

Supporting Information for

Acute and chronic toxicity of indole alkaloids from *Alstonia scholaris* (L.) R. Br. in mice and rats

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S1. Alkaloids quantitative analysis

S1.1. Sample preparation

The sample of total alkaloids was pulverized into fine powder. Then 1.0 mg of the total alkaloids was accurately weighed and extracted with 1.0 mL of 50% methanol in ultrasonic water bath for 30 min at 25 °C. The sample solution was filtered through a 0.22 µm membrane before use. A 10 µL-aliquot was injected for UHPLC/UV quantitative analysis.

S1.2. HPLC/UV quantitative analysis

The quantitative analysis was performed on an Agilent 1290 series HPLC system (Agilent Technologies, Germany) comprised a quaternary pump, an auto-sampler, a column temperature controller and a PDA detector. All samples were separated on an ACQUITY UPLC[®] CSH column (2.1 × 100 mm, 1.7 µm) equipped with a Waters VanGuard pre-column (5 mm × 2.1 mm I.D., 1.8 µm). The mobile phase consisted of acetonitrile (A) and water containing 0.5% trifluoroacetic acid (v/v, B) at the ratio of 18 : 82. The following linear elution gradient was used: 0-10 min, 4-16% A; 10-15 min, 16-20% A; 15-18 min, 20% A; 18-20min, 20-95% A. The flow rate was 0.20 mL/min. The column temperature was maintained at 45 °C. The sample tray temperature was maintained at 25 °C. The detection wavelength was set from 190 to 600 nm, and the samples were detected at 285 nm in accordance with the maximum absorption of the analytes.

Table S1 Mean food intake of rats after treatment with TA

Rats	Weeks	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Female	1	96.85 ± 8.68	100.04 ± 19.22	90.38 ± 4.02	117.64 ± 43.94
	2	89.43 ± 3.55	89.59 ± 14.93	87.92 ± 17.29	103.80 ± 28.15
	3	88.49 ± 9.17	89.93 ± 12.65	85.32 ± 6.15	98.55 ± 26.57
	4	79.64 ± 6.57	88.37 ± 12.21	85.37 ± 12.68	102.58 ± 35.90
	5	101.82 ± 37.45	77.36 ± 5.65	82.62 ± 12.90	104.98 ± 51.85
	6	101.02 ± 44.82	80.61 ± 6.35	80.41 ± 8.93	100.49 ± 36.08
	7	90.19 ± 26.48	87.32 ± 29.09	89.47 ± 21.14	86.15 ± 18.60
	8	104.29 ± 33.91	84.24 ± 34.93	71.34 ± 17.97	70.22 ± 8.82
	9	70.47 ± 10.92	82.47 ± 29.79	77.43 ± 18.84	69.21 ± 7.26
	10	82.47 ± 20.40	74.94 ± 19.74	87.02 ± 15.92	91.27 ± 31.31
	11	68.91 ± 10.53	69.26 ± 15.89	72.68 ± 11.72	67.50 ± 4.36
	12	59.43 ± 8.39	61.43 ± 2.82	64.95 ± 6.75	70.96 ± 14.97
	13	69.19 ± 10.58	62.15 ± 2.13	65.49 ± 12.73	69.06 ± 9.28
	14	61.54 ± 4.63	57.35 ± 2.51	47.10 ± 0.63	45.84 ± 5.83
	15	57.05 ± 3.99	56.04 ± 3.74	61.02 ± 6.14	78.90 ± 29.19
	16	60.71 ± 6.84	59.54 ± 2.29	54.33 ± 33.81	42.33 ± 20.97
	17	63.05 ± 7.52	63.52 ± 4.47	55.70 ± 0.72	79.82 ± 26.28
Male	1	86.34 ± 8.14	89.29 ± 3.87	91.97 ± 3.08	83.89 ± 15.00
	2	84.08 ± 5.19	84.51 ± 4.49	87.55 ± 3.64	81.65 ± 7.49
	3	72.58 ± 2.99	80.64 ± 2.54 ^{*▽}	79.44 ± 1.80 ^{*▽}	72.45 ± 7.75
	4	68.24 ± 6.59	70.60 ± 1.12	73.97 ± 2.77	65.99 ± 6.05
	5	63.48 ± 6.29	68.34 ± 1.45	68.69 ± 0.98	66.89 ± 7.31
	6	61.30 ± 6.79	65.50 ± 1.88	67.17 ± 1.51	64.59 ± 7.02
	7	63.88 ± 4.15	61.60 ± 1.39	59.95 ± 5.09	58.83 ± 5.43
	8	58.91 ± 5.72	51.56 ± 5.24 ^{*▲▽▽}	57.37 ± 1.27	59.63 ± 0.95
	9	58.78 ± 2.33	58.72 ± 2.74	58.62 ± 1.46	60.30 ± 1.28
	10	56.07 ± 1.94	55.81 ± 0.78	53.28 ± 4.69	57.10 ± 0.89
	11	54.07 ± 3.77	53.78 ± 2.16	54.43 ± 1.79	57.23 ± 2.30
	12	50.98 ± 3.49	51.32 ± 1.43	51.95 ± 0.81	53.47 ± 1.52
	13	51.54 ± 3.02	50.55 ± 1.02	50.19 ± 0.68	49.85 ± 3.45
	14	48.87 ± 1.76	43.39 ± 2.12	46.90 ± 1.23	48.55 ± 1.69
	15	45.20 ± 3.39	47.65 ± 2.35	47.34 ± 2.92	50.30 ± 1.05
	16	49.39 ± 2.23	45.19 ± 0.19	45.17 ± 5.09	48.40 ± 1.47
	17	49.16 ± 0.57	46.71 ± 0.17	50.01 ± 3.52	51.06 ± 1.10

Results were expressed as means ± SD. n: the number of rats. n = 20 at 7 week; n = 15 at 13 week; n = 5 at 17 week for single-sex.

* $p < 0.05$ was compared with the control group.

▲ $p < 0.05$ was compared with the 100 mg/kg.bw group.

▽/▽▽ $p < 0.05/0.01$ was compared with the 300 mg/kg.bw group.

Unit: g/kg/d.

Table S2 Mean water consumption of rats after treatment with TA

Rats	Weeks	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Female	1	136.30 ± 13.45	120.59 ± 5.23 ^{▲▲▽}	145.44 ± 19.54	138.96 ± 9.58
	2	155.16 ± 11.41	127.32 ± 23.07	164.24 ± 29.75	148.46 ± 6.92
	3	139.25 ± 16.02	122.38 ± 6.51 ^{▲▲▽}	155.93 ± 20.23	143.86 ± 14.41
	4	136.69 ± 11.89	132.17 ± 19.23	156.77 ± 29.18	131.58 ± 17.54
	5	132.33 ± 10.11	109.72 ± 7.29 ^{*▲▲}	142.01 ± 28.92	108.36 ± 11.98 ^{*▲▲}
	6	139.21 ± 10.53	112.88 ± 10.98 ^{*▲▽}	143.53 ± 29.34	127.51 ± 7.61
	7	134.51 ± 11.96	99.10 ± 10.70 ^{*▲}	142.37 ± 37.53	104.78 ± 13.83 [*]
	8	115.00 ± 15.11	91.54 ± 8.66 ^{*▲}	115.29 ± 18.19	91.14 ± 12.92 ^{*▲}
	9	109.63 ± 10.59	109.22 ± 17.78	120.40 ± 18.40	110.88 ± 9.98
	10	126.21 ± 29.99	110.46 ± 32.15	142.25 ± 53.76	117.71 ± 38.73
	11	106.71 ± 13.78	84.86 ± 16.00	108.33 ± 29.37	91.04 ± 14.70
	12	111.15 ± 15.37	97.09 ± 27.37	109.66 ± 24.22	100.77 ± 12.32
	13	109.10 ± 20.04	92.76 ± 11.42	111.85 ± 25.18	86.09 ± 18.77
	14	98.20 ± 16.91	92.66 ± 10.65	84.50 ± 20.89	89.99 ± 12.81
	15	112.08 ± 22.05	112.40 ± 17.18	102.36 ± 15.26	103.83 ± 10.75
	16	87.05 ± 17.05	97.96 ± 32.29	93.60 ± 35.29	81.40 ± 7.10
	17	82.64 ± 19.17	82.45 ± 2.34	83.98 ± 19.08	87.45 ± 1.38
Male	1	143.51 ± 6.54	136.17 ± 9.03	145.42 ± 17.90	167.84 ± 41.28
	2	145.43 ± 15.05	138.73 ± 21.90	144.78 ± 13.35	152.59 ± 14.53
	3	134.83 ± 7.12	122.74 ± 10.05 ^{▲▲▽}	144.37 ± 8.66	138.47 ± 15.00
	4	142.20 ± 9.91	128.69 ± 18.37	134.51 ± 6.81	140.33 ± 18.47
	5	117.44 ± 13.98	106.00 ± 10.09	120.79 ± 16.25	119.99 ± 17.95
	6	109.08 ± 20.62	107.43 ± 19.00	115.09 ± 6.42	117.46 ± 16.15
	7	112.43 ± 13.03	101.26 ± 10.30	122.52 ± 19.29	112.07 ± 16.72
	8	99.94 ± 10.65	82.94 ± 9.87	96.69 ± 14.70	96.57 ± 15.17
	9	101.63 ± 13.59	84.85 ± 8.16	87.85 ± 9.02	91.45 ± 20.35
	10	103.14 ± 15.12	83.38 ± 10.80	83.63 ± 5.27	105.11 ± 25.25
	11	94.95 ± 14.35	70.76 ± 9.47 ^{***▽}	75.09 ± 5.85 ^{**}	87.82 ± 10.94
	12	89.57 ± 17.99	72.85 ± 5.10	77.96 ± 10.58	87.18 ± 15.01
	13	90.86 ± 17.41	66.96 ± 11.55	70.89 ± 10.91	86.17 ± 20.21
	14	71.61 ± 16.28	72.11 ± 7.85	77.91 ± 9.15	73.02 ± 8.31
	15	75.11 ± 8.23	78.10 ± 13.27	82.68 ± 1.32	103.31 ± 26.98
	16	67.02 ± 21.64	65.76 ± 13.42	65.58 ± 10.00	62.10 ± 18.46
	17	61.71 ± 16.61	64.60 ± 16.21	67.11 ± 0.84	86.38 ± 4.17

Results were expressed as means ± SD. n: the number of rats. n = 20 at 7 week; n = 15 at 13 week; n = 5 at 17 week for single-sex.

