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Original Research Article

Acute Toxicity of Aqueous Extract of a Diabetic Folklore Recipe Thai Traditional Medicine in Rats

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ABSTRACT

Thai traditional medicine is still widely used in taking care of health in daily life. A recipe from TTM composes of *Clerodendrum paniculatum*, *Arcangelisia flava*, *Suregada multifloraa*, *Dendrophthoe pentandra*, *Tectona grandis*, *Derris scandens*, and *Salacia chinensis* is recommended for use as diabetic treatment in the folk medicine of Thailand. The study determined the acute toxicity of aqueous extract from the recipe in male and female Wistar rats. The OECD 420 guidelines were followed in performing the acute toxicity investigation. The extracts were given orally to male and female Wistar rats once at doses. The body weights were measured in weeks 0, 1, and 2. At the end of the experiments, internal organ weights were recorded. The blood biochemistry, liver and kidney histology, and hematological parameters were investigated. The results showed that no doses of the recipe produced any signs or symptoms of toxicity during the first 24 hours and no rat died within 14 days. All of the treatments cause the rats to gain weight. Rats given the extracts orally showed no changes in hematological parameters. The blood biochemical values changes including Cr, AST, ALT, ALP, and TG levels were significantly altered in the treated groups ($P< 0.05$). These altered levels, however, were still within normal ranges. Additionally, liver and kidney tissues did not show any signs of inflammation. In conclusion, these findings demonstrated that the aqueous extract had no acute toxicity but slightly altered some liver and kidney functions.

Keywords: Acute toxicity, Aqueous extract, Folklore recipe, Thai traditional medicine .

Introduction

Each area of the world has a unique traditional medicine for treating various ailments based on geography, weather, lifestyle, social beliefs, culture, and natural resources. Thailand, located on Southeast Asia's Indochina peninsula, is recognized for its wide variety of medicinal plants. Thai traditional medicine (TTM) is a type of folklore medicine acquired from Thai ancestors which people take as medication to treat various ailments from the past to the present. Each recipe may have a distinct plant, dose, herbal component, and indication of usage.[1,2] A recipe from TTM, which composes of a mixed powder of seven medicinal plants from *Clerodendrum paniculatum* root, *Arcangelisia flava* stem, *Suregada multifloraa* wood, *Dendrophthoe pentandra* whole, *Tectona grandis* leaf, *Derris scandens* stem and *Salacia chinensis* stem. The recipe had been widely used in folk medicine on rural region in Thailand for the treatment of many diseases especially diabetes.

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Some biological activities for each component herb of recipe have been previously studied such as:the antioxidant, anti-inflammatory and antimicrobial activity[3-4] of *C. paniculatum* (Lamiaceae), antioxidant, antidiabetic activity by α-amylase and α-glucosidase inhibition,[5] and antihypercholesterol activity[6] of *A. flava* (Menispermaceae), antioxidant, antibacterial, cytotoxic,[7] of *S. multifloraa* (Euphorbiaceae), hepatoprotective, antihyperglycemic and antidiabetic,[8] anti-inflammatory,[9] of *D. pentandra* (Loranthaceae). antioxidant,[10] antifungal,[11] antidiabetic,[12-14] and antimicrobial,[15] of *T. grandis* (Lamiaceae), antioxidant, anti-lipid peroxidation,[16] musculoskeletal pain treatment,[17] hepatocellular carcinoma cell line.[18] of *D. scandens* (Leguminosae). Whereas *S. chinensis* (Leguminosae) had antioxidant.[19-21]

However, the combination of plants in the recipe, on the other hand, has a lot of literature to analyze on biological activity. Furthermore, the recipe is still widely used as an ethno-pharmaceutical to treat a variety of diseases, and there has not been a scientific report on its safety and toxicity. As a result, the purpose of this study is to use the OECD 420 guidelines to evaluate the oral acute toxicity of an aqueous extract of a diabetic folklore recipe from Thai traditional medicine in male and female rats.

Materials and Methods

Sample collection

The seven plants in the recipe were collected from a local cultivation area in Maha Sarakham Province, Northeastern Thailand in May-June 2020. The specimens were identified by Asst. prof. Piyaphong Yupparach and deposited at the Faculty of Medicine, Mahasarakham

University, Thailand (code; *C.paniculatum*: MSU.MED-CP0001/AK, code; *A. flava*: MSU.MED AF0001/AK, code; *S.multiflora*: MSU.MED SM0001/AK, code; *D. pentandra*: MSU.MED-DP0001/AK, code; *T. grandis*: MSU.MED-TG0001/AK, code; *D. scandens*: MSU.MED-DS0001/AK and code; *S. chinensis*: MSU.MED- SC0001/AK). The fresh materials were cleaned and dried at 60°C for 24 hr in a hot air oven and then powdered.

Preparation of crude extracts
The preparation of aqueous extract from the recipe of *C. paniculatum*, *A. flava*, *S.multiflora*, *D. pentandra*, *T. grandis*, *D. scandens*, and *S. chinensis* (1:1:1:1:1:1:1 W/W) by boiling with distilled water for 15 min (1:10 w/v). The boiling process was repeated twice. The residue powder was filtrated by using filter papers (Whatman®, Germany). The filtrate was concentrated by using a rotary evaporator at 85 °C (Buchi Rotavapor® R-300, Switzerland) and then, freeze-dried to obtain dark brown extract. The extracts were kept in the refrigerator at a temperature below 4 °C for future *in vivo* research.

