

Attached list 1 The water consumption of all rats at different time points

Groups	Water consumption (mL)												
	W0	W1	W2	W3	W4	W5	W6	W7	W8	W12	W16	W20	W24
C	25.6±2.8	31.6±3.7	32.4±2.8	33.8±2.6	37.7±3.5	42.4±3.1	41.1±2.2	40.5±3.7	42.0±2.6	43.0±2.3	40.8±2.9	43.0±3.1	41.2±2.7
L	27.7±2.2	30.7±3.5	33.4±3.3	33.4±3.2	39.7±3.3	43.7±3.1	41.4±3.3	42.8±3.5	44.7±2.3	40.5±2.7	41.3±3.4	42.4±2.5	42.9±3.0
M	26.9±3.5	28.9±3.8	31.0±3.7	31.8±3.4	38.6±1.9	39.9±3.5	39.2±2.5	39.9±2.5	41.1±1.5	41.1±3.0	40.7±3.5	41.2±3.7	40.4±2.0
H	25.6±2.4	28.6±3.9	29.8±3.5	30.8±2.5	36.3±3.2	38.9±3.2	38.8±2.8	38.8±3.2	40.0±3.8	39.2±3.2	39.0±3.1	40.4±3.4	39.3±3.0

C, control group; L, low-dose group; M, middle-dose group; H, high-dose group; w, weeks. Values expressed as mean ± SD. The water consumption was stable after 8 weeks, so it was described briefly.

Attached list 2 Summary of intensity values of biomarkers detected in positive ESI mode in rats' plasma

Times (week)	Group s	Peak intensity (mean ± SD, n = 5)										
		Indoleacrylic acid	C16 sphinganine	C17 sphinganine	Phytosphingosine	LysoPC(15:0)	LysoPC(16:0)	LysoPC(O-18 :0)	LysoPC(P-19:1 (12Z)/0:0)	LysoPC(18:1 (9Z))	LysoPC (18:0)	LysoPC(20:4(5Z, 8Z,11Z,14Z))
4w	C	222.3±18.4	25.3±5.7	26.7±4.2	16.0±4.9	15.2±1.1	606.3±92.3	6.1±1.0	639.7±33.4	26.3±15.1	141.8±29.8	500.7±26.6
	L	212.0±33.7	30.0±5.4	22.9±4.0	17.5±5.8	17.8±1.5	684.8±89.6	5.4±0.4	657.4±74.2	31.6±2.8	138.7±32.6	510.4±19.9
	M	247.6±23.5	34.0±7.2	24.5±4.1	18.9±5.5	17.3±3.2	656.8±101.4	5.5±0.7	626.3±30.3	29.9±3.4	144.0±31.5	531.6±31.8
	H	219.6±29.9	30.0±2.2	24.1±4.0	17.4±0.6	17.8±1.9	661.9±117.1	5.6±1.2	628.5±64.1	33.8±7.5	153.1±34.2	546.9±44.9
8w	C	236.0±36.1	29.5±4.5	25.1±2.2	20.8±7.8	14.6±4.1	746.7±55.7	9.2±1.2	614.4±52.7	35.9±5.8	154.4±41.7	529.5±44.6
	L	245.2±22.8	33.7±7.1	21.7±3.7	18.5±5.7	16.7±2.0	775.9±34.0	14.7±4.0	603.4±39	34.9±5.6	156.0±25.0	540.4±55.3
	M	215.6±59.8	32.3±9.5	21.4±4.9	18.8±6.7	15.4±2.0	689.1±49.6	16.4±1.1*	611.9±49.6	41.8±9.8	151.6±16.2	608.9±72.1*