*/** $p < 0.05/0.01$ was compared with the control group.

▲/▲▲ $p < 0.05/0.01$ was compared with the 100 mg/kg.bw group.

▽ $p < 0.05$ was compared with the 300 mg/kg.bw group.

Unit: mL/kg/d.

Table S3 The body weight of female rats after treatment with TA

Weeks	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
0	140.04 ± 6.91	140.04 ± 8.26	140.02 ± 7.12	140.75 ± 7.80
0.5	154.28 ± 8.77	152.54 ± 8.14	151.67 ± 9.40	150.47 ± 9.76
1	168.56 ± 9.62	167.13 ± 8.78	166.13 ± 9.01	164.68 ± 10.17
1.5	178.98 ± 11.68	177.66 ± 10.52	173.90 ± 11.89	173.37 ± 11.80
2	189.80 ± 12.38	189.44 ± 11.23	185.52 ± 9.49	184.38 ± 12.54
2.5	199.80 ± 14.19	197.61 ± 12.50	195.33 ± 9.69	194.92 ± 12.59
3	209.94 ± 15.72	210.50 ± 13.77	205.16 ± 10.78	204.57 ± 12.91
3.5	216.26 ± 17.48	215.96 ± 15.21	214.25 ± 11.24	214.28 ± 14.52
4	227.42 ± 18.93	225.10 ± 16.22	223.58 ± 11.34	222.55 ± 16.19
4.5	234.12 ± 19.10	230.72 ± 16.68	230.12 ± 12.92	228.55 ± 16.82
5	241.44 ± 19.55	241.08 ± 14.89	237.91 ± 13.54	234.14 ± 18.30
5.5	250.25 ± 21.43	249.06 ± 17.77	245.04 ± 12.83	239.51 ± 17.71
6	254.90 ± 20.89	253.54 ± 17.12	249.30 ± 11.57	243.55 ± 18.11
6.5	259.70 ± 22.39	259.28 ± 17.48	255.58 ± 13.08	239.51 ± 17.71 ^{**ΔΔ▲▲}
7	261.14 ± 22.26	260.54 ± 16.30	256.51 ± 11.61	248.88 ± 21.31
7.5	267.52 ± 24.23	260.71 ± 13.58	260.58 ± 13.49	257.20 ± 20.67
8	273.74 ± 24.63	266.00 ± 13.42	266.37 ± 14.19	261.56 ± 19.84
8.5	277.25 ± 25.93	275.39 ± 15.65	269.47 ± 16.06	265.25 ± 20.15
9	281.21 ± 26.70	276.76 ± 16.51	273.05 ± 15.83	266.51 ± 19.75
9.5	284.37 ± 26.05	281.61 ± 18.00	275.65 ± 17.05	268.72 ± 21.00
10	287.43 ± 26.40	285.99 ± 19.01	278.40 ± 17.52	272.17 ± 20.41
10.5	289.47 ± 25.74	287.69 ± 17.45	281.97 ± 16.99	276.23 ± 19.06
11	292.69 ± 26.67	291.14 ± 17.48	284.61 ± 18.13	276.76 ± 20.24
11.5	295.45 ± 29.16	293.05 ± 17.90	287.12 ± 19.15	276.34 ± 23.21
12	301.00 ± 28.76	296.31 ± 17.56	292.13 ± 19.08	280.61 ± 24.34
12.5	302.18 ± 30.39	298.77 ± 19.79	294.51 ± 20.14	283.10 ± 26.91
13	293.85 ± 29.95	292.15 ± 18.96	287.66 ± 18.17	276.49 ± 23.43
13.5	311.58 ± 38.54	299.10 ± 19.41	296.50 ± 10.01	286.08 ± 21.97
14	315.56 ± 41.07	300.58 ± 19.85	300.82 ± 11.23	291.58 ± 21.17
14.5	319.62 ± 39.18	303.82 ± 17.88	303.98 ± 13.26	292.54 ± 16.04
15	321.12 ± 41.36	306.74 ± 17.69	310.14 ± 16.57	295.90 ± 15.07
15.5	330.04 ± 44.76	308.24 ± 15.66	311.42 ± 13.84	296.76 ± 19.98
16	327.74 ± 44.22	309.06 ± 18.24	311.96 ± 15.78	301.88 ± 17.57
16.5	332.76 ± 44.92	311.86 ± 15.97	314.74 ± 16.74	305.78 ± 14.57
17	322.72 ± 43.19	302.92 ± 15.80	304.90 ± 17.59	298.74 ± 19.04

Results were expressed as means ± SD. n: the number of rats. n = 20 at 7 week; n = 15 at 13 week; n = 5 at 17 week for single-sex.

^{**} $p < 0.01$ was compared with the control group.

^{ΔΔ} $p < 0.01$ was compared with the 50 mg/kg.bw group.

^{▲▲} $p < 0.01$ was compared with the 100 mg/kg.bw group.

Unit: g.

Table S4 The body weight of male rats after treatment with TA

Weeks	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
0	170.90 ± 9.17	171.12 ± 10.27	170.82 ± 8.04	170.87 ± 10.11
0.5	192.42 ± 9.72	194.28 ± 9.64	192.88 ± 7.70	191.67 ± 8.83
1	219.54 ± 15.78	220.22 ± 13.79	216.87 ± 9.72	218.48 ± 8.88
1.5	240.22 ± 16.86	240.92 ± 14.49	236.59 ± 12.57	239.36 ± 8.77
2	266.06 ± 17.72	262.62 ± 17.27	258.23 ± 17.09	262.09 ± 9.93
2.5	284.00 ± 22.79	278.26 ± 19.60	275.98 ± 19.27	276.90 ± 11.86
3	302.58 ± 30.24	295.18 ± 22.60	294.13 ± 23.04	292.69 ± 13.81
3.5	319.60 ± 31.69	308.56 ± 25.42	310.26 ± 24.83	305.76 ± 15.27
4	336.99 ± 32.19	324.79 ± 29.38	324.14 ± 26.02	318.70 ± 17.42
4.5	350.95 ± 34.83	334.50 ± 30.98	335.52 ± 28.46	329.44 ± 20.21
5	366.01 ± 36.78	349.00 ± 32.39	348.66 ± 29.41	343.62 ± 21.93
5.5	380.01 ± 38.12	362.06 ± 33.96	361.32 ± 30.36	356.44 ± 24.06
6	392.62 ± 39.34	372.31 ± 35.05	373.26 ± 28.69	368.30 ± 25.78
6.5	405.02 ± 38.54	384.26 ± 35.16	385.93 ± 29.60	378.10 ± 26.86
7	413.77 ± 41.55	390.66 ± 37.45	394.04 ± 33.54	383.93 ± 28.58
7.5	428.19 ± 44.96	406.31 ± 36.06	410.87 ± 34.51	394.93 ± 26.38
8	442.02 ± 44.27	419.91 ± 35.70	424.67 ± 33.65	406.53 ± 27.43
8.5	453.11 ± 45.99	430.71 ± 36.27	434.63 ± 34.12	416.03 ± 27.91
9	464.25 ± 47.48	439.33 ± 37.36	445.39 ± 32.45	424.73 ± 27.96**
9.5	471.28 ± 47.64	446.97 ± 37.96	453.13 ± 31.44	433.86 ± 29.25
10	480.67 ± 48.00	453.49 ± 38.08	459.27 ± 32.33	441.27 ± 29.92
10.5	488.15 ± 47.44	462.39 ± 38.13	468.75 ± 34.73	450.65 ± 32.97
11	496.75 ± 48.98	470.04 ± 39.61	477.01 ± 34.32	452.37 ± 48.08
11.5	501.81 ± 48.70	473.25 ± 37.16	483.94 ± 33.27	465.87 ± 35.95
12	510.91 ± 48.89	480.01 ± 37.85*	488.19 ± 33.02	470.71 ± 37.64**
12.5	515.74 ± 49.72	483.63 ± 37.87*	492.09 ± 33.09	472.09 ± 38.43**
13	505.69 ± 50.86	474.05 ± 33.69*	484.21 ± 33.09	465.16 ± 40.56**
0.5	535.62 ± 75.67	468.64 ± 35.87	505.16 ± 40.89	509.36 ± 37.57
1	545.58 ± 79.25	479.92 ± 36.84	517.86 ± 42.28	519.78 ± 38.50
1.5	551.82 ± 78.93	483.02 ± 36.06	522.42 ± 39.97	525.24 ± 36.96
2	548.28 ± 83.08	487.62 ± 32.74	525.62 ± 39.25	518.64 ± 38.68
2.5	565.94 ± 83.61	493.26 ± 33.99	531.92 ± 38.73	534.48 ± 37.82
3	574.84 ± 85.07	498.94 ± 34.49	535.32 ± 40.07	539.74 ± 41.41
3.5	578.54 ± 89.57	501.82 ± 32.04	541.40 ± 41.25	546.98 ± 42.39
4	566.36 ± 83.17	492.38 ± 32.03	524.84 ± 39.70	529.46 ± 38.42

Results were expressed as means ± SD. n, the number of rats. n = 20 at 7 week; n = 15 at 13 week; n = 5 at 17 week for single-sex.