Preparation of animals
The OECD 420 guideline was followed in the performing of the acute toxicity study. In this investigation, male and female Wistar rats weighing 150-200 g were used. They were acquired and kept at the Northeastern Laboratory Animal Center, Khon Khaen University, Khon Kaen, Thailand, which is an Animal Biosafety Level 1 (ABSL1) facility. The animal protocol was approved by the Institutional Animal Care and Use Committee of Khon Kaen University, Thailand (Ethic record No. IACUC-KKU-67/2020).

Experimental designs
The Wistar rats with body weight of 150-200 g were divided into ten animals (5 males and 5 females), in accordance with the OECD 420 guidelines for acute toxicity studies. Group I was normal control rats treated orally with distill water; groups II, III, IV, and V were normal rats administrated orally aqueous extracts (5, 50, 300, and 2,000 mg/kg b.w.). The extracts were administered orally once by using an orogastric tube. The volume of administration was 1 mL for each animal. After day 14, the rats were fasted overnight and sacrificed under thiopental sodium anaesthesia. The blood samples were obtained by cardiac puncture. The hematological parameters including red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), white blood cells (WBC), lymphocytes (L) and monocytes (M) were determined using an automatic blood analyzer (Swelab Alfa, Biozen, Sweden). The biochemical data including blood urea nitrogen (BUN), creatinine (Cr), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein (HDL) were measured using an automatic blood chemical analyzer (BT 2000 plus, Germany) at the Community Clinical Laboratory Faculty of Associated Medical Science Khon Kaen Univesity, Thailand.
The liver, kidney, heart, lung, and spleen, were removed. They were weighed using a digital balance, and the relative organ weight was computed as follows:

$$\text{Relative organ weight (\%)} = \frac{\text{organ weight (g)}}{\text{body weight (g)}} \text{ x } 100$$

Liver and kidney tissues were preserved in 10% neutral formalin for histological analysis. The tissues were promptly fixed in 10 % formalin for 72 hr, with a daily replacement of the fixative, after being thoroughly rinsed with normal saline. The subsequent sequence of alcohols and xylene in the tissue processor machine dehydrated the tissues. Small portions of the dehydrated tissues were cut and put in cassettes. The tissues were sliced with a rotary microtome at a thickness level of micron; 10^{-6} meters after being fixed in paraffin. To remove paraffin, the ribbon-like tissues were submerged in a warm water bath. Hematoxylin and eosin were used to stain the tissues after they had been fixed onto a microscope slide. The histology of these tissues was investigated under a light microscope. The histopathological micrographs were taken using a Olympus BX51TF light microscope (Olympus Inc., Japan) with a digital camera EP50 (Olympus Inc., Germany).[22]

Statistical analysis
All data were expressed as mean ± standard error of mean (SEM). Statistical analysis was carried out using *F*-test one-way analysis of variance (One-way ANOVA) was used to evaluate mean comparisons. Utilizing SPSS software version 23. The statistical significance was at a *p*-value less than 0.05.

Results and Discussion

The results showed that the doses of the aqueous extract did not produced any signs or symptoms of toxicity during the first 24 hr. There were no behavioral changes such as irregular movement, loss of appetite, weight loss, and mortality. within 14 days. The increase in body weight of all administered groups were not different (Tables 1 and 2). Additionally, rats treated with the extracts at doses of 5, 50, 300, and 2,000 mg/kg did not differ statistically from controls in terms of their relative organ weights for the liver, kidney, heart, lung, and spleen (Tables 3 and 4).
The hematological parameters in male and female rates including RBC, Hb, Hct, platelet, MCV, MCH, MCHC, WBC, lymphocytes, and monocytes in each group did not exhibit any harmful effects (Table 5 and 6). The aqueous extracts had no effect on the red blood cells, lymphocytes, neutrophils, and monocytes (Figure 1 and 2).
The extract did not negatively affect the clinical chemistry values including BUN, ALT, TC, and HDL in the male rats. The extract at the doses of 5, 50, and 2,000 mg/kg significantly (p<0.05) lower the AST level. The creatinine and ALP levels in the controls and the rats in all experimental groups were comparable. The extracts at the doses of 5 and 50 mg/kg showed that the TG level was similar to the normal control, but not the doses of 500 and 2,000 mg/kg, which significantly (p<0.05) increased TG values (Table 7).
The clinical chemistry values including BUN, creatinine (Cr), AST, TC, and HDL in the female rats were not negatively affected. The extracts at the doses of 5 and 50 mg/kg showed that ALT and ALP were similar to the normal control, but not the doses of 500 mg/kg and 2,000 mg/kg which significantly (p<0.05) increased ALT and ALP values.

Table 1: Effects of aqueous extract of a diabetic folklore recipe on body weight gain in treated and control male rats during the course of the 14 days experiment.

Groups and treatments		Increase body weight (%) (mean ± S.E.M)	
		Week 1	Week 2
I	Control	13.18 ± 0.71	7.31 ± 0.20
II	5 mg/kg	13.12 ± 0.87	7.44 ± 0.33
III	50 mg/kg	11.90 ± 0.44	7.14 ± 0.20
IV	500 mg/kg	14.05 ± 1.29	7.64 ± 0.25
V	2,000 mg/kg	13.19 ± 1.78	6.98 ± 0.36

Table 2: Effects of aqueous extract of a diabetic folklore recipe on body weight gain in treated and control female male rats during the course of the 14 days experiment.

Groups and treatments		Increase body weight (%) (mean ± S.E.M)	
		Week 1	Week 2
I	Control	6.61 ± 1.36	4.40 ± 0.33
II	5 mg/kg	8.58 ± 0.62	3.90 ± 0.51
III	50 mg/kg	13.63 ± 2.56	4.25 ± 0.43
IV	500 mg/kg	8.08 ± 1.28	4.10 ± 0.74
V	2,000 mg/kg	9.17 ± 0.68	3.88 ± 0.52

Table 3: Effects of aqueous extract of a diabetic folklore recipe on relative organ weight during the 14 days experiment in male rats.

