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SUBCHRONIC TOXICITY OF MALAYSIAN ACALYPHA INDICA: BIOCHEMISTRY AND HAEMATOLOGY ANALYSIS OF RAT

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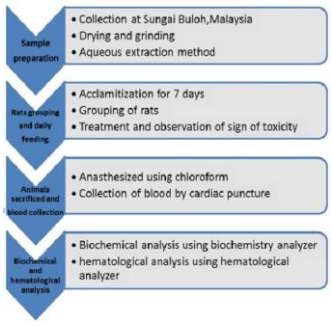
Graphical abstract



Abstract

Acalypha indica is one of the medicinal plants that have been used since ages to treat various diseases such as pneumoniae, asthma and skin diseases. This study aimed to explore the subchronic toxicity effect of Acalypha indica on Sprague Dawley rats based on haematological and biochemical parameters. The extract of Acalypha indica was prepared by aqueous extraction technique. 48 Sprague Dawley rats aged 7 weeks, weighing 150-200g were randomly divided into four groups, 6 animals per gender. A control group received water vehicle while three treated groups received the extract at dosage of 100 (low dosage group), 200 (medium dosage group) and 300 (high dosage group) mg/kg body weight. The sample was administered orally by using oral gavage daily for 90 days. No sign of toxicity and mortality was recorded in all groups throughout the study. There were no significant different ($p>0.05$) in body weight gain, food and water intake between control and treatment group. However, there was significant different in uric acid between control and high dosage group of male and female rats but the mean were in normal range. There were also reduced in mean of urea and creatinine in all dosage group of male and urea for all dosage group of female. Statistically significant reduced in urea was recorded between control and high dosage group of male only. Other parameters showed no significant different between control and treatment groups. Therefore, Acalypha indica is safe for human consumption and might be potential in reducing kidney damage problem.

Keywords: Odour, Volatile Organic Compounds (VOCs), Decomposition, Local food waste

1.0 INTRODUCTION

Herbal species is one of the living heritage in Malaysia that widely been explored due to its medicinal properties. Medicinal herbs usually contain active compounds that contribute to the healing properties such as flavonoid, tannin, saponin, minerals and glycosides. Previous studies have reported the presence of phytochemical compound in leaf extracts of *Acalypha hispida, A. racemosa, A. manniana* and *A.wilkesianam*that varied within the plants [1–5].

The root of plant is believed to treat nerve paralysis that cause stroke [6]. Furthermore, the leaves is known to help in wound healing [7], respiratory problems and gastrointestinal infection [8]. The whole plant extract of *Acalypha indica* has anti-arthritic properties and possess a potential to heal rhematoid arthritis However, there is lack of evaluation regarding the safety consumption of the plant. This study aimed to explore the subchronic toxicity effect of *Acalypha indica* on Sprague Dawley rats based on haematological and biochemical parameters.

2.0 EXPERIMENTAL

2.1 Sample Preparation

The herbs were collected from Sungai Buloh, Selangor, Malaysia. The plants were dried in the oven at 40 - 50 for three days. The dried whole plant was grounded to 1-2mm size. Then, about 5 kg of dried whole plant was extracted in 100 L reverse osmosis water for three times with ratio 1:20 (w/v). The aqueous extraction procedure was conducted using fabricated local pilot plant extractor 1000 L for three hours at 100. The extracts were filtered using Whatman filter paper No.1 and kept at -80 prior to freeze-drying process. The samples were freeze-dried at -52, 0.63 mbar. The freeze-dried powder retrieved was stored in an air-tight container at 4 for further analysis

2.2 Rats Grouping and Daily Feeding

Male and female Sprague Dawley rats weighing from 200 to 250g were acclimatized for 7 days prior to the study.The animals were maintained at 21-23^{0}C, 12 hours light, and 12 hours dark with unlimited supply of rodent pellet and *ad libitum* water. The study was conducted according to 408 OECD guideline (Repeated Dose 90-day Oral Toxicity Study in Rodents) [10] and approved by Institution Animal Care and Use Committee, International Islamic University Malaysia, Kuantan, Malaysia.

