

## Supplementary materials

Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Heart		Aorta		Spinal cord	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Lung		Kidney		Bladder	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Uterus		Ovary		Mammary gland	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Salivary gland		Esophagus		Pancreas	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Adrenal gland		Thyroid		Parathyroid gland	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Ischiadic nerve		Hypophysis		Trachea	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Stomach		Small intestine		Large intestine	

**Supplementary Figure 1. Pathological characteristics of the heart, aorta, spinal cord, etc. in healthy rats after administration of nanoparticle polymeric micellar paclitaxel (Pm-Pac) (40 mg/kg) for 5 consecutive weeks.** The organs, including the heart, aorta, spinal cord, lung, kidney, bladder, uterus, ovary, mammary gland, salivary gland, esophagus, pancreas, adrenal gland, thyroid, parathyroid gland, ischiadic nerve, hypophysis, trachea, stomach, small intestine, and large intestine, were normal ( $n = 10$ , HE $\times$ 100).



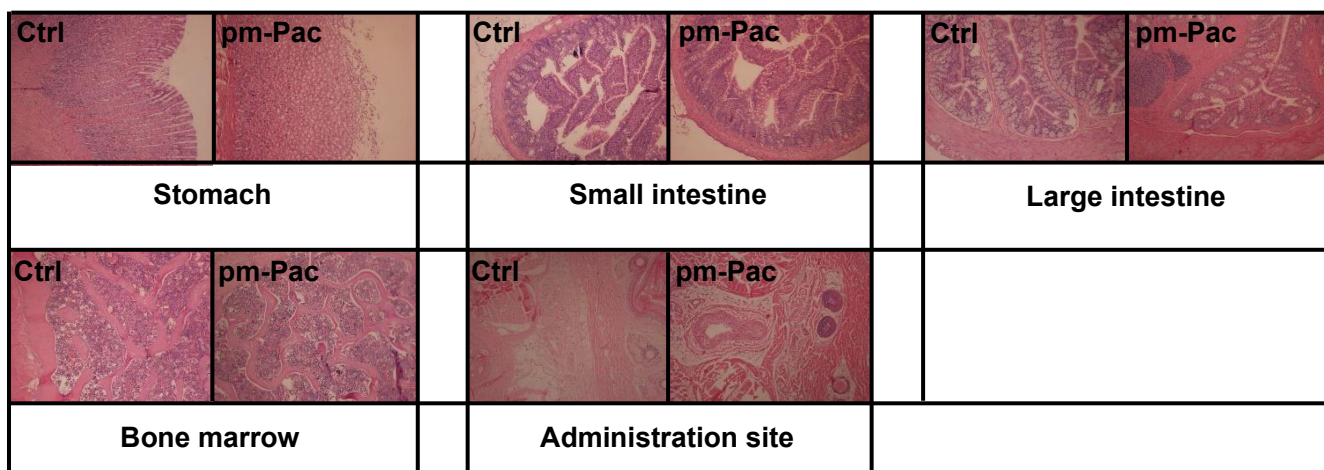
	Ctrl	pm	Sb-Pac	Pm-Pac		
				Low	Medium	High
Liver						
Spleen						
Lymph gland						
Thymus gland						
Bone marrow						
Cerebrum						
Cerebellum						
Epididymis						
Prostate						

Supplementary Figure 2. Pathological evaluation of nanoparticle polymeric micellar paclitaxel (Pm-Pac)-induced short-term toxicity in healthy rats. Liver:

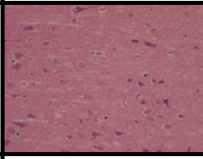
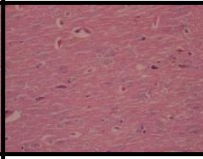
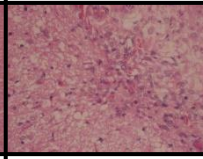
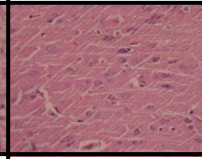
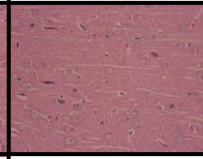
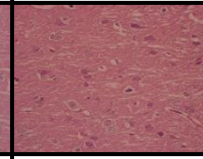
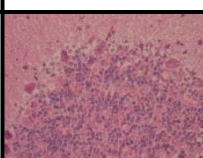
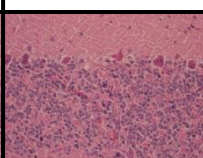
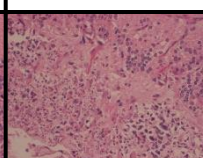
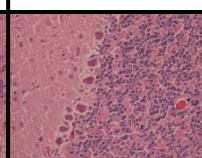
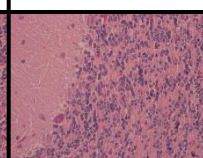
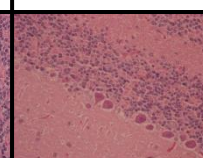