Relative organ weight (%) mean ± S.E.M.	Groups and treatments				
	I	II	III	IV	V
	Control	5 mg/kg	50 mg/kg	500 mg/kg	2,000 mg/kg
Liver	3.72 ± 0.19	3.62 ± 0.14	3.69 ± 0.14	3.66 ± 0.07	3.79 ± 0.09
Kidney	0.83 ± 0.01	0.78 ± 0.01	0.85 ± 0.02	0.81 ± 0.03	0.86 ± 0.04
Heart	0.38 ± 0.04	0.34 ± 0.01	0.35 ± 0.01	0.49 ± 0.16	0.33 ± 0.01
Lung	0.45 ± 0.01	0.42 ± 0.01	0.43 ± 0.01	0.41 ± 0.01	0.42 ± 0.01
Spleen	0.29 ± 0.01	0.29 ± 0.02	0.29 ± 0.01	0.28 ± 0.02	0.30 ± 0.02

Table 4: Effects of aqueous extract of a diabetic folklore recipe on relative organ weight during the 14 days experiment in female rats.

Relative organ weight (%) mean ± S.E.M.	Groups and treatments				
	I	II	III	IV	V
	Control	5 mg/kg	50 mg/kg	500 mg/kg	2,000 mg/kg
Liver	3.94 ± 0.13	3.97 ± 0.28	3.81 ± 0.15	3.89 ± 0.11	3.63 ± 0.09
Kidney	0.85 ± 0.04	0.93 ± 0.04	0.85 ± 0.02	0.89 ± 0.02	0.87 ± 0.02
Heart	0.36 ± 0.01	0.36 ± 0.01	0.36 ± 0.02	0.37 ± 0.01	0.36 ± 0.01
Lung	0.52 ± 0.02	0.52 ± 0.01	0.50 ± 0.02	0.56 ± 0.02	0.51 ± 0.01
Spleen	0.28 ± 0.01	0.30 ± 0.01	0.27 ± 0.02	0.31 ± 0.01	0.28 ± 0.02

Table 5: The hematological parameters including red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), platelet (PLT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cells (WBC), lymphocytes (L), and monocytes (M) of different doses from the aqueous extract of a diabetic folklore recipe in male rats during the course of the 14 days investigation.

Hematological parameters in male rats	Groups and treatments				
	I	II	III	IV	V
	Control	5 mg/kg	50 mg/kg	500 mg/kg	2,000 mg/kg
RBC (10^3/µL)	7.21 ± 0.09	7.09 ± 0.09	7.26 ± 0.08	7.15 ± 0.16	7.30 ± 0.14
Hb (g/dL)	14.62 ± 0.32$^{a, b}$	14.18 ± 0.25^{b}	13.78 ± 0.16^{a}	13.92 ± 0.30^{a}	14.06 ± 0.20$^{a, b}$
Hct (%)	46.00 ± 1.48$^{a, b}$	44.40 ± 0.93^{b}	42.40 ± 0.40$^{a, b}$	43.60 ± 1.21^{a}	44.20 ± 1.07$^{a, b}$
MCV (fL)	63.74 ± 1.86$^{a, b}$	62.62 ± 1.56^{b}	57.92 ± 0.50^{b}	60.90 ± 0.86^{a}	60.52 ± 0.92$^{a, b}$
MCH (pg)	20.28 ± 0.35$^{a, b}$	20.04 ± 0.45^{c}	18.96 ± 0.16$^{b, c}$	19.50 ± 0.23^{a}	19.28 ± 0.15$^{a, b, c}$
MCHC (g/dL)	31.84 ± 0.40	31.98 ± 0.33	32.78 ± 0.13	31.98 ± 0.28	31.86 ± 0.43
PLT (10^3/µL)	5.97 ± 1.23	7.06 ± 0.61	5.56 ± 0.44	6.78 ± 0.81	6.43 ± 1.21
WBC (10^3/µL)	5.97 ± 1.23	7.06 ± 0.61	5.56 ± 0.44	6.78 ± 0.81	6.43 ± 1.21
L (10^3/µL)	79.46 ± 1.69^{a}	79.44 ± 0.90^{a}	82.90 ± 1.20$^{a, b}$	84.54 ± 0.96^{b}	83.58 ± 0.48^{b}
M (10^3/µL)	4.32 ± 0.89	3.40 ± 0.39	3.30 ± 0.44	3.48 ± 0.26	3.26 ± 0.24

$^{a, b, c}$ Different letters in the same row indicated significantly difference at *p*-values less than 0.05.

The extracts at the doses of 5 and 50 mg/kg showed that the TG was similar to the normal control, but not the doses of 500 and 2,000 mg/kg which significantly ($p<0.05$) increased TG values (Table 8).

The hepatocytes and central veins in the liver tissues of treated male and female rats were normally arranged. No necrosis or lipid accumulation was found (Figure 3). In addition, there was no change in the size of the glomerulus and Bowman's capsule space in kidney tissues of treated male and female rats. No necrosis was found in the renal corpuscle and renal tubule (Figure 4).

The recipe had reported pharmacological properties, for example, hepatoprotective,[8] and anti-diabetic properties.[5,8,12,14] The recipe extracts also exhibited antihypercholesterol activity,[6] and anti-lipid peroxidation,[17] and inflammation reduction.[9] It could be implied that the secondary metabolites found in the aqueous extract of a diabetic folklore recipe are not toxic substances. suggesting that the aqueous extract from a diabetic folklore recipe could be safe for consumption in the treatment of diabetes.