The rats were divided into six rats per group per gender and housed separately in polypropylene cages. The treatment group received *Acalypha indica* extract at doses of 100 (low dose), 200 (medium dose) and 300(high dose) mg/kg while the control group received reverse osmosis water. The treatment was administered through force feeding daily for 90 days.

Daily observation was conducted for toxicity signs such as behavior change, physical change (skin, fur), tremor, salivation, diarrhea, sleeping pattern, body weight changes, and mortality. The weights of rats were recorded weekly.

2.3 Animals Sacrificed and Blood Collection

Prior to sacrifice, the rats were fasted overnight with free access of water. About 6 mL of blood was drawn from each rat by cardiac puncture technique after the rats being anesthetized by using chloroform. The blood was kept in vacutainer tube before further analysis.

2.3 Animals Sacrificed and Blood Collection

The whole blood samples were allowed to clot completely and were centrifuged at 3000 rpm for 15 minutes. The serum was collected and tested for parameters such as alanine transminase (ALT), alkaline phosphatase (ALP) and aspartate transaminase (AST), creatinine and urea.

The blood was kept in vacutainer tube containing anticoagulant to prevent blood clotting and analyzed using automated haematology analyzer (XS 800-i, Japan). The haematological parameters was tested to obtain data such as red blood cell (RBC) count, white blood cell (WBC) count, hematocrit, platelet, leukocytes, neutrophil, eosinophil, basophil, lymphocyte, monocyte, mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH).

2.4 Statistical Analysis

The data was analyzed using SPSS software to check the significant of the result. The results were reported as mean ± S.D. The statistical analysis was performed using one way ANOVA.

3.0 RESULTS AND DISCUSSON

3.1 General Behaviour

No sign of toxicity and mortality was recorded in all groups throughout the study. There were no significant different ($p>0.05$) in body weight gain, food and water intake between control and treatment group. Increase trend of weight gain in Figure 1 indicate a normal growth of the rats. Body weight help in determining the dose that is toxic in toxicological study [11].

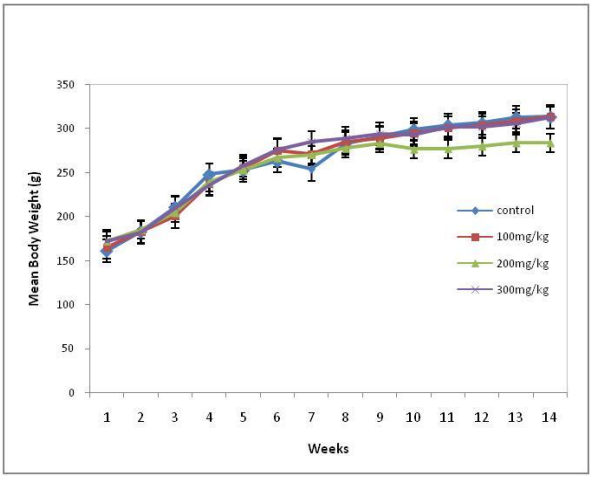


Figure 1 Effect of *Acalypha indica* on mean body weight of rats. Values are presented expressed as mean± S.E.M (n=6). ᵃ *p*-values <0.05 were considered as statistically significant by ANOVA followed by Games-Howell post-test

3.2 Hematological Analysis

There were no significant different ($p>0.05$) between male and female rats in control and treatment groups for all haematological parameters (Table 1 and Table 2). Furthermore, the value recorded were within normal range [2, 12, 13]. Blood function as a

carrier of nutrients and oxygen and transport the waste from cells [11]. Besides that, the white blood cells fight against external bacteria and viruses as well as diseases [14].

3.2 Biochemical Analysis

Table 3 and 4 showed the biochemical analysis of male and female rats. The analysis of urea, creatinine and uric acid was conducted to evaluate the function of kidney. There was significant increase in uric acid between control and high dose group of both male and female rats but the mean were in normal range. Increase in serum urea and creatinine accompanied by elevation of serum electrolyte could contribute to renal failure [15]. However, all urea and creatinine level of male and female rats in all groups were within normal range.