*** $p < 0.05/0.01$ was compared with the control group.

Unit: g.

Table S5 Hematological examination of rats treated with TA for 7 weeks

Rats	Indexes	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Female (n = 5)	WBC ($\times 10^9/L$)	6.22 $\pm$ 1.48	6.12 $\pm$ 1.36	6.20 $\pm$ 1.36	6.49 $\pm$ 2.48
	NE%	34.86 $\pm$ 4.14	33.75 $\pm$ 1.93	29.63 $\pm$ 3.48	33.35 $\pm$ 2.97
	LY%	58.70 $\pm$ 6.21	59.12 $\pm$ 5.15	65.66 $\pm$ 3.77	61.63 $\pm$ 2.34
	MO%	4.52 $\pm$ 5.09	5.50 $\pm$ 5.30	2.72 $\pm$ 0.34	2.78 $\pm$ 0.43
	RBC ($\times 10^{12}/L$)	6.15 $\pm$ 0.64	6.58 $\pm$ 0.34	6.03 $\pm$ 0.71	6.42 $\pm$ 0.30
	Hb (g/L)	124.80 $\pm$ 10.06	132.00 $\pm$ 5.10	126.00 $\pm$ 7.07	133.20 $\pm$ 3.03
	RDW (%)	17.42 $\pm$ 1.22	16.56 $\pm$ 0.61	18.00 $\pm$ 1.46	16.74 $\pm$ 0.54
	MCV (fL)	45.86 $\pm$ 2.71	44.58 $\pm$ 2.07	45.82 $\pm$ 3.18	46.08 $\pm$ 1.59
	MCH (pg)	20.28 $\pm$ 0.97	20.04 $\pm$ 0.78	21.06 $\pm$ 1.52	20.76 $\pm$ 0.68
	MCHC (g/L)	446.80 $\pm$ 14.96	448.80 $\pm$ 8.04	459.60 $\pm$ 3.13	453.80 $\pm$ 2.95
	PLT ($\times 10^9/L$)	914.80 $\pm$ 192.32	853.20 $\pm$ 30.74	859.20 $\pm$ 75.96	915.20 $\pm$ 133.87
	PT (Sec)	13.46 $\pm$ 0.48	12.98 $\pm$ 0.27* [▲] [▽]	14.62 $\pm$ 1.30*	14.40 $\pm$ 0.92*
	RET (%)	1.10 $\pm$ 0.20	1.44 $\pm$ 0.57	1.68 $\pm$ 0.44	1.42 $\pm$ 0.54
Male (n = 5)	WBC ($\times 10^9/L$)	6.59 $\pm$ 1.30	6.76 $\pm$ 0.74	7.41 $\pm$ 1.56	9.43 $\pm$ 1.56** ^{△△} [▲]
	NE%	28.74 $\pm$ 1.42	30.72 $\pm$ 2.09	30.91 $\pm$ 2.11	30.85 $\pm$ 1.62
	LY%	64.95 $\pm$ 2.99	62.52 $\pm$ 2.13	63.46 $\pm$ 1.86	63.45 $\pm$ 2.02
	MO%	3.70 $\pm$ 0.95	4.18 $\pm$ 0.63	3.13 $\pm$ 0.59	3.37 $\pm$ 0.44
	RBC ($\times 10^{12}/L$)	7.12 $\pm$ 0.40	7.39 $\pm$ 0.51	7.20 $\pm$ 0.46	7.10 $\pm$ 0.34
	Hb (g/L)	135.60 $\pm$ 2.97	140.40 $\pm$ 8.53	138.00 $\pm$ 6.16	138.40 $\pm$ 2.97
	RDW (%)	17.20 $\pm$ 0.67	17.92 $\pm$ 0.68	17.34 $\pm$ 0.27	17.52 $\pm$ 1.09
	MCV (fL)	41.40 $\pm$ 1.34	42.08 $\pm$ 0.61	41.70 $\pm$ 1.66	42.98 $\pm$ 1.56
	MCH (pg)	19.10 $\pm$ 0.71	18.98 $\pm$ 0.70	19.14 $\pm$ 0.78	19.48 $\pm$ 0.59
	MCHC (g/L)	463.20 $\pm$ 3.03	456.00 $\pm$ 12.41	459.40 $\pm$ 4.50	454.40 $\pm$ 5.37
	PLT ($\times 10^9/L$)	931.20 $\pm$ 77.36	864.40 $\pm$ 40.38	903.20 $\pm$ 139.17	843.20 $\pm$ 81.74
	PT (Sec)	14.06 $\pm$ 1.49	14.08 $\pm$ 1.81	13.64 $\pm$ 0.27	13.56 $\pm$ 0.38
	RET (%)	2.20 $\pm$ 0.69	1.58 $\pm$ 0.58	1.80 $\pm$ 0.87	1.42 $\pm$ 0.74

Results were expressed as means $\pm$ SD.

*** $p < 0.05/0.01$ was compared with the control group.

^{△△} $p < 0.01$ was compared with the 50 mg/kg.bw group.

[▲] $p < 0.05$ was compared with the 100 mg/kg.bw group.

[▽] $p < 0.05$ was compared with the 300 mg/kg.bw group.

Table S6 Hematological examination of rats treated with TA for 13 weeks

Rats	Indexes	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Female (n = 10)	WBC ($\times 10^9/L$)	5.24 $\pm$ 1.25	5.49 $\pm$ 1.04	6.03 $\pm$ 1.78	7.15 $\pm$ 1.14 ^{***$\Delta\Delta$}
	NE%	30.34 $\pm$ 1.55	30.08 $\pm$ 1.67	29.40 $\pm$ 3.59	31.01 $\pm$ 3.34
	LY%	63.88 $\pm$ 1.14	62.82 $\pm$ 1.69	63.63 $\pm$ 2.93	62.68 $\pm$ 2.72
	MO%	3.45 $\pm$ 0.82	4.32 $\pm$ 0.57 ^{*∇}	4.32 $\pm$ 0.93 ^{*∇}	3.46 $\pm$ 0.60
	RBC ($\times 10^{12}/L$)	6.49 $\pm$ 0.29	6.14 $\pm$ 0.52	6.29 $\pm$ 0.48	6.24 $\pm$ 0.75
	Hb (g/L)	130.00 $\pm$ 5.33	127.00 $\pm$ 10.30	125.40 $\pm$ 7.37	157.10 $\pm$ 62.37
	RDW (%)	18.33 $\pm$ 0.76	18.32 $\pm$ 0.92	18.06 $\pm$ 0.36	17.18 $\pm$ 1.50 ^{*Δ}
	MCV (fL)	44.63 $\pm$ 1.32	45.17 $\pm$ 1.25	45.22 $\pm$ 1.87	44.00 $\pm$ 9.10
	MCH (pg)	20.01 $\pm$ 0.70	19.63 $\pm$ 3.07	20.23 $\pm$ 0.90	20.55 $\pm$ 1.44
	MCHC (g/L)	446.30 $\pm$ 8.15	432.30 $\pm$ 64.83	420.90 $\pm$ 84.82	377.90 $\pm$ 112.88
	PLT ($\times 10^9/L$)	856.40 $\pm$ 113.82	811.50 $\pm$ 64.16	799.60 $\pm$ 118.06	791.80 $\pm$ 81.55
	PT (Sec)	15.00 $\pm$ 0.76	14.84 $\pm$ 0.37	14.71 $\pm$ 1.16	15.30 $\pm$ 1.44
	RET (%)	1.63 $\pm$ 0.33	1.56 $\pm$ 0.62	1.69 $\pm$ 0.57	1.49 $\pm$ 0.42
Male (n = 10)	WBC ($\times 10^9/L$)	9.13 $\pm$ 2.72	7.48 $\pm$ 1.01	6.56 $\pm$ 2.27 ^{*∇}	9.00 $\pm$ 2.07
	NE%	31.65 $\pm$ 2.67	30.42 $\pm$ 1.16	31.02 $\pm$ 1.18	31.48 $\pm$ 1.21
	LY%	61.66 $\pm$ 2.58	62.54 $\pm$ 1.62	62.24 $\pm$ 1.08	62.31 $\pm$ 1.01
	MO%	3.98 $\pm$ 0.61	4.22 $\pm$ 0.55	3.95 $\pm$ 0.33	3.73 $\pm$ 0.65
	RBC ($\times 10^{12}/L$)	7.37 $\pm$ 0.65	7.58 $\pm$ 0.78	7.56 $\pm$ 0.70	7.00 $\pm$ 0.82
	Hb (g/L)	137.40 $\pm$ 5.34	137.20 $\pm$ 5.43	155.20 $\pm$ 50.45	131.60 $\pm$ 9.46
	RDW (%)	18.07 $\pm$ 0.55	18.02 $\pm$ 0.77	17.58 $\pm$ 0.89	18.08 $\pm$ 0.92
	MCV (fL)	41.85 $\pm$ 1.74	42.33 $\pm$ 2.44	41.04 $\pm$ 2.14	42.90 $\pm$ 1.69
	MCH (pg)	18.66 $\pm$ 1.11	18.42 $\pm$ 1.35	18.22 $\pm$ 0.90	18.94 $\pm$ 1.03
	MCHC (g/L)	446.90 $\pm$ 10.78	435.80 $\pm$ 11.56	418.70 $\pm$ 80.74	443.80 $\pm$ 9.50
	PLT ($\times 10^9/L$)	878.80 $\pm$ 63.10	872.80 $\pm$ 52.13	818.80 $\pm$ 40.74	868.20 $\pm$ 96.41
	PT (Sec)	15.10 $\pm$ 0.59	15.00 $\pm$ 0.65	14.56 $\pm$ 0.54	14.84 $\pm$ 0.66
	RET (%)	1.40 $\pm$ 0.26	1.50 $\pm$ 0.44	1.61 $\pm$ 0.33	1.62 $\pm$ 0.33

Results were expressed as means $\pm$ SD.