Conclusion

These results suggest that the aqueous extract of a diabetic folklore recipe did not exhibit any acute toxicity signs or symptoms. Further, isolation, identification, chemical compositions, and the major active compounds of the recipe responsible for the hypoglycemic effect should be undertaken in order to confirm and clarify the mechanism behind this activity.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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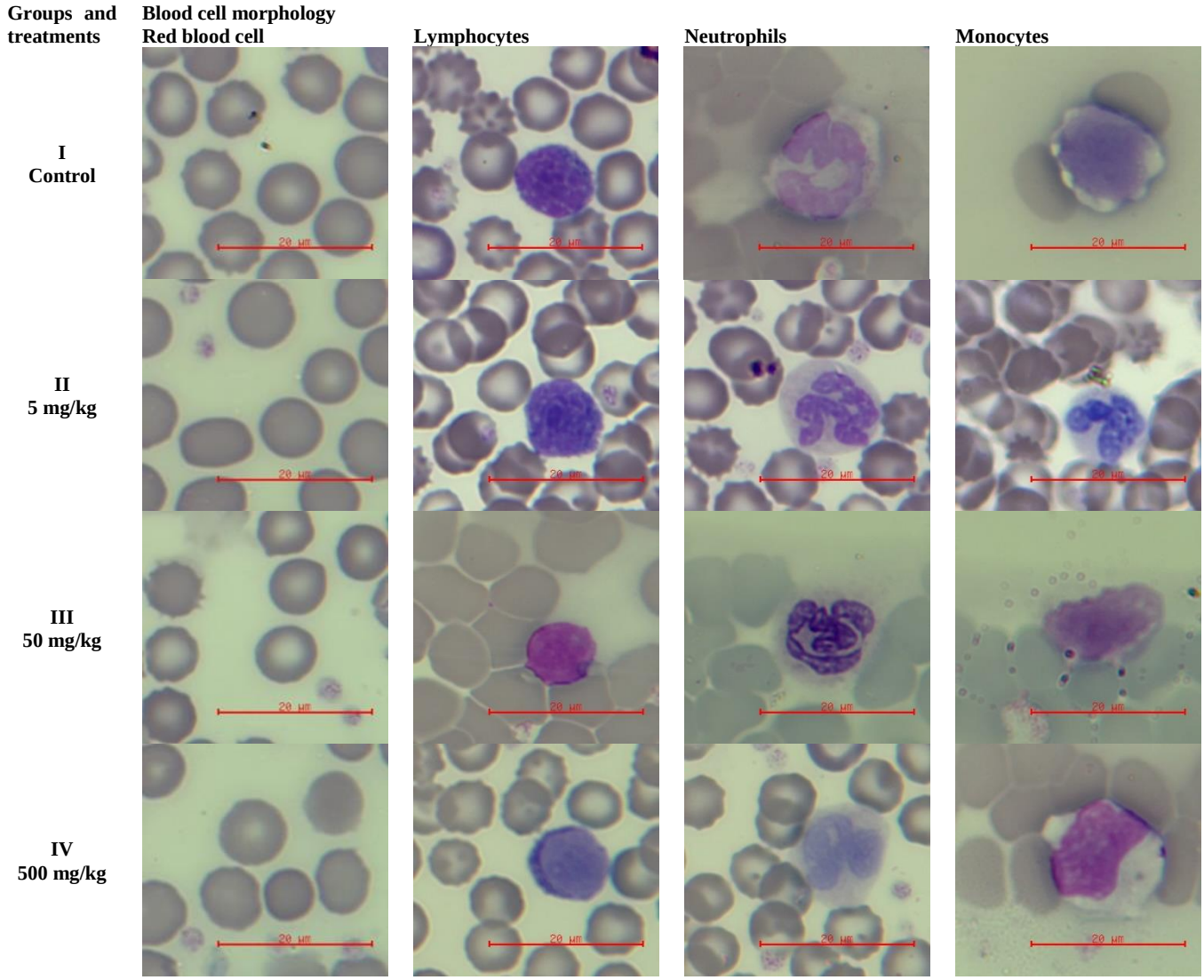
Table 6: The hematological parameters including red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), platelet (PLT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cells (WBC), lymphocytes (L), and monocytes (M) of different doses from the aqueous extract of a diabetic folklore recipe in female rats during the course of the 14 days investigation.

Hematological parameters in female rats	Groups and treatments				
	I	II	III	IV	V
	Control	5 mg/kg	50 mg/kg	500 mg/kg	2,000 mg/kg
RBC (10^3/µL)	7.19 ± 0.16[a]	8.20 ± 0.52[b]	7.08 ± 0.19[a]	7.11 ± 0.15[a]	7.28 ± 0.07[a]
Hb (g/dL)	14.08 ± 0.30[a]	15.90 ± 1.00[b]	14.00 ± 0.27[a]	13.66 ± 0.12[a]	14.22 ± 0.04[a]
Hct (%)	43.60 ± 0.40	43.80 ± 0.49	43.80 ± 0.37	44.00 ± 0.45	43.20 ± 0.20
MCV (fL)	58.56 ± 0.67	58.12 ± 0.70	57.89 ± 0.49	58.56 ± 0.57	58.32 ± 0.51
MCH (pg)	19.58 ± 0.12	19.40 ± 0.34	19.80 ± 0.17	19.22 ± 0.30	19.54 ± 0.16
MCHC (g/dL)	32.82 ± 0.27	33.36 ± 0.43	32.84 ± 0.31	32.70 ± 0.09	32.90 ± 0.13
PLT (10^3/µL)	1,338.40 ± 65.73	1,255.20 ± 69.22	1,226.40 ± 72.84	1,216.20 ± 54.58	1,307.20 ± 84.24
WBC (10^3/µL)	4.50 ± 0.49[a]	9.17 ± 0.67[b]	4.96 ± 0.54[a]	4.43 ± 0.37[a]	4.74 ± 0.61[a]
L (10^3/µL)	85.26 ± 1.99	83.38 ± 0.98	84.62 ± 2.04	83.48 ± 2.29	86.14 ± 1.80
M (10^3/µL)	2.86 ± 0.45	4.02 ± 1.04	2.58 ± 0.31	3.36 ± 0.60	2.68 ± 0.26