Besides, significant increase in potassium was recorded between control and medium dose male group. Although there were no significant different recorded in female serum potassium level, the 300 mg/kg dose group showed a high level of potassium (7.47±2.34). Increase in serum potassium level typically related with cardiac function and acute renal failure [16, 17]. However, the leaf extract of *Acalypha indica* has potential to aid in cardiac problem as it rich with flavonoid [18]. Further analysis of glomerular filtration rate could assist in determining the main cause of problem.

Liver serum biochemistry analysis was conducted to evaluate the condition of liver and can be an indicator for liver failure [19]. Increase in liver transaminase (ALT and AST) as well as alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) might due to hepatotoxicity of toxic agent [20]. Significant increase of AST was recorded between control and 300 mg/kg dose group of male rats. However, all rats in other groups including male rats showed a high level of AST. AST is not liver specific as it also present in high concentration in muscle [21]. Thus, elevation of the AST alone cannot be an indicator of liver failure.

The total proteins of all groups of male and female rats were increased except for control and low dose group of male rats. However, there was no significant different observed between control and treatment group. The globulin level of all rats and were also elevated but with no significant different between control and treatment group. Increase in serum total protein and alteration in albumin-globulin ratio due to increase in globulin associated with infection [22, 23]. Other parameters showed no significant different between control and treatment groups. Therefore, the changes in biochemical parameters might not due to the treatment and caused by external factor such as infection or unfavourable condition of environment. A study on toxicity of *Baccaurea angulata* reported that when there was no significant pattern of dose, the difference between control and treatment subjects was not caused by the extract [24].

Table 1 Hematological analysis of male rats in subchronic toxicity study of *Acalypha indica*

	Control	100 mg/kg	200 mg/kg	300 mg/kg	Normal range
Red blood cell (x10^{12}/L)	7.34±1.04	8.20±0.78	8.67±0.55	8.60±0.52	8.15-9.75[a]
Haemoglobin (g/L)	139.83±7.57	132.67±25.32	140.33±11.82	140.33±16.24	134.00-158.00[a]
PCV(L/L)	0.43±0.06	0.47±0.04	0.48±0.04	0.46±0.03	0.44-0.53[a]
MCV (fL)	57.17±2.14	57.50±3.33	54.50±1.97	53.83±1.72	51.80-63.60[b]
MCH (pg)	18.50±0.55	19.17±1.94	17.67±0.52	18.33±1.37	17.90-20.90[b]
MCHC (g/L)	321.33±13.94	334.33±26.21	325.67±10.35	338.17±23.39	306.00-368.00[b]
RDW (%)	15.02±0.99	15.92±1.47	16.77±1.09	16.57±1.48*	9.70-16.50[b]
White blood cell (x10^{9}/L)	10.15±2.05	10.35±3.51	11.08±6.12	8.53±2.52	8.00-11.80[a]
Neutrophil (x10^{9}/L)	2.03±0.56	2.57±1.18	3.03±1.49	1.75±0.94	1.95-2.88[a]
Lymphocyte (x10^{9}/L)	6.82±1.70	6.65±1.99	7.05±4.87	5.85±1.62	6.03-8.90[a]
Monocyte (x10^{9}/L)	0.77±0.28	0.53±0.30	0.47±0.31	0.55±0.60	0.01-0.04[a]
Platelet (x10^{9}/L)	371.17±187.25	321.00±277.62	390.83±157.65	378.67±196.42	784.00-1500.00[b]

[a] [12]
[b] [2]
* *p*-values <0.05 were considered as statistically significant by ANOVA followed by Games-Howell post-test

Table 2 Hematological analysis of female rats in subchronic toxicity study of *Acalypha indica*