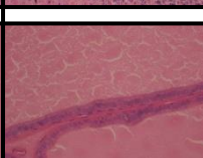
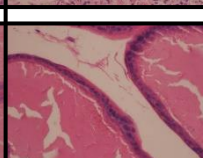
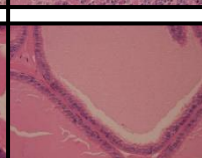
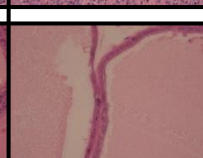
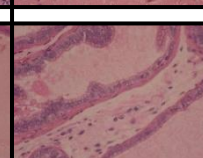
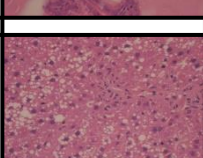
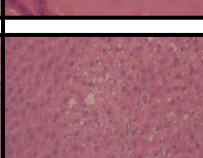
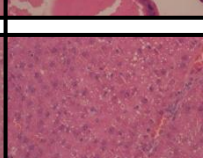
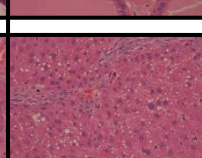
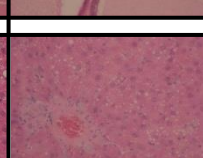
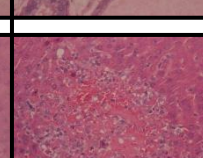
mild extramedullary hematopoiesis in the solvent-based paclitaxel (Sb-Pac) group. Normal in the Pm-Pac group. **Spleen:** mild atrophy along with extramedullary hematopoiesis, reduced number of lymphocytes in splenic node and periarterial lymphatic sheath, accumulation of lymphocyte-like cell groups in red pulp, and increased multinuclear giant cells in Sb-Pac group. Mild atrophy and reduced number of lymphocytes in splenic nodes in the Pm-Pac (low and medium) groups. Mild atrophy, a reduced number of lymphocytes in splenic nodes, and increased multinuclear giant cells in red pulp were observed in the Pm-Pac (high) group. **Lymph gland:** mild atrophy and decreased lymphocytes in lymphoid nodule and deputy cortex in all Pm-Pac and Sb-Pac groups. **Thymus gland:** atrophy, decreased thymic cells, and epithelioid hyperplasia in all Pm-Pac and Sb-Pac groups. **Bone marrow:** atrophy and decreased levels of hematopoietic cells in the bone marrow cavity in all Pm-Pac and Sb-Pac groups. **Cerebrum:** multiple histiomalacia of cortex, nuclear debris and increased macrophages, gliocyte hyperplasia along with vacuolar degeneration of nerve fibers in the Sb-Pac group. Eight of 10 rats showed these pathological changes. Normal in all Pm-Pac groups. **Cerebellum:** degeneration and necrosis of neurocytes in the stratum granulosum, necrosis, nuclear pyknotic and histocyte infiltration in lesions. Three of 10 rats showed pathological changes. Normal in all Pm-Pac groups. **Epididymis:** atrophy, vacuolar lesions, interstitial edema, and diffuse hyperplasia of interstitial cells in all Pm-Pac and Sb-Pac groups. **Prostate:** atrophy in all Pm-Pac and Sb-Pac groups. ( $n = 10$ , HE $\times$ 100).



Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Heart		Aorta		Spinal cord	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Spleen		Lymph node		Thymus gland	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Lung		Kidney		Bladder	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Uterus		Ovary		Mammary gland	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Salivary gland		Esophagus		Pancreas	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Adrenal gland		Thyroid gland		Parathyrin gland	
Ctrl	pm-Pac	Ctrl	pm-Pac	Ctrl	pm-Pac
Ischiadic nerve		Hypophysis		Trachea	



**Supplementary Figure 3. Pathological characteristics of the heart, aorta, spinal cord, etc. in healthy rats after administration of nanoparticle polymeric micellar paclitaxel (Pm-Pac) (40 mg/kg) for 5 consecutive weeks and then recovery for 6 weeks.** The organs, including the heart, aorta, spinal cord, spleen, lymph gland, thymus gland, lung, kidney, bladder, uterus, ovary, mammary gland, salivary gland, esophagus, pancreas, adrenal gland, thyroid, parathyroid gland, ischiadic nerve, hypophysis, trachea, stomach, small intestine, large intestine, bone marrow and administration site, were normal ( $n = 10$ , HE $\times$ 100).

