 2004).

Five of the oxindole alkaloids have been clinically documented with anti-leukemic properties and various root and bark extracts have demonstrated anti-tumorous and antimutagenic properties (Stuppner, 1992; Rizzi, 1993). Based on different studies cat's claw was suggested to be used for accelerating recovery of patients from leucopenia (Akesson and Ivars, 2003). Reports on observatory trials with cancer patients taking cat's claw in conjunction with traditional cancer therapies like chemotherapy and radiation reported fewer side effects to the traditional therapies, e.g., hair loss, weight loss, nausea, secondary infections and skin problems.

Some nutritionists consider cat's claw being beneficial in the treatment of cancer, arthritis, bursitis, rheumatism, genital herpes and herpes zoster, allergies, ulcers, systemic candidiasis, post menopausal symptoms and irregularities of the female cycle, environmental toxin poisoning, numerous bowel and intestinal disorders, organic depression and HIV. Some others cited its usefulness in treating diverticulitis, hemorrhoids, peptic ulcers, colitis, gastritis, parasites and leaky bowel syndrome (Yano, 1991).

Toxicity studies performed showed no toxicity for cat's claw at the dosages used by Santa Maria *et al*. (1997). Cat's claw is officially registered with the ministry of health, Saudi Arabia as antirheumatic with a

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recommended dose of 350 mg twice daily. No toxicity data were available in official files. Therefore, the present study was designed to investigate acute, subacute and chronic toxicity effects of cat's claw capsules.

MATERIALS AND METHODS

Ether, haematoxylin, eosin, methanol, formalin, may-gruenwald solution and Giemsa stain all purchased from (Sigma-Aldrich). Test combination reagents (Boehringer Mannheim GmbH, Diagnostica, Germany).

Instruments: Coulter counter, spectrophotometer, introspect II (LKB). American optical rotary microtome. Optical microscope centrifuge (Beckman coulter).

Animals: Toxicity studies were conducted using male and female mice adopting acute, sub acute and chronic modes. Swiss albino mice (SWR) aged 6-7 weeks and weighing 20-25 g (home breed) were used. The animals were maintained under standard conditions of humidity, temperature and light (12 h dark/12 h light). The animals were fed with Purina chow diet with free access to water.

Acute toxicity evaluation: The dose selected for acute toxicity was (150 mg kg^{-1}), which is 15 times the therapeutic dose. The drug in each case was suspended separately and homogenously in 1% Carboxymethyl Cellulose (CMC) solution and administered orally (0.5 mL $mouse^{-1}$) in a single acute dose. The control group received equal amount of vehicle. The animals were observed for 7 days after treatment. Each of the control and treatment groups contained randomly allotted 10 male and 10 female mice kept separately. The animals were observed for any sign of toxicity.

Subacute toxicity evaluation: The study on subacute treatment involved repeated dose exposures for short term histopathology. A dose of 50 mg kg^{-1} was given orally each other day for 7 days. The control group received vehicle in the same dose (0.5 mL). The parameters included in this study were based on standard toxicological screening program (Robin *et al*., 1982; Chan *et al*., 1982) and included screening on general toxicity systems, mortality, body and organ weight, hematology, biochemistry, genotoxicity and histopathology.

Chronic toxicity evaluation: For chronic toxicity test, the prolonged treatment for a period of 90 days is suggested to be sufficient in short lived rodents in order to predict the hazards of long term low dose exposure of a particular drug (Mossberg and Hayes, 1989). A dose of 10 mg kg^{-1} was given orally for 90 days. The aim of this investigation was to evaluate the effect of prolonged treatment on the target organs and the physiological and metabolic tolerance of the drug product at low doses. The parameters included in the study were based on the standard toxicological screening program (Robin *et al*., 1982; Chan *et al*., 1982; Mossberg and Hayes, 1989). The findings were substantiated by histopathological studies.

Metabolic measurements: The animals were anesthetized with ether and blood was taken from the heart by direct puncture.

Biochemistry: The blood was collected, serum samples were separated, stored at -20°C and analyzed for alanine aminotransferase (ALT/GPT), aspartate aminostrasnferase (AST/GOT), enzyme MB of Creatine Kinase (CK-MB), glucose, urea and creatinine. The parameters were analyzed by an enzymatic colorimetric method using test combination reagents. The measurements were carried out in a spectrophotometer.