[a, b] Different letters in the same row indicated significantly difference at *p*-values less than 0.05.



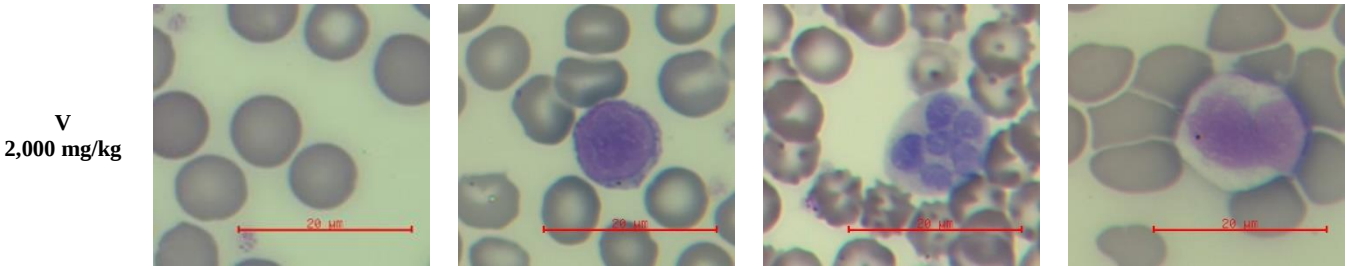
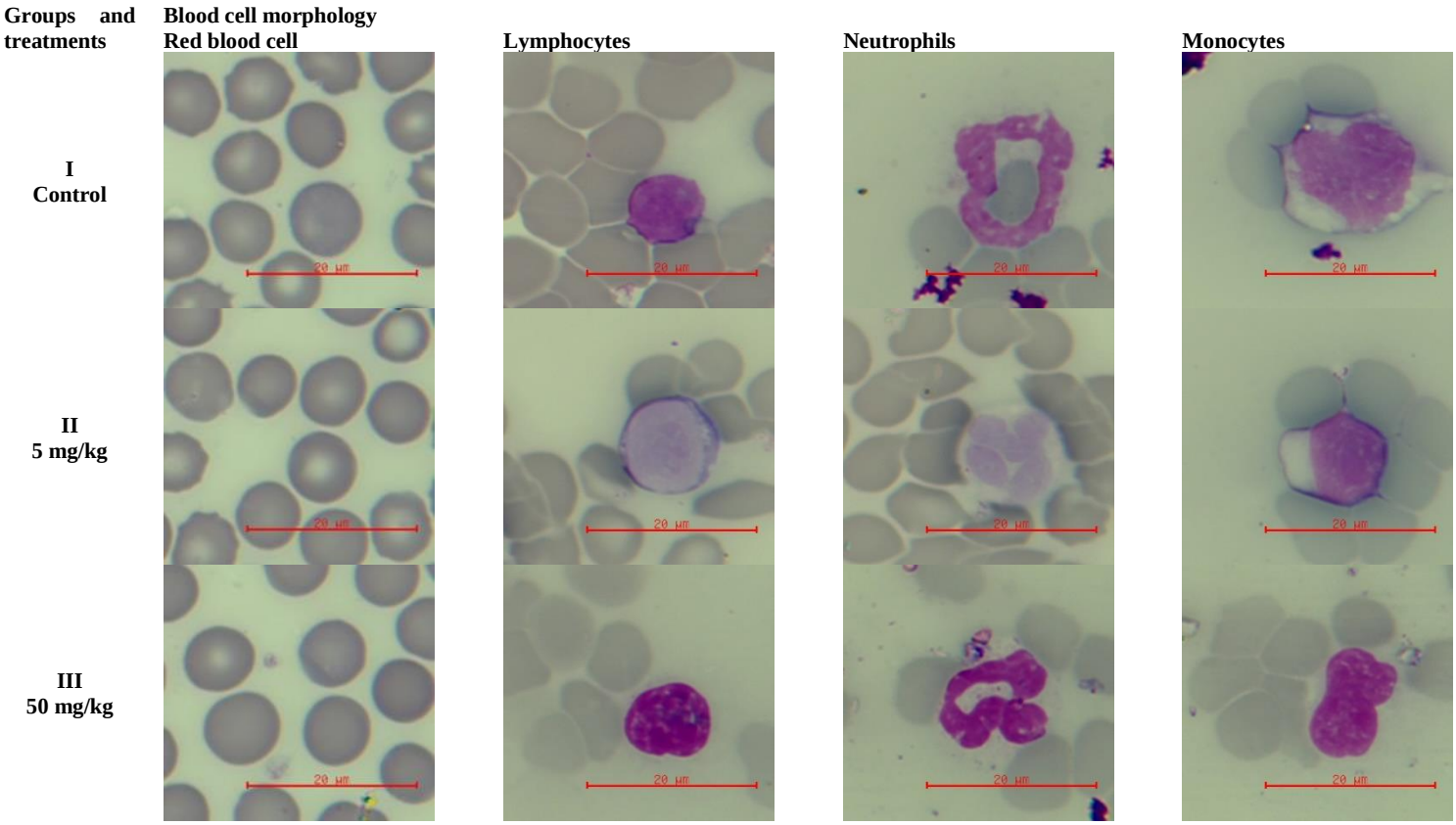


Figure 1: Blood cell morphology of the controls and male rats treated with aqueous extract of a diabetic folklore recipe for 14 days (magnification at 100X).