	Ctrl	pm	Sb-Pac	Pm-Pac		
				Low	Medium	High
Cerebrum						
Cerebellum						
Prostate						
Liver						

**Supplementary Figure 4. Pathological evaluation of nanoparticle polymeric micellar paclitaxel (Pm-Pac)-induced long-term toxicity in healthy rats. Cerebrum:** multiple histiomalacia of the cortex, nuclear debris, increased macrophages, and gliocyte hyperplasia along with vacuolar degeneration of nerve fibers in the Sb-Pac group. Two of 10 rats showed these pathological changes. Normal in all Pm-Pac groups. **Cerebellum:** degeneration and necrosis of neurocytes in the stratum granulosum, necrosis, nuclear pyknotic and histocyte infiltration in lesions. One of 10 rats showed pathological changes in the Sb-Pac group. Normal in all Pm-Pac groups. **Prostate:** mild atrophy in the Pm-Pac (medium and high) groups. Normal in the Sb-Pac group and Pm-Pac (low) group. **Liver:** microfocal necrosis, eosinophilic necrosis, and inflammatory cell infiltration in the Pm-Pac (high) group. One of 10 rats showed pathological changes. The other groups were normal. ( $n = 10$ , HE $\times$ 100).



## Supplementary Tables

**Supplementary Table 1. Pm-Pac-induced changes of organs' weight (Mean±SD, g) and index (Mean± SD,%) in healthy male rats.**

	Time	Body weight (g)	Thymus gland		Testis		Epididymis	
			Weight (g)	Index	Weight (g)	Index	Weight (g)	Index
<b>Ctrl</b>	At 5 weeks	420.2±25.3	0.65±0.08	0.16±0.02	3.10±0.25	0.74±0.08	1.11±0.11	0.27±0.02
	At 11 weeks	530.2±19.6	0.45±0.07	0.09±0.01	3.31±0.26	0.62±0.03	1.26±0.07	0.24±0.01
<b>Pm</b>	At 5 weeks	404.8±15.8	0.56±0.09	0.14±0.02	3.06±0.27	0.76±0.05	0.99±0.05	0.25±0.01
	At 11 weeks	495.2±24.3	0.42±0.09	0.09±0.02	2.64±0.88	0.53±0.16	1.20±0.24	0.24±0.04
<b>Sb-Pac</b>	At 5 weeks	323.6±23.8	0.12±0.02**	0.04±0.01**	3.29±0.48	1.02±0.12**	1.01±0.29	0.31±0.08
	At 11 weeks	474.4±18.0	0.46±0.09	0.10±0.01	3.14±0.41	0.66±0.09	1.08±0.14	0.23±0.04
<b>Pm-Pac (Low)</b>	At 5 weeks	325.4±20.4	0.14±0.04***#	0.04±0.01***#	2.31±0.25***#@@	0.71±0.10@@	0.66±0.12***#@	0.20±0.03*#@
	At 11 weeks	441.4±30.2	0.29±0.03***#@@	0.07±0.01*#@@	2.35±0.57**#@	0.53±0.11@	0.81±0.21***#@	0.18±0.04***#@
<b>Pm-Pac (Medium)</b>	At 5 weeks	256.8±14.8	0.12±0.10***#	0.05±0.04***#	0.85±0.12***#@@	0.33±0.05***#@@	0.33±0.09***#@@	0.13±0.03***#@@
	At 11 weeks	417.6±28.9	0.34±0.03*	0.08±0.01	1.07±0.13***#@@	0.25±0.03***#@@	0.56±0.11***#@@	0.13±0.02***#@@
<b>Pm-Pac (High)</b>	At 5 weeks	168.8±42.6	0.18±0.09***#	0.09±0.06***#	0.68±0.21***#@@	0.33±0.05***#@@	0.28±0.12***#@@	0.13±0.03***#@@
	At 11 weeks	282.0±92.0	0.24±0.07***#@@	0.09±0.01	0.77±0.19***#@@	0.28±0.04***#@@	0.42±0.09***#@@	0.15±0.02***#@@

Note: \* represents  $P<0.05$  compared to Ctrl, \*\* represents  $P<0.01$  compared to Ctrl; # represents  $P<0.05$  compared to Pm, ## represents  $P<0.01$  compared to Pm; @ represents  $P<0.05$  compared to Sb-Pac, @@ represents  $P<0.01$  compared to Sb-Pac.