Hematology: The blood was analyzed on a coulter counter for the quantification of different hematological indices, such as WBC, RBC, hemoglobin, haematocrit, platelets and MCV.

Histopathological procedures: Tissue samples of liver, heart and kidney were preserved in 10% buffered formalin and processed for routine paraffin block preparation. Using an American optical rotary microtome, sections of thickness of about 5 μm were cut and stained with haematoxylin and eosin. The preparations were analyzed using an optical microscope compared to control animal preparation.

Genotoxic studies: The adhering soft tissue and epiphyses of both the tibiae were removed. The marrow was aspirated from each femur in fetal calf serum and transferred to centrifuge tubes. After centrifugation at 1000 rpm for 5 min the supernatant was discarded and the residual cells were spread on slides and air dried. The slides were fixed in methanol, stained in May-Gruenwald solution followed by Giemsa stain. The coded slides were screened for the presence of micronuclei in polychromatic erythrocytes, which Indicated non-disjunction, chromosomal breaks and structural or numerical changes in the chromosomes. The bone marrow depression (mitotic index) was evaluated on the basis of the ratio of polychromatic to normochromatic erythrocytes (PCE/NCE ratio) (Al-Harbi *et al*., 1994).

Statistical analysis: For the evaluation of results obtained during acute, subacute and chronic toxicity studies: student's t-test and Chi-square (χ^2) test were used to assess the significance of the values obtained in the treated groups as compared to controls.

RESULTS

Acute toxicity: The result of acute toxicity studies in mice demonstrated that there was statistically non significant gain in body weight of animals in the treatment and control groups. Among the vital organs there was slight increase in the weight of liver and kidney in male mice. Biochemical parameters for control and treatment groups showed statistically significant changes. There was statistically significant increase ($p<0.05$) in urea, AST and ALT levels following cat's claw treatment in male and female mice as compared to the control as shown in Table 1 and 2. Hematological studies revealed a significant reduction in WBC levels ($p<0.05$) in treated male and female mice. Results were shown in Table 3 and 4. There was also a moderate increase in the platelet count in treated male mice. Other hematological parameters (RBC, hemoglobin, MCV and HCT) for both the treated female and male animals remained comparable with the control without significant changes. Histopathological investigation confirmed that all the vital organs studied (heart, kidney, liver, lungs, spleen and testis) were normal and comparable to the control.

Clastogenic effects for control and treatment groups showed statistically non-significant changes. The results obtained in the acute toxicity experiment necessitated further cofimation. It was thus, deemed appropriate to carry out subacute toxicity studies.

Subacute toxicity: During subacute toxicity studies the body weight increase in the control male and female groups was significant ($p<0.01$). There was also a significant gain in the body weight ($p<0.01$) in the male treatment group. However, the body weight changes in the female treatment group were non significant.

There was no significant difference in the vital organ weights of animals in the treatment groups as compared to the control except for an increase ($p<0.05$) in the weight of liver of male animals. Biochemical studies showed a significant rise ($p<0.01$) in the levels of AST and ALT of cat's claw treated animals as compared to the control.

Hematological studies revealed some decrease in WBC levels of cat's claw treated male and female as compared to the control, however, this decrease was statistically non-significant in female treatment group. Histopathological studies revealed heart, kidney, liver, lungs, testicles, pancreas, bone marrow, spleen, skeletal muscles and bone to be normal except mild congestion in liver and lungs.