Table 7: The biochemical data including blood urea nitrogen (BUN), creatinine (Cr), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) of different doses from the aqueous extract of a diabetic folklore recipe in male rats during the course of the 14 days investigation.

Blood chemistry parameters in male rats	Groups and treatments				
	I	II	III	IV	V
	Control	5 mg/kg	50 mg/kg	300 mg/kg	2,000 mg/kg
BUN (mg/dL)	12.80 ± 0.66	12.60 ± 0.68	13.20 ± 1.28	12.80 ± 0.80	14.00 ± 0.71
Cr (mg/dL)	0.20 ± 0.00[a]	0.28 ± 0.02[b]	0.20 ± 0.00[a]	0.20 ± 0.00[a]	0.20 ± 0.00[a]
AST (U/L)	134.80 ± 10.64[a, b]	108.60 ± 12.38[a]	105.40 ± 2.60[a]	151.40 ± 9.58[b]	120.20 ± 7.79[a]
ALT (U/L)	39.00 ± 0.63	36.80 ± 1.83	37.40 ± 1.86	35.20 ± 0.37	35.60 ± 1.81
ALP (U/L)	145.60 ± 11.40[a, b]	166.00 ± 12.13[b]	129.40 ± 7.74[a]	157.40 ± 5.56[a, b]	130.20 ± 11.00[a]
TG (mg/dL)	53.00 ± 4.94[a]	50.40 ± 7.97[a]	60.60 ± 5.67[a, b]	67.60 ± 11.11[a, b]	78.40 ± 4.17[b]
TC (mg/dL)	61.20 ± 1.93	62.60 ± 2.32	62.00 ± 6.23	61.40 ± 3.14	59.40 ± 2.77
HDL (mg/dL)	34.20 ± 1.36	38.00 ± 1.79	36.60 ± 4.42	36.20 ± 2.35	34.00 ± 2.49

[a, b] Different letters in the same row indicated significantly difference at *p*-values less than 0.05.



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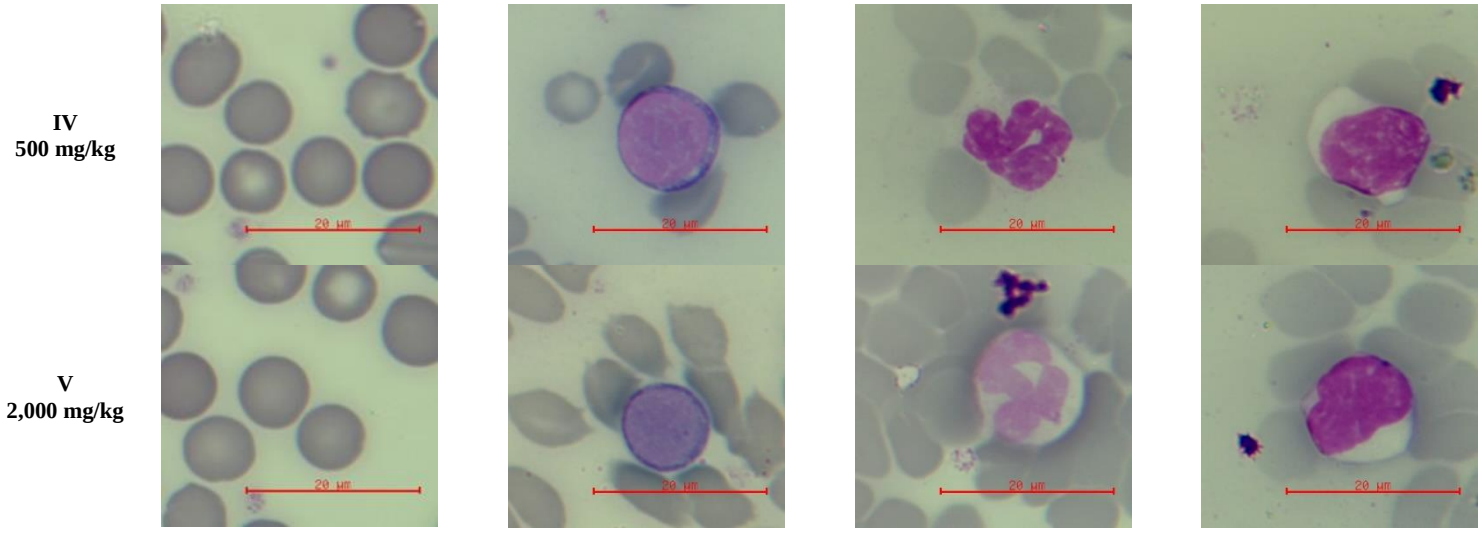
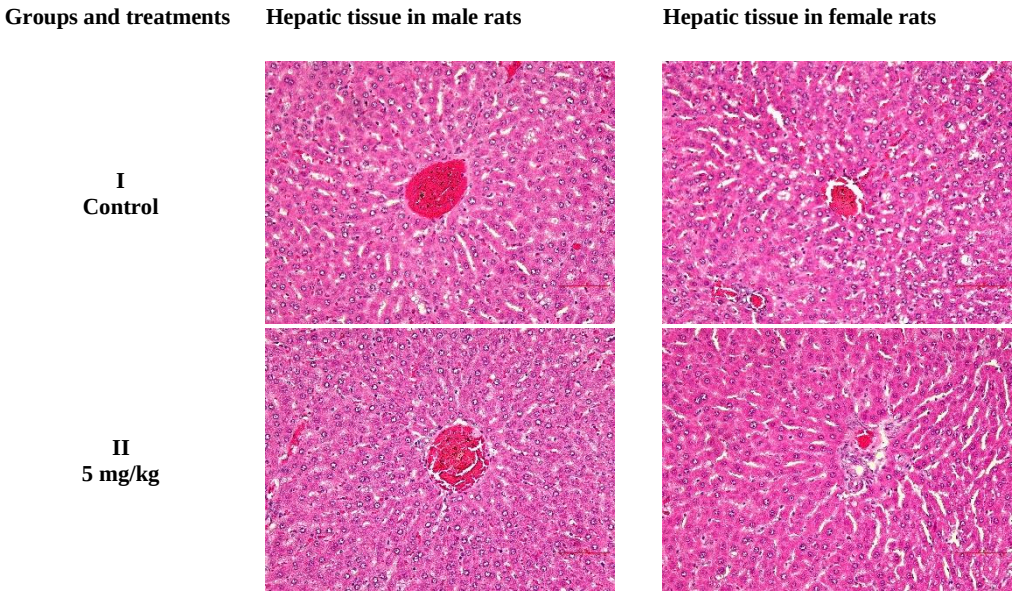