^{***} $p < 0.05/0.01$ was compared with the control group.

^{$\Delta/\Delta\Delta$} $p < 0.05/0.01$ was compared with the 50 mg/kg.bw group.

^{∇} $p < 0.05$ was compared with the 300 mg/kg.bw group.

Table S7 Hematological examination of rats after the 4-week recovery period

Rats	Indexes	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Female (n = 5)	WBC ($\times 10^9/L$)	5.18 $\pm$ 0.91	5.50 $\pm$ 0.87	6.38 $\pm$ 1.79	5.22 $\pm$ 1.05
	NE%	31.82 $\pm$ 0.94	32.19 $\pm$ 1.68	31.00 $\pm$ 1.18	31.22 $\pm$ 0.96
	LY%	62.42 $\pm$ 0.76	61.63 $\pm$ 1.70	61.42 $\pm$ 1.65	61.98 $\pm$ 1.09
	MO%	3.77 $\pm$ 0.44	4.27 $\pm$ 0.87	4.87 $\pm$ 1.18	4.40 $\pm$ 0.71
	RBC ($\times 10^{12}/L$)	6.17 $\pm$ 0.30	6.12 $\pm$ 0.34	6.17 $\pm$ 0.29	6.78 $\pm$ 0.50 ^{*$\Delta\Delta$}
	Hb (g/L)	124.80 $\pm$ 3.63	127.20 $\pm$ 3.35	125.20 $\pm$ 4.15	134.80 $\pm$ 3.03 ^{*$\Delta\Delta$}
	RDW (%)	17.68 $\pm$ 0.90	17.92 $\pm$ 0.91	18.12 $\pm$ 0.70	17.68 $\pm$ 0.55
	MCV (fL)	45.14 $\pm$ 1.32	46.14 $\pm$ 1.11	45.64 $\pm$ 0.97	44.74 $\pm$ 2.08
	MCH (pg)	20.24 $\pm$ 0.63	20.88 $\pm$ 0.57	20.34 $\pm$ 0.59	19.96 $\pm$ 0.97
	MCHC (g/L)	448.60 $\pm$ 2.70	449.00 $\pm$ 6.36	443.80 $\pm$ 3.56	443.80 $\pm$ 3.42
	PLT ($\times 10^9/L$)	808.00 $\pm$ 64.06	850.40 $\pm$ 73.86	787.60 $\pm$ 83.41	858.80 $\pm$ 106.36
	PT (Sec)	14.46 $\pm$ 1.28	14.00 $\pm$ 0.84	13.22 $\pm$ 2.29	13.10 $\pm$ 0.46
	RET (%)	1.68 $\pm$ 0.18	2.28 $\pm$ 0.55	1.98 $\pm$ 1.11	1.44 $\pm$ 0.38
Male (n = 5)	WBC ($\times 10^9/L$)	6.99 $\pm$ 1.62	7.11 $\pm$ 1.03	6.71 $\pm$ 0.80	7.19 $\pm$ 2.02
	NE%	30.91 $\pm$ 1.38	30.45 $\pm$ 1.07	31.61 $\pm$ 0.89	30.62 $\pm$ 0.86
	LY%	62.11 $\pm$ 1.09	61.13 $\pm$ 1.58	61.20 $\pm$ 1.60	62.06 $\pm$ 0.52
	MO%	4.79 $\pm$ 0.44	5.89 $\pm$ 0.23 ^{**$\Delta\Delta$}	4.80 $\pm$ 0.76	5.29 $\pm$ 0.57
	RBC ($\times 10^{12}/L$)	7.49 $\pm$ 0.70	7.60 $\pm$ 0.24	7.98 $\pm$ 0.41	7.87 $\pm$ 0.56
	Hb (g/L)	135.60 $\pm$ 4.56	134.80 $\pm$ 6.10	139.60 $\pm$ 2.61	136.00 $\pm$ 5.10
	RDW (%)	17.24 $\pm$ 1.91	17.98 $\pm$ 1.01	17.60 $\pm$ 1.33	17.86 $\pm$ 1.14
	MCV (fL)	41.98 $\pm$ 2.24	40.56 $\pm$ 1.23	40.00 $\pm$ 1.30	40.10 $\pm$ 1.90
	MCH (pg)	18.14 $\pm$ 1.31	17.72 $\pm$ 0.58	17.52 $\pm$ 0.70	17.34 $\pm$ 0.97
	MCHC (g/L)	430.60 $\pm$ 9.07	439.20 $\pm$ 5.89	434.60 $\pm$ 8.90	434.00 $\pm$ 9.11
	PLT ($\times 10^9/L$)	808.40 $\pm$ 106.38	835.20 $\pm$ 111.16	818.80 $\pm$ 80.11	854.80 $\pm$ 84.20
	PT (Sec)	15.38 $\pm$ 1.19	15.56 $\pm$ 2.89	14.94 $\pm$ 2.00	12.42 $\pm$ 6.29
	RET (%)	1.52 $\pm$ 0.36	1.70 $\pm$ 0.47	1.46 $\pm$ 0.54	1.78 $\pm$ 0.42

Results were expressed as means $\pm$ SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

^{Δ} $p < 0.05$ was compared with the 50 mg/kg.bw group.

^{$\Delta/\Delta\Delta$} $p < 0.05/0.01$ was compared with the 100 mg/kg.bw group.

Table S8 Serum chemistry values of rats treated with TA for 7 weeks

Indexes	Female (n = 5)				Male (n = 5)			
	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
ALT (U/L)	32.80 ± 12.64	30.20 ± 4.09	30.80 ± 10.59	25.00 ± 3.81	34.20 ± 5.63	34.00 ± 3.94	29.60 ± 3.13	32.60 ± 11.19
AST (U/L)	86.00 ± 12.59	82.80 ± 8.79	76.80 ± 17.21	74.20 ± 16.74	87.20 ± 14.84	88.80 ± 7.19	77.20 ± 14.72 ^Δ	79.20 ± 6.30
ALP (U/L)	79.00 ± 17.65	78.60 ± 13.13	84.00 ± 12.02	75.00 ± 13.27	124.40 ± 6.54	117.60 ± 15.66	131.20 ± 8.79	119.00 ± 30.11
BUN (mmol/L)	5.02 ± 0.33	4.90 ± 0.42	4.40 ± 0.60	4.06 ± 0.51 ^{**Δ}	4.12 ± 0.36	3.80 ± 0.43	3.94 ± 0.25	4.18 ± 0.41
CRE (μmol/L)	87.60 ± 12.78	94.20 ± 12.83	86.00 ± 11.22	88.40 ± 10.57	136.40 ± 58.45	104.40 ± 24.39	99.00 ± 32.95	121.60 ± 60.45
TP (g/L)	78.24 ± 10.69	75.78 ± 9.93	73.66 ± 5.96	77.06 ± 8.28	77.16 ± 3.81	73.16 ± 5.28	76.50 ± 17.93	91.88 ± 16.25
ALB (g/L)	31.40 ± 5.29	32.92 ± 3.53	33.18 ± 2.08	33.72 ± 3.06	32.80 ± 1.53	33.10 ± 0.39	32.30 ± 1.74	33.00 ± 2.67
Glu (mmol/L)	6.26 ± 0.36	6.42 ± 0.51	6.56 ± 0.40	7.54 ± 0.67 ^{**ΔΔ▲▲}	6.58 ± 0.69	6.22 ± 0.80	6.64 ± 1.19	6.80 ± 0.34
TBIL (μmol/L)	2.58 ± 1.27	3.42 ± 0.80	3.98 ± 0.84 [*]	4.34 ± 0.22 ^{**}	4.56 ± 2.30	4.78 ± 1.22	5.18 ± 2.25	5.52 ± 1.96
TC (mmol/L)	1.50 ± 0.17	1.57 ± 0.47	1.78 ± 0.19	1.77 ± 0.32	1.57 ± 0.36	1.30 ± 0.09	1.13 ± 0.14 ^{**▽}	1.44 ± 0.18
TG (mmol/L)	0.67 ± 0.20	0.60 ± 0.13	0.52 ± 0.24	0.60 ± 0.08	1.47 ± 0.54	1.17 ± 0.46	0.93 ± 0.29	1.06 ± 0.43
CK (U/L)	405.40 ± 214.36	378.40 ± 120.94	288.20 ± 123.62	434.40 ± 246.16	265.20 ± 37.88	247.40 ± 59.11	299.20 ± 131.85	274.20 ± 47.28
K ⁺ (mmol/L)	3.89 ± 0.40	4.22 ± 0.16	4.11 ± 0.37	4.25 ± 0.32	4.14 ± 0.35	4.09 ± 0.17	3.97 ± 0.36	4.05 ± 0.15
Na ⁺ (mmol/L)	139.26 ± 0.97	138.94 ± 0.98	139.46 ± 1.85	140.16 ± 1.37	140.48 ± 1.40	140.96 ± 1.20	139.22 ± 1.05	140.40 ± 1.25
Cl ⁻ (mmol/L)	107.44 ± 0.72	108.42 ± 1.22	109.08 ± 1.25 ^{*▽}	107.20 ± 1.00	107.00 ± 0.49	108.08 ± 1.72	107.70 ± 1.87	107.48 ± 1.46
iCa (mmol/L)	1.08 ± 0.03	1.14 ± 0.11	1.10 ± 0.12	1.07 ± 0.08	1.07 ± 0.05	1.06 ± 0.06	1.10 ± 0.07	1.09 ± 0.06

TCa (mmol/L)	2.11 ± 0.05	2.22 ± 0.21	2.15 ± 0.22	2.09 ± 0.15	2.08 ± 0.09	2.06 ± 0.11	2.14 ± 0.14	2.12 ± 0.11
pH	7.49 ± 0.004	7.50 ± 0.004	7.49 ± 0.01	7.50 ± 0.005	7.50 ± 0.004	7.49 ± 0.01	7.50 ± 0.009	7.50 ± 0.02

Results were expressed as means ± SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

^{Δ/ΔΔ} $p < 0.05/0.01$ was compared with the 50 mg/kg.bw group.