Chronic toxicity: During chronic toxicity studies there was a highly significant increase ($p<0.001$) in the body

Table 1: Biochemical studies on male mice after acute treatment (150 mg kg^{-1}) with cat's claw

	Biochemical indices (mean±SE)					
Treatment groups	AST (μ L^{-1})	ALT (μ L^{-1})	CK-MB (μ L^{-1})	Creat. (μmol L^{-1})	Urea (mmol L^{-1})	Glucose (mmol L^{-1})
Control	17.6±1.92	11.08 ±1.29	138.96±8.15	127.56±3.12	6.66±0.16	5.64±0.12
Cat's claw	31.2±3.45*	18.58±2.36*	135.17±7.38	135.15±2.90	8.30±0.44*	5.89±0.08

*$p<0.05$ (student's t-test); 5 male mice were used in each group

Table 2: Biochemical studies on female mice after acute treatment with (150 mg kg^{-1}) cat's claw

	Biochemical indices (mean±SE)					
Treatment groups	AST (μ L^{-1})	ALT (μ L^{-1})	CK-MB (μ L^{-1})	Creat. (μmol L^{-1})	Urea (mmol L^{-1})	Glucose (mmol L^{-1})
Control	16.91±1.50	12.33 ±0.09	130.91±7.90	130.65±2.99	6.66±0.16	5.48±1.19
Cat's claw	20.40±1.61*	12.59±1.50*	129.63±8.72	132.39±4.61	7.80±0.20*	5.40±0.22

Table 3: Hematological studies on male mice after acute treatment (150 mg kg^{-1}) with cat's claw

	Hematological indices (mean±SE)					
Treatment groups	WBC (×10^9 L^{-1})	RBC (×10^{12} L^{-1})	Hemoglobin (g dL^{-1})	Platelets (10^9 L^{-1})	MCV (fL)	HCT ratio (%)
Control	6.12±0.25	7.40±0.11	12.36±0.13	438±21.30	67.42±0.19	38.58±0.09
Cat's claw	4.94±0.21*	7.32±0.10	12.60±0.19	496±24.50*	69.19±0.22	38.74±0.28

Table 4: Hematological studies on female mice after acute treatment (150 mg kg^{-1}) with cat's claw

	Hematological indices (mean±SE)					
Treatment groups	WBC (×10^9 L^{-1})	RBC (×10^{12} L^{-1})	Hemoglobin (g dL^{-1})	Platelets (10^9 L^{-1})	MCV (fL)	HCT ratio (%)
Control	5.94±0.17	7.28±0.15	13.18±0.16	464±27.30	68.30±0.24	38.42±0.29
Cat's claw	5.30±0.19*	7.32±0.19	13.22±0.16	485±30.61	70.18±0.30	39.26±0.17

*$p<0.05$ (student's t-test); 5 female mice were used in each group; treatment group was statistically compared with the control groups

Table 5: Hematological studies on male mice after chronic treatment (10 mg/kg/day) with cat's claw

	Hematological indices (mean±SE)					
Treatment groups	WBC ($\times 10^9$ L^{-1})	RBC ($\times 10^{12}$ L^{-1})	Hemoglobin (g dL^{-1})	Platelets (10^9 L^{-1})	MCV (fL)	HCT ratio (%)
Control	5.86±0.21	6.74±0.24	13.16±0.22	522±15.1	51.84±0.73	38.48±0.46
Cat's claw	5.69±0.23	7.00±0.19	13.66±0.26	558±16.9*	52.26±0.36	39.60±0.32

*p<0.05 (student's t-test); 5 female mice were used in each group; treatment group was statistically compared with the control groups

Table 6: Hematological studies on female mice after chronic treatment (10 mg/kg/day) with cat's claw

	Hematological indices (mean±SE)					
Treatment groups	WBC ($\times 10^9$ L^{-1})	RBC ($\times 10^{12}$ L^{-1})	Hemoglobin (g dL^{-1})	Platelets (10^9 L^{-1})	MCV (fL)	HCT ratio (%)
Control	6.84±0.22	6.74±0.24	12.78±0.18	514±16.4	51.92±0.43	38.62±1.17
Cat's claw	5.69±0.47	6.92±0.22	12.94±0.33	555±28.9	52.12±0.35	39.40±0.33

*p<0.05 (student's t-test); 5 male mice were used in each group; treatment group was statistically compared with the control groups

Table 7: Quantitative data on the average weight of selective organs of male mice (per 100 g body weight) after chronic treatment (10 mg/kg/day) with cat's claw

	Mean organ weight/100 g body (weight±SE)					
Treatment groups	Heart	Lungs	Liver	Kidney	Spleen	Testis
Control	0.73±0.01	1.50±0.05	8.54±0.14	2.40±0.10	0.70±0.01	1.32±0.05
Cat's claw	0.75±0.01	1.40±0.04*	9.10±0.09*	2.68±0.09	0.77±0.02*	1.42±0.07

*p<0.05 (student's t-test); 5 randomly selected animals were used in each group; The treatment group was compared with the control group

weight of treated male and female animals. This increase in the body weight was similar and comparable to the animals in the control groups.