Figure 2: Blood cell morphology of the controls and female rats treated with aqueous extract of a diabetic folklore recipe for 14 days (magnification at 100X).

Table 8: The biochemical data including blood urea nitrogen (BUN), creatinine (Cr), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) of different doses from the aqueous extract of a diabetic folklore recipe in female rats during the course of the 14 days investigation.

Blood chemistry parameters in female rats	Groups and treatments				
	I	II	III	IV	V
	Control	5 mg/kg	50 mg/kg	300 mg/kg	2,000 mg/kg
BUN (mg/dL)	15.20 ± 1.11	14.80 ± 1.24	13.20 ± 0.58	13.80 ± 1.20	15.20 ± 0.58
Cr (mg/dL)	0.26 ± 0.02	0.22 ± 0.02	0.26 ± 0.02	0.28 ± 0.02	0.24 ± 0.02
AST (U/L)	145.00 ± 13.60	162.80 ± 29.13	126.20 ± 9.75	123.60 ± 7.97	138.20 ± 11.10
ALT (U/L)	29.60 ± 1.40[a]	44.00 ± 7.87[b]	31.60 ± 2.54[a]	32.80 ± 1.74[a, b]	29.60 ± 1.12[a]
ALP (U/L)	81.80 ± 6.64[a]	125.40 ± 9.41[b]	82.20 ± 3.68[a]	89.80 ± 7.41[a]	81.00 ± 4.62[a]
TG (mg/dL)	27.80 ± 1.93[a]	44.80 ± 4.13[b]	43.40 ± 6.80[b]	27.80 ± 2.52[a]	29.60 ± 1.72[a]
TC (mg/dL)	62.60 ± 3.59	65.40 ± 2.99	67.00 ± 4.85	66.60 ± 3.41	58.20 ± 5.49
HDL (mg/dL)	44.00 ± 2.47	40.60 ± 2.86	43.00 ± 3.19	41.80 ± 2.31	34.60 ± 4.78

[a, b] Different letters in the same row indicated significantly difference at *p*-values less than 0.05.