	Control	100 mg/kg	200 mg/kg	300 mg/kg	Normal range
Red blood cell (x10^{12}/L)	7.40±0.34	7.48±0.58	7.46±0.63	7.44±0.76	6.76-9.20[a]
Haemoglobin (g/L)	142.67±6.44	139.17±10.94	140.33±11.83	143.33±11.94	115.00-161.00[a]
PCV(L/L)	0.44±0.03	0.44±0.02	0.46±0.03	0.44±0.04	0.36-0.53[a]
MCV (fL)	60.33±2.73	58.83±2.79	61.33±3.33	58.83±2.04	51.90-65.50[a]
MCH (pg)	19.17±0.75	17.67±2.58	18.67±0.82	18.83±0.41	17.30-21.30[b]
MCHC (g/L)	316.17±13.35	302.17±54.78	307.50±16.31	320.67±13.72	306.00-360.00[b]
RDW (%)	13.82±0.96	14.36±1.38	14.83±1.09	14.92±0.93	9.70-16.50[b]
White blood cell (x10^9/L)	8.17±3.30	10.53±3.81	7.52±3.93	8.08±3.69	6.60-12.60[a]
Neutrophil (x10^9/L)	1.68±0.38	2.80±1.27	1.10±0.98	1.54±1.07	1.77-3.38[a]
Lymphocyte (x10^9/L)	5.37±2.45	6.95±2.63	5.38±3.20	5.42±2.98	4.78-9.12[a]
Monocyte (x10^9/L)	0.45±0.33	0.50±0.30	0.26±0.11	0.32±0.13	0.02-0.04[a]
Platelet (x10^9/L)	313.20±146.08	494.33±248.24	514.50±488.55	599.17±309.51	815.00-1397.00[b]

[a][12] [b] [2] [c] [13]
* *p*-values <0.05 were considered as statistically significant by ANOVA followed by Games-Howell post-test

Table 3 Biochemical analysis of male rats in subchronic toxicity study of *Acalypha indica*

	Control	100 mg/kg	200 mg/kg	300 mg/kg	Normal range
Glucose (mmol/L)*	7.28±3.17	10.53±2.42	5.60±1.86	6.82±1.55	2.77-7.49[a]
Liver function test					
Total protein (g/L)	85.83±8.30	87.00±4.82	79.50±4.89	81.50±5.39	56.00-76.00[a]
Total bilirubin (umol/L)	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	2.00-9.45[a]
Albumin (g/L)	46.33±5.50	44.83±2.14	42.50±3.15	43.17±5.46	26.90-42.70[b]
Globulin (g/L)	39.50±3.62	42.17±3.87	37.00±5.14	38.00±2.97	18.00-30.00[a]
Albumin/globulin ratio	1.17±0.10	1.07±0.10	1.17±0.21	1.13±0.14	0.96-1.97[b]
AST (U/L)	286.83±88.28	260.17±66.12	237.33±119.99	605.33±209.36*	67.30-166.00[b]
ALT (U/L)	82.00±35.09	83.17±20.93	61.83±21.12	98.17±16.52	19.20-48.7[b]
ALP (U/L)	79.00±26.62	189.17±36.41	92.83±39.65	80.67±25.06	59.00-196.00[b]
GGT (U/L)	7.83±6.21	8.67±5.43	3.67±1.21	9.50±4.68	NA
Kidney function test					
Urea (mmol/L)	9.85±0.83	8.95±0.57	9.40±1.55	8.17±0.99	4.18-10.14[b]
Creatinine (umol/L)	51.00±9.65	52.67±9.93	48.33±14.11	53.17±5.42	2563-55.70[b]
Uric acid (mmol/L)	0.17±0.04	0.17±0.05	0.21±0.14	0.33±0.10*	0.07-0.45[b]
Electrolyte					
Sodium (mmol/L)	140.50±2.66	138.33±2.88	140.17±5.04	140.83±7.52	139.00-148.00[b]
Potassium (mmol/L)	5.98±0.89	5.87±1.46	7.47±2.34*	5.88±1.10	3.97-5.70[b]
Chloride (mmol/L)	103.00±2.00	102.00±1.55	104.00±1.79	110.17±5.71	104.00-113.00[b]
Lipid profile					
Total cholesterol (mmol/L)	2.20±1.21	1.50±0.78	1.40±0.97	2.50±0.89	1.03-3.36[a]
Triglyceride (mmol/L)	0.81±0.34	0.81±0.32	0.59±0.55	0.54±0.24	0.29-1.64[a]
HDL (mmol/L)	0.48±0.12	0.39±0.14	0.30±0.08	0.45±0.27	NA
LDL (mmol/L)	1.35±0.76	0.74±0.31	0.83±0.57	1.80±1.16	NA
Total cholesterol/HDL ratio	4.60±1.57	3.80±1.19	4.70±0.86	5.60±1.02	NA