^{▲▲} $p < 0.01$ was compared with the 100 mg/kg.bw group.

[▽] $p < 0.05$ was compared with the 300 mg/kg.bw group.

Table S9 Serum chemistry values of rats treated with TA for 13 weeks

Indexes	Female (n = 10)				Male (n = 10)			
	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
ALT (U/L)	26.30 ± 4.30	30.50 ± 4.14	25.50 ± 3.27	27.50 ± 5.17	36.70 ± 5.70	33.40 ± 7.06	37.70 ± 4.22	29.30 ± 7.24*▲▲
AST (U/L)	76.70 ± 12.55	79.50 ± 11.85	69.50 ± 8.15 ^Δ	63.30 ± 9.63 ^{**ΔΔ}	80.70 ± 10.98	82.30 ± 11.88	85.00 ± 10.06	72.00 ± 13.55
ALP (U/L)	56.90 ± 12.62	61.30 ± 7.12	61.30 ± 7.90	75.20 ± 14.97 ^{**ΔΔ▲▲}	100.70 ± 9.26	96.00 ± 15.54	108.30 ± 16.01	104.50 ± 14.57
BUN (mmol/L)	3.85 ± 0.53	3.67 ± 0.40	3.85 ± 0.53	3.79 ± 0.56	4.04 ± 0.38	3.93 ± 0.56	3.80 ± 0.45	3.72 ± 0.70
CRE (μmol/L)	113.80 ± 34.65	114.50 ± 40.02	99.90 ± 12.93	100.70 ± 16.74	86.00 ± 7.04	90.90 ± 14.20	92.70 ± 20.28	92.00 ± 14.53
TP (g/L)	91.05 ± 12.70	92.92 ± 14.25	87.95 ± 16.12	93.81 ± 6.98	79.62 ± 9.02	82.98 ± 2.47	81.23 ± 6.35	81.63 ± 14.43
ALB (g/L)	35.58 ± 2.49	35.12 ± 1.70	35.53 ± 2.62	37.27 ± 2.98	32.67 ± 1.58	34.28 ± 0.81	33.47 ± 1.90	33.23 ± 2.14
Glu (mmol/L)	6.40 ± 0.64	6.55 ± 0.51	6.74 ± 0.68	8.11 ± 1.18 ^{**ΔΔ▲▲}	7.58 ± 1.84	6.95 ± 0.53	7.05 ± 0.48	6.92 ± 1.09
TBIL (μmol/L)	4.17 ± 1.83	4.37 ± 1.56	3.88 ± 1.01	4.16 ± 1.07	4.38 ± 1.09	4.26 ± 1.74	3.90 ± 1.31	4.49 ± 0.62
TC (mmol/L)	1.35 ± 0.18	1.43 ± 0.20	1.40 ± 0.17	1.56 ± 0.21	1.52 ± 0.22	1.57 ± 0.26	1.61 ± 0.25	1.74 ± 0.26
TG (mmol/L)	0.38 ± 0.19	0.43 ± 0.15	0.32 ± 0.15	0.52 ± 0.20	0.69 ± 0.27	0.99 ± 0.31 [*]	1.04 ± 0.37 [*]	1.01 ± 0.26 [*]
CK (U/L)	210.10 ± 68.46	214.40 ± 77.52	203.80 ± 97.50	200.20 ± 86.45	175.00 ± 34.45	161.20 ± 50.25	168.00 ± 22.99	151.80 ± 64.51
K ⁺ (mmol/L)	3.42 ± 0.24	3.42 ± 0.21	3.49 ± 0.34	3.17 ± 0.37	3.28 ± 0.22	3.44 ± 0.26	3.44 ± 0.22	3.37 ± 0.21
Na ⁺ (mmol/L)	135.49 ± 1.10	135.43 ± 1.08	134.65 ± 0.71	134.59 ± 1.26	135.45 ± 0.96	135.15 ± 1.00	135.07 ± 1.35	135.06 ± 0.86
Cl ⁻ (mmol/L)	102.59 ± 1.76	102.06 ± 2.17	102.14 ± 2.20	100.24 ± 0.93 ^{**Δ▲}	98.94 ± 2.44	98.84 ± 0.93	98.56 ± 1.25	98.14 ± 0.95
iCa (mmol/L)	1.03 ± 0.10	1.10 ± 0.09	1.08 ± 0.11	1.03 ± 0.05	0.99 ± 0.04	1.02 ± 0.03	1.03 ± 0.06	1.03 ± 0.06
TCa (mmol/L)	2.00 ± 0.20	2.14 ± 0.17	2.11 ± 0.22	2.01 ± 0.10	1.93 ± 0.08	1.99 ± 0.06	2.01 ± 0.12	2.01 ± 0.12
pH	7.52 ± 0.03	7.54 ± 0.03	7.53 ± 0.02	7.52 ± 0.01	7.51 ± 0.01	7.52 ± 0.01	7.52 ± 0.02	7.52 ± 0.01

Results were expressed as means $\pm$ SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

^{$\Delta/\Delta\Delta$} $p < 0.05/0.01$ was compared with the 50 mg/kg.bw group.

^{$\blacktriangle/\blacktriangle\blacktriangle$} $p < 0.05/0.01$ was compared with the 100 mg/kg.bw group.

Table S10 Serum chemistry values of rats after the 4-week recovery period

Indexes	Female (n = 5)				Male (n = 5)			
	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
ALT (U/L)	30.60 ± 6.02	34.00 ± 10.65	25.60 ± 5.18	26.60 ± 6.35	32.60 ± 2.07	35.00 ± 4.95	31.40 ± 4.39	36.40 ± 3.58
AST (U/L)	79.40 ± 12.34	71.80 ± 10.35	59.20 ± 7.01** ^Δ	61.00 ± 5.79**	84.00 ± 10.42	72.80 ± 15.99	73.60 ± 12.56	79.60 ± 7.76
ALP (U/L)	71.20 ± 36.19	70.20 ± 9.65	53.00 ± 8.34	93.80 ± 40.76	102.00 ± 11.73	105.00 ± 22.59	91.40 ± 9.86	77.60 ± 9.21* ^{ΔΔ}
BUN (mmol/L)	3.80 ± 0.55	3.84 ± 0.55	3.68 ± 0.33	4.18 ± 0.50	4.16 ± 0.28	3.68 ± 0.26*	3.98 ± 0.41	3.24 ± 0.17** ^{Δ▲▲}
CRE (μmol/L)	88.20 ± 4.09	91.20 ± 10.47	90.60 ± 10.06	92.40 ± 16.83	85.40 ± 7.92	82.60 ± 2.70	80.60 ± 4.67	93.60 ± 16.32
TP (g/L)	94.64 ± 18.32	82.16 ± 4.44	82.64 ± 4.56	95.80 ± 15.54	76.14 ± 4.79	75.20 ± 3.83	81.16 ± 11.76	80.32 ± 15.16
ALB (g/L)	34.08 ± 0.08	34.14 ± 0.22	34.10 ± 0.22	34.06 ± 0.25	34.18 ± 0.19	34.30 ± 0.39	34.22 ± 0.16	34.30 ± 0.07
Glu (mmol/L)	6.58 ± 0.52	6.12 ± 0.79	6.64 ± 0.86	6.86 ± 0.39	6.54 ± 0.21	6.66 ± 0.80	6.36 ± 0.52	6.60 ± 0.67
TBIL (μmol/L)	2.84 ± 0.88	3.40 ± 1.43	3.62 ± 0.75	4.20 ± 2.14	4.14 ± 0.23	3.52 ± 0.54	3.34 ± 0.49	4.22 ± 0.78
TC (mmol/L)	2.04 ± 0.31	2.18 ± 0.22	2.10 ± 0.20	2.25 ± 0.30	1.93 ± 0.21	1.89 ± 0.18	1.73 ± 0.24	1.98 ± 0.42
TG (mmol/L)	0.70 ± 0.36	0.59 ± 0.44	0.57 ± 0.15	0.89 ± 0.78	1.50 ± 0.31	1.17 ± 0.53	0.89 ± 0.31	1.32 ± 0.66
CK (U/L)	231.40 ± 191.06	164.40 ± 60.74	122.40 ± 34.92	118.40 ± 34.52	241.00 ± 131.03	135.80 ± 9.83	216.60 ± 78.06	176.20 ± 66.16
K ⁺ (mmol/L)	3.79 ± 0.33	3.91 ± 0.18	3.70 ± 0.17	3.55 ± 0.19	3.96 ± 0.14	3.68 ± 0.26	3.81 ± 0.11	3.87 ± 0.10
Na ⁺ (mmol/L)	142.80 ± 1.26	142.20 ± 1.77	142.18 ± 1.63	143.52 ± 1.46	142.44 ± 1.98	143.10 ± 1.45	144.78 ± 1.55	142.94 ± 2.06
Cl ⁻ (mmol/L)	116.56 ± 1.93	117.32 ± 1.66	118.58 ± 1.29	117.98 ± 2.10	115.76 ± 1.26	115.04 ± 5.42	116.42 ± 1.16	115.88 ± 2.49
iCa (mmol/L)	1.18 ± 0.07	1.15 ± 0.06	1.16 ± 0.06	1.13 ± 0.03	1.15 ± 0.09	1.14 ± 0.12	1.07 ± 0.07	1.14 ± 0.10
TCa (mmol/L)	2.30 ± 0.14	2.24 ± 0.12	2.27 ± 0.12	2.20 ± 0.06	2.23 ± 0.18	2.23 ± 0.22	2.08 ± 0.15	2.23 ± 0.20
pH	7.50 ± 0.008	7.50 ± 0.01	7.50 ± 0.01	7.50 ± 0.02	7.49 ± 0.02	7.50 ± 0.02	7.49 ± 0.01	7.50 ± 0.01

Results were expressed as means $\pm$ SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

$\Delta/\Delta\Delta$ $p < 0.05/0.01$ was compared with the 50 mg/kg.bw group.