**Supplementary Table 2. Pm-Pac-induced hemopoietic toxicity in healthy SD rats (Mean ± SD).**

		Ctrl	Pm	Sb-Pac	Pm-Pac (Low)	Pm-Pac (Medium)	Pm-Pac (High)
<b>Rats (n)</b>	At 5 weeks	10	10	10	10	10	8
	At 11 weeks	10	10	10	10	10	10
<b>WBC (10<sup>3</sup>/uL)</b>	At 5 weeks	7.95±2.16	6.78±1.76	4.66±1.28**	4.32±1.34***#	3.62±0.72##	3.51±1.78***#
	At 11 weeks	6.89±2.68	6.94±2.80	4.63±1.36*	4.69±1.80**	4.73±1.80**	4.60±2.49
<b>RBC (10<sup>6</sup>/uL)</b>	At 5 weeks	8.00±0.54	7.58±0.87	7.72±0.44	7.63±0.39	7.58±0.71	8.56±0.35***#
	At 11 weeks	8.46±0.79	8.46±0.75	8.13±0.80	8.30±0.35	8.38±0.47	8.27±0.45
<b>HGB (g/dL)</b>	At 5 weeks	139.8±4.64	135.6±11.82	138.10±8.48	136.00±5.60	135.70±6.04	142.75±7.74
	At 11 weeks	138.70±4.45	139.60±6.47	135.10±10.49	139.50±3.47	140.10±5.09	138.70±4.95
<b>HCT (%)</b>	At 5 weeks	40.67±2.61	38.63±3.86	41.53±2.98	40.86±2.13	40.17±3.51	42.68±1.89#
	At 11 weeks	51.13±2.92	50.50±3.79	49.45±3.74	50.63±1.93	50.73±2.21	50.55±2.16
<b>MCV (fL)</b>	At 5 weeks	50.89±1.07	51.03±1.15	53.77±1.95***#	53.56±1.53***#	53.03±0.93***#	49.88±1.29
	At 11 weeks	60.66±2.54	59.77±1.39	61.02±2.05	61.00±0.45#	60.60±1.96	61.20±1.85
<b>MCH (pg)</b>	At 5 weeks	17.56±0.84	17.92±0.98	17.88±0.64	17.85±0.37	17.99±1.13	16.69±0.72***#
	At 11 weeks	16.50±1.36	16.57±0.78	16.67±0.79	16.85±0.72	16.75±0.59	16.83±0.97
<b>MCHC (g/dL)</b>	At 5 weeks	345±17	351±14	333±9	333±9	339±19	335±11
	At 11 weeks	272±12	277±9	273±10	276±11	276±7	274±9
<b>RDW (%)</b>	At 5 weeks	10.94±0.48	11.08±0.52	14.31±0.97	13.28±0.38***#@@	14.22±0.97***#	12.21±0.72***#@@
	At 11 weeks	12.07±0.59	12.08±0.68	12.25±2.47	11.76±0.63	11.84±0.56	12.14±1.17
<b>PLT (10<sup>3</sup>/uL)</b>	At 5 weeks	1278±151	1175±138	1188±156	1301±91	1308±158	1272±188
	At 11 weeks	1060±243	1100±127	1106±241	1164±65	1154±116	1265±136
<b>MPV (fL)</b>	At 5 weeks	7.37±1.97	8.43±1.66	7.95±0.89	7.73±0.91	8.76±1.74	7.86±1.36
	At 11 weeks	7.23±1.07	7.56±1.24	7.70±0.89	8.18±0.86*	8.05±0.73	8.49±0.87**