	H	210.0±34.2	24.9±3.9	19.4±4.6*	18.8±4.3	15.2±3.1	765.3±80.8	18.2±8.8*	665±47.4	33.0±4.5	184.8±10.9	632.4±39.5**
12w	C	228.1±32.2	28.8±6.6	21.3±6.1	16.4±3.8	12±2.2	636±89.2	10.9±2.1	480.2±77.5	30.8±9.6	119.8±27.4	512.0±88.8
	L	200.9±28.1	21.7±6.5	14.2±3.2*	14.7±2.8	14.7±3.2	645.5±116.3	8.3±1.9*	502.6±73.5	37.3±6.9	134.1±34.1	607.5±54.4*
	M	165.8±40.9*	21.3±4.8	15.0±1.5*	9.7±3.4**	15.0±1.9	781.9±51.0**	8.1±1.9*	534.9±76.7	39.1±4.5	162.1±21.8*	622.2±36.7*
	H	164.6±36.2*	15.8±2.2*	15.2±4.8*	9.7±2.5**	15.8±1.2*	834.8±65.4**	6.9±0.9**	649.3±64.7**	45.1±7.8**	171.7±12.2**	615.0±59.8**
16w	C	212.4±32.1	29.6±4.3	21.1±3.4	17.6±4.7	13.3±1.0	574.1±36.1	8.4±1.8	479.8±47.1	35.5±6.8	121.2±16.2	500.0±52.7
	L	169.9±9.3*	21.4±2.5*	14.6±2.8*	10.8±1.6**	17.9±1.4**	672.2±26.3**	13.7±3.8**	561.6±20.7*	50.1±6.9**	151.2±23.1*	580.5±30.1*
	M	180.9±24.8*	20.9±1.9*	14.3±1.2*	9.1±1.5**	18.5±3.5**	720.6±49**	13.2±2.2**	568.8±46.0**	50.1±5.2**	175.4±15**	588.7±29.0**
	H	179.1±19.0*	17.9±1.4*	12.5±7.2**	7.3±1.3**	19.4±2.7**	705.8±66.7**	15.6±1.2**	605.8±55.1**	49.2±9.2**	168.1±24**	605.9±66.2**
20w	C	193.4±10.9	28.3±2.9	19.6±2.7	19.0±2.4	12.2±1.2	707.1±29.3	10.0±2.6	395.3±44.5	32.9±6.2	117.6±9.7	539.4±25.2
	L	160.1±16.3**	22.6±4.8*	13.8±1.0*	10.7±3.1**	18.1±2.7**	763.8±24.6**	15.8±0.9**	518.3±40.8**	43.9±7.5**	161.3±13.6**	609.0±47.5*
	M	157.2±24.5**	22.7±5.6*	13.1±3.4*	11.8±4.4**	19.3±3.5**	813.1±31.7**	15.2±2.6**	487.3±61.6**	47.6±4.7**	154.9±32.9**	644.4±52.6**
	H	148.9±13.4**	20.7±2.5*	10.8±6.8**	10.6±2.8**	19.1±1.3**	764.9±28.6**	18.8±1.6**	560.4±76.7**	45.8±3.2**	155.8±26.9**	619.9±40.3**
24w	C	200.1±26.2	28.1±5.5	21.6±3.2	16.4±2.5	13.4±3.2	558.3±19.6	10.0±2.9	479.9±60.7	32.0±7.7	120.0±22.7	504.3±38.4
	L	153.8±20.9**	19.2±2.7*	13.9±3.3**	9.7±2.5**	20.2±1.5**	635±32.6**	15.7±3.8**	595.3±38.4**	45.6±7.9**	153.7±17.5**	602.8±64.9*
	M	158.8±10.5**	17.1±4.0*	13.5±1.2**	8.1±2.4**	22.2±3.7**	697.4±53.2**	18.0±0.2**	610.7±39.4**	48.7±5.5**	158.9±17.9**	648.0±85.0**
	H	147.0±7.7**	21.2±2.8*	14.8±1.5**	11.4±3.0**	23.8±3.3**	690.1±48.6**	18.5±0.7**	617.0±56.2**	51.9±8.3**	166.5±10.8**	631.0±69.0**