$\blacktriangle\blacktriangle$ $p < 0.05/0.01$ was compared with the 100 mg/kg.bw group.

Table S11 Organ weights and coefficients of rats treated with TA for 7 weeks

Items	Female (n = 5)				Male (n = 5)			
	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Brain (g)	1.90 ± 0.04	1.94 ± 0.08	1.91 ± 0.03	1.86 ± 0.08	2.06 ± 0.07	2.04 ± 0.06	2.00 ± 0.04	2.03 ± 0.05
(%)	0.75 ± 0.06	0.75 ± 0.03	0.75 ± 0.02	0.80 ± 0.09	0.52 ± 0.04	0.56 ± 0.05	0.54 ± 0.03	0.55 ± 0.05
Heart (g)	0.95 ± 0.28	0.93 ± 0.07	0.93 ± 0.09	0.82 ± 0.06	1.42 ± 0.13	1.20 ± 0.13	1.33 ± 0.13	1.21 ± 0.14
(%)	0.37 ± 0.09	0.36 ± 0.03	0.36 ± 0.03	0.35 ± 0.02	0.35 ± 0.01	0.33 ± 0.04	0.36 ± 0.04	0.32 ± 0.03
Liver (g)	6.83 ± 0.70	7.20 ± 0.56	7.06 ± 0.67	7.83 ± 0.70	11.78 ± 1.92	10.31 ± 1.10	11.25 ± 0.86	12.29 ± 1.05
(%)	2.69 ± 0.19	2.78 ± 0.17	2.76 ± 0.18	3.37 ± 0.24** $\Delta\Delta\Delta$	2.91 ± 0.18	2.79 ± 0.05	3.05 ± 0.22	3.31 ± 0.10* Δ
Spleen (g)	0.79 ± 0.21	0.71 ± 0.05	0.67 ± 0.13	0.65 ± 0.13	0.88 ± 0.09	0.88 ± 0.20	0.78 ± 0.15	0.80 ± 0.11
(%)	0.31 ± 0.08	0.28 ± 0.02	0.26 ± 0.05	0.28 ± 0.04	0.22 ± 0.02	0.24 ± 0.05	0.21 ± 0.04	0.22 ± 0.04
Lung (g)	1.12 ± 0.06	1.13 ± 0.17	1.17 ± 0.10	1.24 ± 0.38	1.31 ± 0.08	1.44 ± 0.08	1.31 ± 0.13	1.40 ± 0.22
(%)	0.44 ± 0.04	0.43 ± 0.04	0.46 ± 0.02	0.53 ± 0.14	0.33 ± 0.04	0.39 ± 0.02	0.35 ± 0.02	0.38 ± 0.06
Kidney (g)	1.59 ± 0.17	1.66 ± 0.05	1.57 ± 0.06	1.63 ± 0.17	2.62 ± 0.34	2.42 ± 0.18	2.47 ± 0.10	2.45 ± 0.17
(%)	0.63 ± 0.04	0.64 ± 0.04	0.62 ± 0.03	0.70 ± 0.01** $\Delta\Delta\Delta$	0.65 ± 0.03	0.66 ± 0.02	0.67 ± 0.02	0.66 ± 0.05
Adrenal gland (g)	0.071 ± 0.003	0.073 ± 0.006	0.071 ± 0.010	0.077 ± 0.010	0.048 ± 0.004	0.045 ± 0.007	0.049 ± 0.004	0.042 ± 0.004
(%)	0.028 ± 0.002	0.028 ± 0.002	0.028 ± 0.004	0.033 ± 0.004	0.012 ± 0.001	0.012 ± 0.002	0.013 ± 0.002	0.011 ± 0.002
Thymus (g)	0.38 ± 0.07	0.43 ± 0.14	0.43 ± 0.09	0.39 ± 0.06	0.44 ± 0.14	0.36 ± 0.07	0.36 ± 0.13	0.39 ± 0.08
(%)	0.15 ± 0.02	0.16 ± 0.05	0.17 ± 0.04	0.17 ± 0.03	0.11 ± 0.03	0.10 ± 0.02	0.10 ± 0.04	0.10 ± 0.02
Uterus/ Testis (g)	0.40 ± 0.07	0.40 ± 0.10	0.50 ± 0.18	0.64 ± 0.29	2.72 ± 0.45	2.77 ± 0.18	2.75 ± 0.10	2.66 ± 0.26
(%)	0.16 ± 0.02	0.16 ± 0.04	0.20 ± 0.07	0.27 ± 0.12	0.68 ± 0.14	0.76 ± 0.07	0.75 ± 0.04	0.72 ± 0.05
Ovary/Epididymis (g)	0.112 ± 0.007	0.114 ± 0.010	0.108 ± 0.010	0.101 ± 0.020	0.95 ± 0.12	0.97 ± 0.06	0.96 ± 0.06	0.96 ± 0.06
(%)	0.044 ± 0.006	0.044 ± 0.003	0.042 ± 0.005	0.043 ± 0.006	0.24 ± 0.04	0.26 ± 0.03	0.26 ± 0.02	0.26 ± 0.02

Results were expressed as means ± SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

^{△/△△} $p < 0.05/0.01$ was compared with the 50 mg/kg.bw group.

^{▲/▲▲} $p < 0.05/0.01$ was compared with the 100 mg/kg.bw group.

♀, uterus, ovary; ♂, testis, epididymis.

Table S12 Organ weights and coefficients of rats treated with TA for 13 weeks

Items	Female (n = 10)				Male (n = 10)			
	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Brain (g)	1.99 ± 0.07	2.00 ± 0.08	1.97 ± 0.06	1.95 ± 0.06	2.18 ± 0.08	2.16 ± 0.08	2.16 ± 0.06	2.16 ± 0.09
(%)	0.70 ± 0.06	0.70 ± 0.04	0.69 ± 0.06	0.72 ± 0.07	0.44 ± 0.04	0.45 ± 0.04	0.45 ± 0.02	0.48 ± 0.03**▲▲
Heart (g)	0.96 ± 0.13	1.02 ± 0.15	0.95 ± 0.08	0.92 ± 0.10	1.50 ± 0.13	1.43 ± 0.12	1.48 ± 0.15	1.41 ± 0.09
(%)	0.33 ± 0.03	0.35 ± 0.03	0.33 ± 0.03	0.33 ± 0.03	0.30 ± 0.02	0.30 ± 0.02	0.31 ± 0.03	0.32 ± 0.02
Liver (g)	7.63 ± 0.76	7.49 ± 0.72	7.74 ± 0.86	9.68 ± 1.26**▲▲▲▲	12.64 ± 1.01	13.09 ± 1.02	13.60 ± 0.93*	14.70 ± 0.65**▲▲▲▲
(%)	2.66 ± 0.11	2.59 ± 0.15	2.72 ± 0.20	3.52 ± 0.26*▲▲	2.56 ± 0.10	2.73 ± 0.14**	2.85 ± 0.10**▲	3.31 ± 0.12**▲▲▲▲
Spleen (g)	0.64 ± 0.09	0.68 ± 0.10	0.73 ± 0.14	0.58 ± 0.11▲▲▲	0.90 ± 0.17	0.88 ± 0.12	0.88 ± 0.17	0.84 ± 0.11
(%)	0.23 ± 0.04	0.24 ± 0.02	0.26 ± 0.06	0.21 ± 0.03	0.18 ± 0.03	0.18 ± 0.02	0.18 ± 0.04	0.19 ± 0.02
Lung (g)	1.16 ± 0.21	1.13 ± 0.13	1.09 ± 0.04	1.07 ± 0.07	1.52 ± 0.18	1.40 ± 0.10*	1.46 ± 0.13	1.33 ± 0.05**▲
(%)	0.40 ± 0.06	0.39 ± 0.03	0.38 ± 0.02	0.39 ± 0.02	0.31 ± 0.04	0.29 ± 0.02	0.31 ± 0.02	0.30 ± 0.02
Kidney (g)	1.76 ± 0.15	1.74 ± 0.16	1.72 ± 0.12	1.90 ± 0.24	2.84 ± 0.26	2.82 ± 0.17	2.79 ± 0.17	2.77 ± 0.28
(%)	0.62 ± 0.06	0.60 ± 0.04	0.60 ± 0.04	0.69 ± 0.05**▲▲▲▲	0.58 ± 0.04	0.59 ± 0.04	0.58 ± 0.03	0.62 ± 0.06
Adrenal (g)	0.077 ± 0.010	0.072 ± 0.010	0.074 ± 0.007	0.073 ± 0.008	0.059 ± 0.007	0.053 ± 0.008	0.054 ± 0.009	0.050 ± 0.008
(%)	0.027 ± 0.004	0.025 ± 0.003	0.026 ± 0.003	0.027 ± 0.002	0.012 ± 0.002	0.011 ± 0.002	0.011 ± 0.002	0.011 ± 0.002
Thymus (g)	0.29 ± 0.04	0.29 ± 0.05	0.28 ± 0.05	0.25 ± 0.04	0.28 ± 0.06	0.24 ± 0.05	0.26 ± 0.03	0.26 ± 0.05
(%)	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.02	0.09 ± 0.01	0.057 ± 0.011	0.051 ± 0.010	0.054 ± 0.059	0.058 ± 0.012
Uterus/ Testis (g)	0.55 ± 0.07	0.60 ± 0.16	0.59 ± 0.20	0.55 ± 0.11	3.13 ± 0.19	3.00 ± 0.25	2.87 ± 0.12**	2.99 ± 0.20
(%)	0.19 ± 0.03	0.20 ± 0.05	0.21 ± 0.08	0.20 ± 0.05	0.64 ± 0.06	0.63 ± 0.04▽	0.60 ± 0.04▽▽	0.67 ± 0.06
Ovary/Epididymis (g)	0.115 ± 0.015	0.112 ± 0.012	0.114 ± 0.006	0.108 ± 0.010	1.21 ± 0.09	1.13 ± 0.08	1.23 ± 0.23	1.14 ± 0.07
(%)	0.040 ± 0.006	0.039 ± 0.004	0.040 ± 0.004	0.040 ± 0.004	0.24 ± 0.03	0.24 ± 0.02	0.26 ± 0.07	0.26 ± 0.01