<b>NEUT (10<sup>3</sup>/uL)</b>	At 5 weeks	0.74±0.13	1.39±1.00	0.64±0.31	0.53±0.38 <sup>#</sup>	0.25±0.10 <sup>***#</sup>	0.92±0.47
	At 11 weeks	0.84±0.45	0.86±0.41	0.63±0.21	0.70±0.35	0.81±0.63	0.87±0.48
<b>LYMPH (10<sup>3</sup>/uL)</b>	At 5 weeks	6.86±2.14	5.11±1.59	3.75±0.87 <sup>**</sup>	3.49±0.86 <sup>***#</sup>	3.13±0.58 <sup>***#</sup>	2.42±1.44 <sup>***#</sup>
	At 11 weeks	5.70±2.38	5.78±2.42	3.76±1.11 <sup>*</sup>	3.74±1.43 <sup>**</sup>	3.69±0.87 <sup>**</sup>	3.50±1.91 <sup>**</sup>
<b>MONO (10<sup>3</sup>/uL)</b>	At 5 weeks	0.19±0.06	0.15±0.07	0.12±0.06	0.14±0.08	0.09±0.03 <sup>***</sup>	0.09±0.09 <sup>**</sup>
	At 11 weeks	0.19±0.09	0.17±0.08	0.11±0.05	0.15±0.08	0.13±0.08	0.12±0.12
<b>EOS (10<sup>3</sup>/uL)</b>	At 5 weeks	0.05±0.02	0.04±0.02	0.05±0.03	0.04±0.02	0.02±0.01 <sup>***</sup>	0.04±0.02
	At 11 weeks	0.08±0.04	0.06±0.01	0.04±0.01 <sup>**</sup>	0.04±0.01 <sup>***#</sup>	0.05±0.02	0.04±0.02 <sup>*</sup>
<b>BASO (10<sup>3</sup>/uL)</b>	At 5 weeks	0.02±0.01	0.01±0.01	0.02±0.01	0.01±0.00	0.01±0.00	0.01±0.01
	At 11 weeks	0.02±0.01	0.01±0.01	0.01±0.01	0.01±0.01	0.01±0.01	0.01±0.01
<b>RETIC (10<sup>3</sup>/uL)</b>	At 5 weeks	185±35	150±42	281±96 <sup>**</sup>	315±77 <sup>***#</sup>	424±70 <sup>***#</sup>	115±64 <sup>**</sup>
	At 11 weeks	131±28	108±30	146±149	117±26	104±23	114±51
<b>PT (s)</b>	At 5 weeks	8.5±0.5	8.6±0.3	8.5±0.3	8.5±0.4	8.6±0.3	8.5±0.2
	At 11 weeks	8.8±0.3	8.7±0.3	8.6±0.3 <sup>*</sup>	8.6±0.3	8.6±0.3	8.5±0.3

Note: \* represents  $P<0.05$  compared to Ctrl, \*\* represents  $P<0.01$  compared to Ctrl; # represents  $P<0.05$  compared to Pm, ## represents  $P<0.01$  compared to Pm; @@ represents  $P<0.01$  compared to Sb-Pac.