Note . C, control group; L, low-dose group; M, middle-dose group; H, high-dose group.

*Significantly different from control (0 mg/kg/day) rats at p < 0.05 (ANCOVA).

**Significantly different from control (0 mg/kg/day) rats at p < 0.01 (ANCOVA).

Attached list 3 Summary of intensity values of biomarkers detected in negative ESI mode in rats' plasma

		Peak intensity (mean \pm SD, n = 5)							
Times (week)	Groups	Glutamic acid	4-Pyridoxic acid	Tryptophan	Arachidonic acid	Iodotyrosine	LysoPE(16:0/0:0)	Glycocholic Acid	LysoPC(17:0/0:0)
4w	C	9.4 \pm 4.7	17.3 \pm 2.7	103.2 \pm 7.4	67.6 \pm 22.1	21.4 \pm 3.5	56.4 \pm 8.4	17.7 \pm 3.3	177.7 \pm 11.0
	L	12.5 \pm 1.7	13.2 \pm 3.0	105.0 \pm 18.3	56.5 \pm 25.7	18.4 \pm 4.0	52.3 \pm 7.2	18.1 \pm 3.9	167.3 \pm 15.8
	M	12.5 \pm 1.5	15.1 \pm 1.8	115.6 \pm 4.5	64.2 \pm 14.6	17.0 \pm 0.9	54.7 \pm 9.2	20.0 \pm 5.8	184.8 \pm 24.3
	H	12.2 \pm 2.5	14.0 \pm 3.7	104.5 \pm 17.1	77.3 \pm 34.0	18.5 \pm 3.0	59.8 \pm 9.4	20.5 \pm 4.0	171.9 \pm 45.9
8w	C	9.5 \pm 2.5	14.3 \pm 3.4	156 \pm 29.6	68.1 \pm 9.6	21.5 \pm 1.8	41.5 \pm 6.2	23.6 \pm 4.6	191.3 \pm 27.9
	L	10.2 \pm 3.4	16.4 \pm 4.2	150.3 \pm 31.7	77.6 \pm 24.3	18.4 \pm 6.8	53.4 \pm 15.3	28.4 \pm 8.6	180.7 \pm 15.9
	M	11.3 \pm 0.8	19.8 \pm 4.1*	143.3 \pm 48.1	91.1 \pm 31.2	21.9 \pm 1.3	54.1 \pm 10.3	26.8 \pm 7.1	195.9 \pm 44.6
	H	13.0 \pm 0.6*	20.7 \pm 4.3*	115.2 \pm 16.1	82.6 \pm 12.8	20.4 \pm 1.3	59.3 \pm 13.8*	33.5 \pm 3.3*	174.3 \pm 20.3
12w	C	10.4 \pm 2.1	12.3 \pm 4.2	162.9 \pm 25.0	43.3 \pm 20.1	28.7 \pm 5.3	42.7 \pm 14.3	17.0 \pm 8.4	179.4 \pm 23.0
	L	10.4 \pm 0.7	18.9 \pm 3.3*	155.0 \pm 41.6	66.5 \pm 36.8	26.6 \pm 3.8	46.8 \pm 15.0	26.8 \pm 13.2	189.6 \pm 37.4
	M	14.4 \pm 3.8*	19.1 \pm 4.7*	86.6 \pm 12.0**	76.2 \pm 11.7	21.7 \pm 2.8*	62.1 \pm 5.4*	37.6 \pm 8.2**	216.3 \pm 32.1
	H	17.2 \pm 3.1**	20.1 \pm 4.7*	94.4 \pm 22.9**	91.3 \pm 46.8*	21.0 \pm 2.5**	59.5 \pm 10.2*	36.8 \pm 8.9**	256.9 \pm 30.8**
16w	C	11.4 \pm 2.6	13.9 \pm 2.4	140.1 \pm 8.8	42.4 \pm 2.8	33.2 \pm 3.1	40.8 \pm 5.0	15.4 \pm 10.7	176.6 \pm 17.6
	L	19.6 \pm 3.3*	17.9 \pm 3.1*	108.3 \pm 14.8**	58.6 \pm 8.4	24 \pm 4.8**	58.7 \pm 14.1*	34.5 \pm 17.7*	185.7 \pm 37.1
	M	24.8 \pm 6.4**	19.4 \pm 3.6**	101.0 \pm 13.7**	80.0 \pm 18.1**	22.3 \pm 3.7**	57.4 \pm 10.5*	45.2 \pm 14.5**	218.0 \pm 24.6*
	H	25 \pm 4.8**	22.2 \pm 2.0**	106.3 \pm 22.3**	92.8 \pm 14.7**	20.1 \pm 3.0**	63.9 \pm 9.4**	35.9 \pm 7.8**	242.5 \pm 27.7**
20w	C	12.9 \pm 3.8	12.7 \pm 3.3	152.0 \pm 28.5	38.7 \pm 12.0	32.7 \pm 5.0	37.7 \pm 2.0	21.5 \pm 8.1	156.2 \pm 30.1
	L	26.4 \pm 4.9**	19.6 \pm 2.8**	86.2 \pm 13.5**	59.8 \pm 10.4*	24.2 \pm 0.8**	51.3 \pm 10.1*	36.1 \pm 3.3**	225.9 \pm 39.8**
	M	24.7 \pm 8.1**	19.4 \pm 3.5**	100.2 \pm 12.5**	68.9 \pm 15.6**	23.5 \pm 2.0**	59.1 \pm 8.2**	35.4 \pm 8**	227.4 \pm 41.4**
	H	29.3 \pm 4.6**	20.8 \pm 4.3**	109.5 \pm 10.9**	103.9 \pm 18.7**	19.3 \pm 3.4**	63.9 \pm 9.1**	37.3 \pm 8.9**	238.5 \pm 20.9**
24w	C	12.3 \pm 1.8	14.5 \pm 2.4	143.6 \pm 6.1	53.1 \pm 10.7	34.5 \pm 5.0	34.9 \pm 9.1	23.4 \pm 4.0	163.7 \pm 20.4
	L	25.2 \pm 5.1**	20 \pm 3.6**	107.9 \pm 12.4**	93.6 \pm 14.8**	23.4 \pm 2.9**	51.1 \pm 9.2*	41.2 \pm 14**	222.6 \pm 34.6**
	M	20.3 \pm 1.5**	22.6 \pm 3.8**	84.0 \pm 8.9**	80.7 \pm 13.2**	25.0 \pm 3.1**	57.3 \pm 9.4**	42.3 \pm 1.1**	234.8 \pm 15.5**
	H	27.6 \pm 5.1**	24.7 \pm 4.5**	99.5 \pm 7.5**	90.2 \pm 14.9**	21.1 \pm 2.9**	58.3 \pm 15.3**	47.0 \pm 8.6**	263.1 \pm 26.2**

Note . C, control group; L, low-dose group; M, middle-dose group; H, high-dose group.

*Significantly different from control (0 mg/kg/day) rats at $p < 0.05$ (ANCOVA).

**Significantly different from control (0 mg/kg/day) rats at $p < 0.01$ (ANCOVA).