Results were expressed as means ± SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

^{△/△△} $p < 0.05/0.01$ was compared with the 50 mg/kg.bw group.

^{▲/▲▲} $p < 0.05/0.01$ was compared with the 100 mg/kg.bw group.

♀, uterus, ovary; ♂, testis, epididymis.

Table S13 Organ weights and coefficients of rats after the 4-week recovery period

Items	Female (n = 10)				Male (n = 10)			
	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw	Control	50 mg/kg.bw	100 mg/kg.bw	300 mg/kg.bw
Brain (g)	1.92 ± 0.06	2.01 ± 0.04	2.00 ± 0.07	1.96 ± 0.08	2.20 ± 0.07	2.11 ± 0.03**	2.16 ± 0.05	2.09 ± 0.02**▲
(%)	0.60 ± 0.07	0.66 ± 0.04	0.66 ± 0.04	0.66 ± 0.07	0.39 ± 0.05	0.43 ± 0.02	0.41 ± 0.02	0.40 ± 0.03
Heart (g)	1.15 ± 0.36	1.14 ± 0.34	0.96 ± 0.07	0.93 ± 0.07	1.71 ± 0.23	1.43 ± 0.21	1.62 ± 0.27	1.54 ± 0.22
(%)	0.35 ± 0.06	0.37 ± 0.10	0.31 ± 0.02	0.31 ± 0.04	0.30 ± 0.02	0.29 ± 0.03	0.31 ± 0.03	0.29 ± 0.03
Liver (g)	8.11 ± 1.08	8.20 ± 1.05	7.83 ± 0.96	8.56 ± 1.51	14.70 ± 1.84	12.32 ± 0.81	13.97 ± 1.63	14.30 ± 2.24
(%)	2.52 ± 0.23	2.71 ± 0.36	2.56 ± 0.20	2.86 ± 0.37	2.60 ± 0.08	2.51 ± 0.14	2.66 ± 0.26	2.69 ± 0.26
Spleen (g)	0.63 ± 0.03	0.73 ± 0.11	0.65 ± 0.06	0.54 ± 0.04*▲	0.97 ± 0.19	0.89 ± 0.16	0.86 ± 0.09	0.94 ± 0.19
(%)	0.20 ± 0.02	0.24 ± 0.03*∇∇	0.21 ± 0.02	0.18 ± 0.02	0.17 ± 0.04	0.18 ± 0.03	0.16 ± 0.01	0.18 ± 0.02
Lung (g)	1.24 ± 0.15	1.24 ± 0.13	1.10 ± 0.04	1.08 ± 0.07	1.58 ± 0.23	1.40 ± 0.09	1.50 ± 0.17	1.49 ± 0.07
(%)	0.38 ± 0.01	0.41 ± 0.04	0.36 ± 0.03	0.36 ± 0.03	0.28 ± 0.02	0.28 ± 0.02	0.29 ± 0.02	0.28 ± 0.01
Kidney (g)	1.81 ± 0.23	1.82 ± 0.14	1.80 ± 0.20	1.80 ± 0.17	3.11 ± 0.40	2.76 ± 0.34	3.12 ± 0.35	3.14 ± 0.41
(%)	0.56 ± 0.06	0.60 ± 0.05	0.59 ± 0.06	0.60 ± 0.07	0.55 ± 0.05	0.56 ± 0.04	0.60 ± 0.06	0.59 ± 0.05
Adrenal (g)	0.067 ± 0.006	0.071 ± 0.011	0.069 ± 0.010	0.066 ± 0.005	0.055 ± 0.008	0.051 ± 0.008	0.050 ± 0.008	0.052 ± 0.009
(%)	0.021 ± 0.004	0.024 ± 0.004	0.023 ± 0.004	0.022 ± 0.002	0.010 ± 0.0005	0.010 ± 0.002	0.010 ± 0.001	0.010 ± 0.002
Thymus (g)	0.22 ± 0.07	0.24 ± 0.02	0.28 ± 0.10	0.20 ± 0.06	0.22 ± 0.06	0.24 ± 0.07	0.22 ± 0.08	0.24 ± 0.05
(%)	0.068 ± 0.018	0.080 ± 0.006	0.091 ± 0.030	0.067 ± 0.025	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
Uterus/ Testis (g)	0.56 ± 0.12	0.54 ± 0.21	0.59 ± 0.11	0.71 ± 0.29	3.08 ± 0.41	2.88 ± 0.39	3.03 ± 0.18	3.05 ± 0.19
(%)	0.18 ± 0.06	0.18 ± 0.06	0.19 ± 0.03	0.24 ± 0.10	0.55 ± 0.05	0.58 ± 0.05	0.58 ± 0.02	0.58 ± 0.03
Ovary/Epididymis (g)	0.115 ± 0.011	0.116 ± 0.011	0.110 ± 0.007	0.116 ± 0.004	1.19 ± 0.15	1.11 ± 0.11	1.20 ± 0.14	1.48 ± 0.78
(%)	0.036 ± 0.007	0.038 ± 0.003	0.036 ± 0.004	0.039 ± 0.003	0.21 ± 0.04	0.22 ± 0.02	0.23 ± 0.02	0.28 ± 0.15

Results were expressed as means ± SD.

^{*/**} $p < 0.05/0.01$ was compared with the control group.

^Δ $p < 0.05$ was compared with the 50 mg/kg.bw group.

[▲] $p < 0.05$ was compared with the 100 mg/kg.bw group.

^{▽▽} $p < 0.01$ was compared with the 300 mg/kg.bw group.

♀, uterus, ovary; ♂, testis, epididymis.

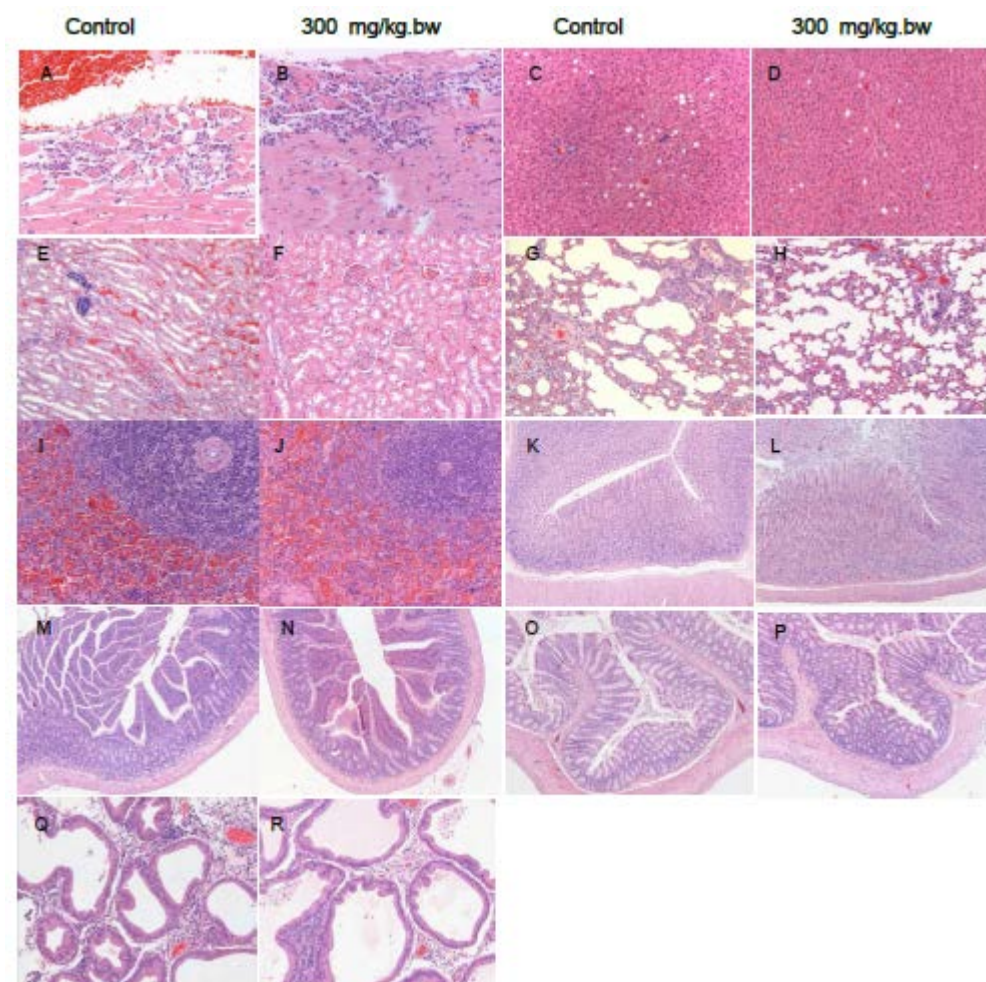


Fig. S1. Representative sections of rats in respect of 7 weeks treatment demonstrating histopathology

A and **B** represented control and 300 mg/kg.bw rat hearts showing local myocarditis ($\times 20$ magnification).