[a][12] [b][2] [c][13]
* *p*-values <0.05 were considered as statistically significant by ANOVA followed by Games-Howell post-test

Table 4 Biochemical analysis of female rats in subchronic toxicity study of *Acalypha indica*

	Control	100 mg/kg	200 mg/kg	300 mg/kg	Normal range
Glucose (mmol/L)*	6.25±2.55	7.31±3.06	6.27±2.57	6.02±2.27	2.77-7.49[a]
Liver function test					
Total protein (g/L)	75.67±4.08	72.50±4.24	77.50±1.87	76.83±3.31	56.00-76.00[a]
Total bilirubin (umol/L)	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	2.00-5.50[a]
Albumin (g/L)	37.50±2.58	37.50±3.02	37.17±2.42	38.33±3.16	26.90-38.60 [b]
Globulin (g/L)	37.83±3.06	35.17±3.31	40.33±2.37	38.83±3.14	18.00-30.00[a]
Albumin/globulin ratio	1.00±0.09	1.07±1.21	0.8±1.21	0.98±0.10	0.93-1.72[a]
AST (U/L)	258.33±114.57	462.33±228.13	426.50±170.94	405.33±130.65	63.90-228.8[b]
ALT (U/L)	74.67±16.54	128.33±78.41	119.50±55.80	85.33±8.51	27.58-101.4[b]
ALP (U/L)	152.50±34.43	134.50±54.37	113.67±5.95	102.50±41.38	132.0-312.0[b]
GGT (U/L)	4.50±2.74	5.50±3.89	7.00±4.29	8.83±5.38	NA
Kidney function test					
Urea (mmol/L)	8.63±0.92	8.03±0.76	7.33±0.80	7.18±0.57	4.21-9.07[b]
*Creatinine (umol/L)**	41.17±5.92	40.50±9.38	40.33±3.88	38.67±3.33	17.68-70.72[a]
Uric acid (mmol/L)	0.13±0.06	0.18±0.12	0.23±0.08	0.28±0.09	0.07-0.45[a]
Electrolyte					
Sodium (mmol/L)	142.67±3.93	139.67±5.79	139.33±2.42	137.67±3.14	143.00-156.00[a]
Potassium (mmol/L)	7.25±3.42	9.12±2.91	13.30±2.35	12.07±3.11	5.40-7.00[a]
Chloride (mmol/L)	102.83±1.47	102.83±1.72	102.33±1.75	102.00±1.41	103.00-110.00[a]
Lipid profile					
Total cholesterol (mmol/L)	1.60±0.23	1.50±0.45	1.40±0.41	2.00±0.63	1.03-3.36[a]
Triglyceride (mmol/L)	0.93±0.54	0.36±0.29	0.39±0.32	0.40±0.16	0.29-1.64[a]
HDL (mmol/L)	0.42±0.17	0.33±0.08	0.29±0.10	0.33±0.09	NA
LDL (mmol/L)	0.75±0.32	1.00±0.88	0.93±0.52	1.49±0.55	NA
Total cholesterol/HDL ratio	3.80±0.62	4.50±0.90	4.80±0.71	6.10±1.23	NA

[a] [12]
[b] [2]
[c] [13]

* *p*-values <0.05 were considered as statistically significant by ANOVA followed by Games-Howell post-test

4.0 CONCLUSION

Therefore, Acalypha indica is safe for human consumption when administered orally. Further clinical toxicological investigation should be conducted to estimate a safe and effective dose level to ensure that the community is being protected from any possible adverse effects.

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