**Supplementary Table 3. Pm-Pac-induced changes of blood biochemical indexes in healthy SD rats (Mean ± SD).**

		Ctrl	Pm	Sb-Pac	Pm-Pac (Low)	Pm-Pac (Medium)	Pm-Pac (High)
<b>Rats (n)</b>	At 5 weeks	10	10	10	10	10	8
	At 11 weeks	10	10	10	10	10	10
<b>ALT(nmol/s.l)</b>	At 5 weeks	759±128	896±158*	658±181	1007±79**@@	1074±167***	1506±605***#
	At 11 weeks	882±94	873±190	840±171	911±149	839±139	1020±161*
<b>AST(nmol/s.l)</b>	At 5 weeks	2188±388	2383±343	2021±294	2100±249#	2192±388	3592±1646**
	At 11 weeks	3334±607	3347±621	3231±558	3215±338	2828±408*#	3254±642
<b>ALP(nmol/s.l)</b>	At 5 weeks	1972±520	2302±731	2386±451	2073±499	1949±484	2309±472
	At 11 weeks	1212±364	1210±386	1472±244	1445±564	1472±545	2042±762***#
<b>GLU(mmol/L)</b>	At 5 weeks	6.94±0.59	6.25±1.01	6.07±0.83*	7.00±1.17	6.55±0.89	5.62±0.98**
	At 11 weeks	5.20±1.44	4.91±1.32	5.02±0.90	5.13±1.33	5.11±1.02	4.32±1.27
<b>T.BIL(umol/L)</b>	At 5 weeks	0.65±.62	0.73±0.71	0.37±0.32	0.68±0.43	1.11±0.25*	0.87±0.49
	At 11 weeks	0.56±0.36	0.76±0.63	0.60±0.25	0.49±0.18	0.67±0.33	0.70±0.34
<b>T.CHO(mmol/L)</b>	At 5 weeks	1.18±0.40	1.36±0.58	1.18±0.20	1.34±0.43	1.45±0.37	1.30±0.18
	At 11 weeks	1.61±0.25	1.43±0.30	1.51±0.28	1.57±0.23	1.44±0.31	1.55±0.27
<b>ALB(g/L)</b>	At 5 weeks	38.66±1.97	37.71±2.31	38.11±1.74	36.56±1.54*@	35.24±1.17***#	35.24±0.98***
	At 11 weeks	38.59±1.79	39.35±1.58	38.72±2.30	38.20±2.01	37.99±1.41	37.56±1.65#
<b>T.P(g/L)</b>	At 5 weeks	59.45±2.31	58.07±3.21	58.67±2.98	57.22±1.40*	55.27±2.05***	54.77±1.81***
	At 11 weeks	67.19±2.45	69.05±1.46	68.44±2.68	69.30±2.22	68.41±2.21	67.11±2.14#
<b>BUN(mmol/L)</b>	At 5 weeks	4.96±0.85	5.13±0.90	5.50±1.03	5.03±0.69	5.28±0.67	6.00±2.03
	At 11 weeks	7.23±1.72	6.91±0.94	7.09±0.63	6.90±1.20	7.24±1.22	7.47±1.24
<b>CREA(umol/L)</b>	At 5 weeks	66.87±2.38	65.66±4.19	65.08±5.62	62.26±3.1**	61.86±3.43***	57.45±3.89***
	At 11 weeks	48.86±4.83	52.70±4.60	51.10±4.82	51.46±4.69	51.11±5.36	47.02±4.22##



<b>CK(nmol/s.l)</b>	At 5 weeks	8701±2812	9925±2141	8807±1466	7542±1848 <sup>#</sup>	7824±3459	7443±3737
	At 11 weeks	9620±2568	10113±3379	9588±2621	8183±1165	7993±2237	9596±2492
<b>TG(mmol/L)</b>	At 5 weeks	0.53±0.22	0.54±0.21	0.44±0.11	0.40±0.06	0.46±0.13	0.35±0.06 <sup>*#</sup>
	At 11 weeks	0.43±0.11	0.46±0.15	0.48±0.28	0.47±0.24	0.38±0.11	0.45±0.30
<b>Na<sup>+</sup>(mmol/L)</b>	At 5 weeks	140.5±0.9	139.8±2.6	140.9±0.9	140.3±0.6	140.9±1.1	144.9±1.9 <sup>**###</sup>
	At 11 weeks	141.8±1.4	142.4±0.8	143.0±0.7 <sup>*</sup>	142.3±1.0	143.3±0.7 <sup>**</sup>	142.9±1.6
<b>K<sup>+</sup>(mmol/L)</b>	At 5 weeks	4.57±0.32	4.56±0.51	4.56±0.39	4.51±0.44	4.17±0.54	3.89±0.35 <sup>**###</sup>
	At 11 weeks	4.62±0.67	4.34±0.46	4.39±0.33	4.39±0.44	4.23±0.40	4.26±0.41
<b>Cl<sup>-</sup>(mmol/L)</b>	At 5 weeks	105.5±1.3	104.6±3.1	105.8±1.1	105.5±1.0	105.3±0.9	109.4±1.6 <sup>**###</sup>
	At 11 weeks	104.5±1.1	104.6±1.0	105.2±1.2	104.7±0.9	105.3±0.7	105.1±1.9
<b>TCa(mmol/L)</b>	At 5 weeks	2.37±0.07	2.32±0.09	2.36±0.06	2.36±0.11	2.38±0.06	2.29±0.12
	At 11 weeks	2.83±0.07	2.80±0.04	2.79±0.03	2.77±0.03 <sup>*</sup>	2.77±0.04 <sup>*</sup>	2.79±0.08

Note: \* represents  $P<0.05$  compared to Ctrl, \*\* represents  $P<0.01$  compared to Ctrl; <sup>#</sup> represents  $P<0.05$  compared to Pm, <sup>###</sup> represents  $P<0.01$  compared to Pm; <sup>@</sup> represents  $P<0.05$  compared to Sb-Pac, <sup>@@</sup> represents  $P<0.01$  compared to Sb-Pac.