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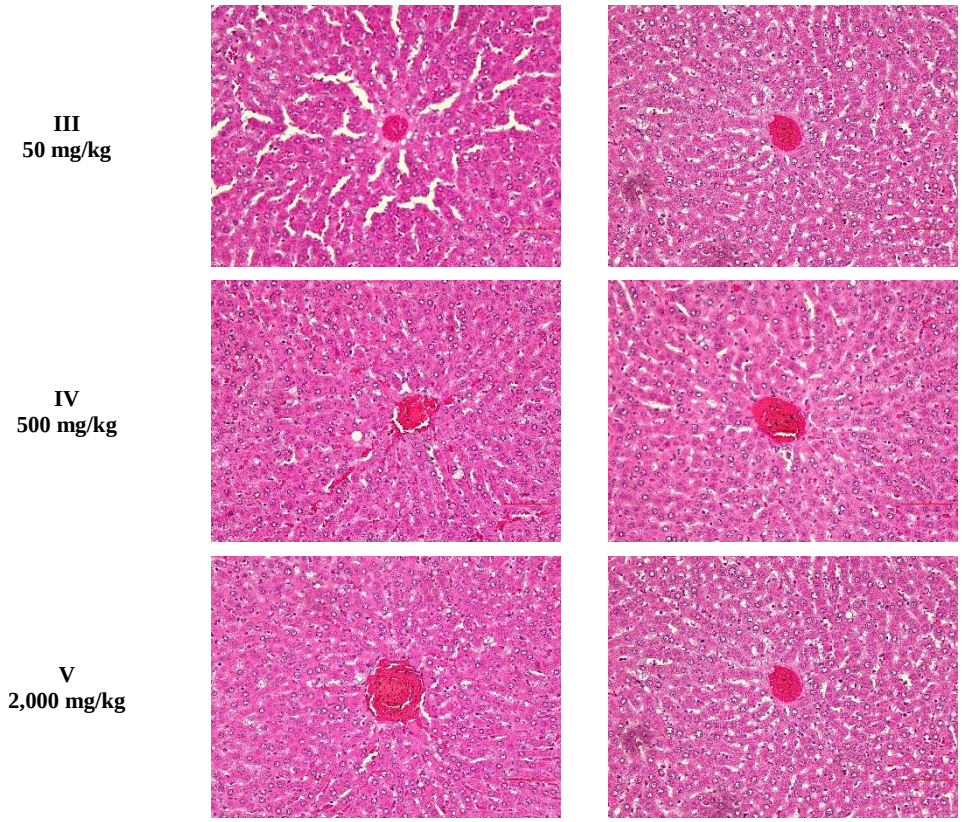
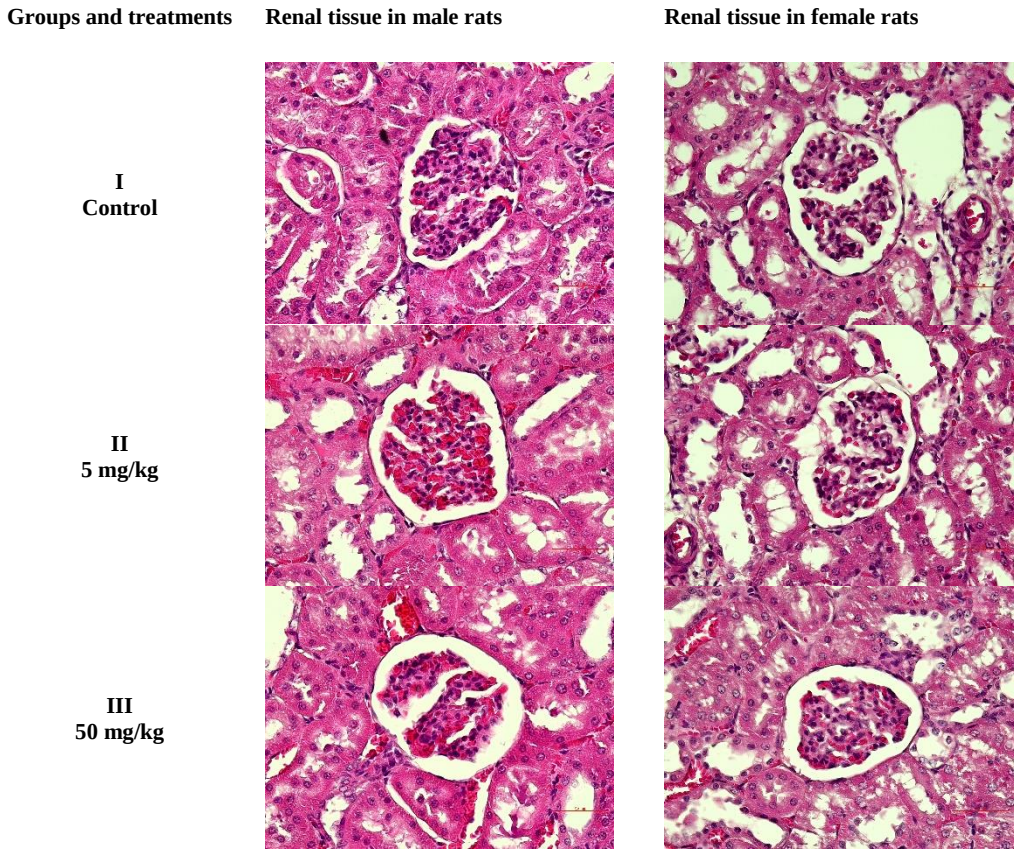


Figure 3: Histopathological illustration of liver in male and female rats treated with aqueous extract of a diabetic folklore recipe for 14 days, stained with hematoxylin and eosin (magnification at 20X).



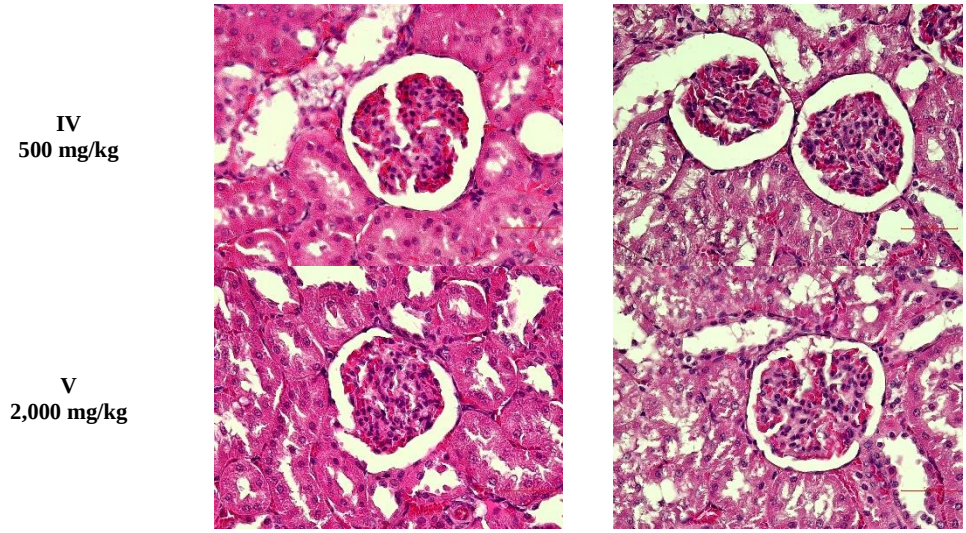


Figure 4: Histopathological illustration of kidney in male and female rats treated with aqueous extract of a diabetic folklore recipe for 14 days, stained with hematoxylin and eosin (magnification at 40X).

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