C and **D** denoted control and 300 mg/kg.bw rat livers illuminating hepatocytes punctate necrotic and scattered cellular steatosis ($\times 10$ magnification).

E and **F** meant control and 300 mg/kg.bw rat kidneys, which demonstrated calcium salt deposited locally at the junction of renal cortex and medulla in the control group and normal kidney architecture in 300 mg/kg.bw ($\times 10$ magnification).

G and **H** represented control and 300 mg/kg.bw rat lungs showing local interstitial pneumonia ($\times 10$ magnification).

I and **J** denoted the normal spleen architectures of rats in control and 300 mg/kg.bw group ($\times 20$ magnification).

K and **L** represented the normal stomach architectures of rats in control and 300 mg/kg.bw group ($\times 5$ magnification).

M and **N** showed the normal small intestine architectures of rats in control and 300 mg/kg.bw group ($\times 5$ magnification).

O and **P** expressed the normal colon architectures of rats in control and 300 mg/kg.bw group ($\times 5$ magnification).

Q and **R** represented control and 300 mg/kg.bw rat prostate glands accompanying by local prostatitis ($\times 10$ magnification).

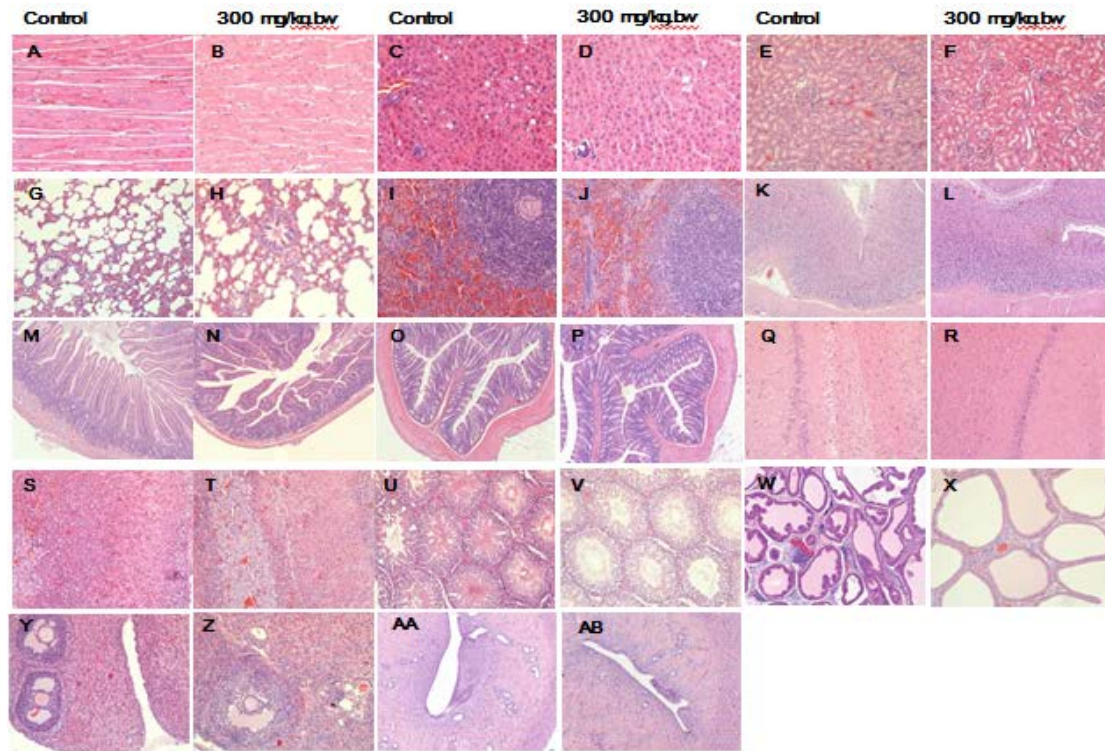


Fig. S2. Representative sections of rats in respect of 13 weeks treatment

demonstrating histopathology

A and **B** the normal heart architectures of rats in control and 300 mg/kg.bw group ($\times 20$ magnification).

C and **D** denoted control and 300 mg/kg.bw rat livers illuminating hepatocytes punctate necrotic and scattered cellular steatosis ($\times 10$ magnification).

E and **F** meant the normal kidney architectures of rats in control and 300 mg/kg.bw group ($\times 10$ magnification).

G and **H** represented control and 300 mg/kg.bw rat lungs showing local interstitial pneumonia ($\times 10$ magnification).

I and **J** denoted the normal spleen architectures of rats in control and 300 mg/kg.bw group ($\times 20$ magnification).

K and **L** represented the normal stomach architectures of rats in control and 300 mg/kg.bw group

(× 5 magnification).

M and **N** showed the normal small intestine architectures of rats in control and 300 mg/kg.bw group (× 5 magnification).

O and **P** expressed the normal colon architectures of rats in control and 300 mg/kg.bw group (× 5 magnification).

Q and **R** meant the normal brain architectures of rats in control and 300 mg/kg.bw group (× 10 magnification).

S and **T** denoted the normal adrenal gland architectures of rats in control and 300 mg/kg.bw group (× 10 magnification).

U and **V** represented the normal testis architectures of rats in control and 300 mg/kg.bw group (× 10 magnification).

W and **X** denoted control and 300 mg/kg.bw rat prostate glands accompanying by local prostatitis (× 10 magnification).

Y and **Z** showed the normal ovary architectures of rats in control and 300 mg/kg.bw group (× 10 magnification).

AA and **AB** expressed the normal uterus architectures of rats in control and 300 mg/kg.bw group (× 5 magnification).

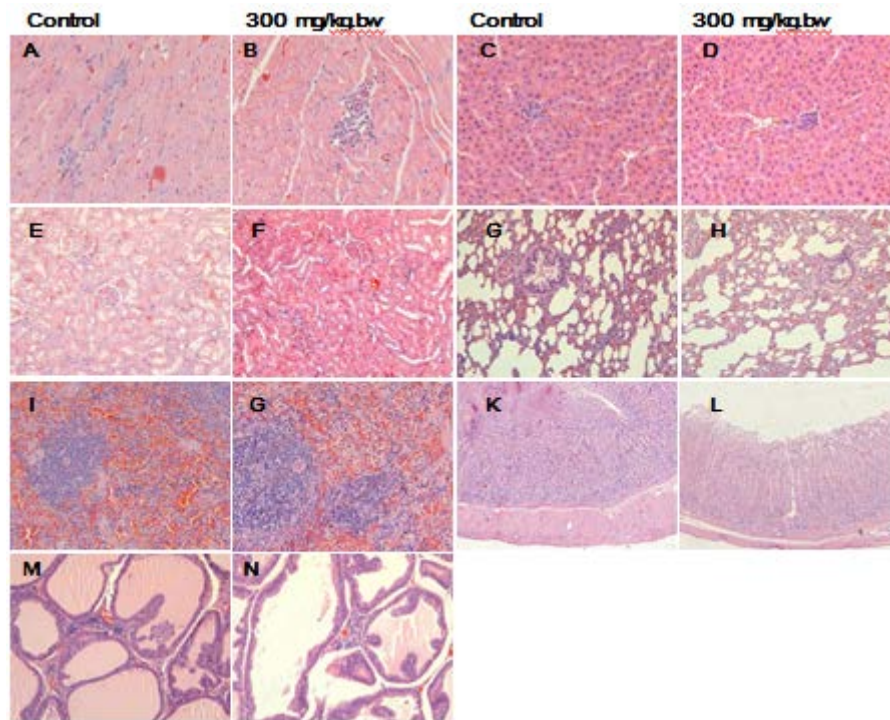


Fig. S3. Representative sections of rats in the recovery period demonstrating histopathology

A and **B** represented control and 300 mg/kg.bw rat hearts showing local myocarditis ($\times 20$ magnification).

C and **D** denoted control and 300 mg/kg.bw rat livers illuminating hepatocytes punctate necrotic and scattered cellular steatosis ($\times 10$ magnification).

E and **F** meant the normal kidney architectures of rats in control and 300 mg/kg.bw group ($\times 10$ magnification).

G and **H** represented control and 300 mg/kg.bw rat lungs showing local interstitial pneumonia ($\times 10$ magnification).

I and **J** denoted the normal spleen architectures of rats in control and 300 mg/kg.bw group ($\times 20$ magnification).

K and **L** represented the normal stomach architectures of rats in control and 300 mg/kg.bw group ($\times 5$ magnification).

M and **N** showed control and 300 mg/kg.bw rat prostate glands accompanying by local prostatitis ($\times 10$ magnification).

References

(S1). Center for Drug Evaluation and Research. Guidance for Industry: Bioanalytical Method Validation. <http://www.fda.gov/>.