The weight increase in liver and spleen of cat's claw treated male mice was significant ($p<0.01$) as compared to the control. There was a reduction ($p<0.05$) in the weight of lungs in the treated male animals as compared to the control. In the treated female mice there was slight increase in the weight of heart and liver. Biochemical studies revealed a non-significant increase in AST and ALT in the male treated group. The increase in the female treatment group was statistically significant.

Hematological studies on the chronically treated male and female mice revealed no appreciable differences as compared to the control, except for a mild increase in platelet count. Histopathological investigations of these organs, showed no significant changes and they were found to be normal and comparable to the control Hematological studies on the chronically treated male and female mice revealed no appreciable differences as compared to the control, except for a mild increase in platelet count as shown in Table 5 and 6. Chronic treatment with cat's claw induced no clastogenic or cytotoxic changes (Table 7).

DISCUSSION

Cat's claw is officially recognized as a medicinal plant Toxicity studies presented in this research involving acute treatment with cat's claw showed moderate reduction in WBC levels and statistically significant increase ($p<0.05$) in platelet count of treated male mice. There was a statistically significant increase in AST, ALT and urea levels in the treatment group as compared to the control. At the end of acute treatment, histopathological investigations confirmed that all the vital organs were normal and comparable to the control. Cat's claw acute treatment was found to be devoid of clastogenic potential. To confirm these finding sub-acute and chronic toxicity studies were conducted.

At the end of treatment for sub-acute, toxicity studies the visceral condition of all animals in the treatment group was found to be normal and comparable to the control.

Histopathological studies confirmed that all vital organs were normal and comparable to the control. However, mild congestion with microscopic foci of inflammatory changes in liver of the animals in the treatment groups was observed. There were no necrotic changes in the liver of mice in the treatment groups. Biochemical studies revealed rise in AST and ALT levels in treated animals as compared to the control.

Studies on the bone marrow revealed no clastogenic or cytotoxic effect in the treatment groups as compared to the control. The results of the current study showed no severe toxicity caused by oral intake of cat's claw preparation.

At the end of the chronic treatment (90 days), a significant increase in the body weight of both treated male and female mice was observed which was comparable to the animals in the control groups. At the end of the study, the visceral condition of all animals was found to be normal and comparable to the control. Hematological and biochemical studies revealed no drastic changes indicating that cat's claw possess non-significant toxicity. Contrary to the acute and sub-acute toxicity results, WBC counts in chronically treated

animals were found to be within normal range and comparable to the control. Histopathological investigations confirmed that all vital organs in the treatment groups were normal and comparable to the control. Chronic treatment with cat's claw induced no clastogenic or cytotoxic effect.

The results of the current study on acute, subacute and chronic toxicity studies indicated relatively low toxicity caused by cat's claw in mice. The results also Provide basic information about the toxicity of cat's claw, which may support the planning of any future studies in human beings.

CONCLUSION

It was concluded that cat's claw possessed relatively low toxicity when used according to the recommended dose (10 mg/kg/day).

Two chemo types of *Uncaria tomentosa* (Cat's claw) with different alkaloid pattern occur in nature where one type contains pentacyclic oxindoles and the other contains tetra cyclic oxindole alkaloids with completely different pharmacological activities. Mixture of these two types of drugs is reported unsuitable for medicinal uses (Heitzman *et al*., 2005; Reinhard, 1999). It is highly recommended to include a limit test for tetracyclic oxindole alkaloid, when registering any product containing cat's claw, to insure its absence.

Overall, this study provides a valuable preliminary data on the toxicity profile of cat's claw that should be useful for the planning of future pre-clinical and clinical studies on this herbal drug. Cat's claw appears to be relatively non-toxic. However, detailed teratogenic studies are needed to complete the safety profile of cat's claw.

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