

Supplementary Table

Table S1.

Basic design for animal study

Group No.	Dose (mg/kg/day)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)	No. of Animals
1 (Vehicle control)	0	0	3	10M, 10F
2 (Low-dose)	6	2	3	10M, 10F
3 (Mid-dose)	12	4	3	10M, 10F
4 (High-dose)	24	8	3	10M, 10F

Table S2.

Items analyzed for Toxicity Study

Hematology	Red blood cell counts (RBC)
	White blood cell counts (WBC)
	Platelet counts (PLT)
	Hemoglobin (HGB)
	Hematocrit (HCT)
	Mean Corpuscular Volume (MCV)
	Mean Corpuscular Hemoglobin (MCH)
	Mean Corpuscular Hemoglobin Concentration (MCHC)
	Reticulocyte (RET)
	WBC differential
	neutrophils (NEUT)
	eosinophils (EOSIN)
	basophils (BASO)
	monocytes (MONO)
	lymphocytes (LYMPH)
Coagulation	Activated partial thromboplastin time (APTT)
	Prothrombin time (PT)
	Fibrinogen (FIB)
	Amylase (AMY)
	Albumin (ALB)
	Alkaline phosphatase (ALP)
	Total bilirubin (T-BIL)

Serum Chemistry	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Gamma-glutamyl transferase (GGT)
	Total bile acids (TBA)
	Total protein (TP)
	Creatinine (CRE)
	Blood Urea nitrogen (BUN)
	Total Cholesterol (CHO)
	Triglycerides (TG)
	Creatine kinase (CK)
	Lactate dehydrogenase (LDH)
	Chloride (Cl)
	Sodium (Na)
	Potassium (K)
	Glucose (GLU)
	Calcium (Ca)
	Phosphorus (P)
	pH
	Specific gravity
Urinalysis	Protein
	Glucose
	Ketone
	Bilirubin
	Urobilinogen
	Occulted blood
	Leukocytes
	Nitrite
	Red blood cell
	White blood cell
Urinary Sediments Examination	Cells
	Casts
	Crystals
	Microbes

Table S3.

A. Mean body weight of rats receiving astaxanthin over 13-week period

Mean Body Weights (g, Mean \pm SD)	
Male	Female

Study	Vehicle Control	Low-dose 6	Mid-dose 12	High-dose 24	Vehicle Control	Low-dose 6	Mid-dose 12	High-dose 24
Day	0 mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	0 mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
Number of animals	10	10	10	10	10	10	10	10
Day 1	182.25 ± 7.90	183.03 ± 9.41	181.76 ± 8.31	182.49 ± 9.05	156.73 ± 7.46	153.36 ± 5.70	156.79 ± 6.96	154.93 ± 7.47
Day 8	241.90 ± 10.10	242.92 ± 15.85	238.14 ± 8.88	236.88 ± 8.53	178.69 ± 8.24	175.25 ± 9.96	173.92 ± 11.31	176.21 ± 7.00
Day 15	299.41 ± 13.36	298.53 ± 23.42	291.20 ± 16.54	289.90 ± 14.95	192.81 ± 7.63	190.58 ± 12.85	187.03 ± 15.17	193.74 ± 5.35
Day 22	351.21 ± 18.00	347.76 ± 33.52	340.45 ± 25.02	337.03 ± 22.26	206.16 ± 11.32	204.25 ± 11.23	202.71 ± 16.74	205.51 ± 4.91
Day 29	392.90 ± 22.96	390.61 ± 43.53	381.23 ± 32.01	376.63 ± 27.66	215.43 ± 13.07	215.26 ± 11.86	215.51 ± 17.32	219.18 ± 7.41
Day 36	429.75 ± 27.87	422.16 ± 49.88	411.88 ± 36.96	406.39 ± 32.03	230.87 ± 14.37	227.68 ± 11.89	226.26 ± 19.57	228.64 ± 7.44
Day 43	458.07 ± 32.25	450.94 ± 52.13	437.34 ± 42.09	431.71 ± 33.91	237.20 ± 16.45	237.29 ± 12.44	233.95 ± 18.43	241.09 ± 6.78
Day 50	485.62 ± 33.43	474.10 ± 58.69	457.29 ± 46.49	453.31 ± 39.23	243.31 ± 18.40	241.73 ± 12.90	240.75 ± 19.40	243.02 ± 6.38
Day 57	508.60 ± 35.79	501.29 ± 64.23	477.82 ± 48.82	474.56 ± 41.96	248.55 ± 18.13	246.12 ± 13.47	245.19 ± 19.19	246.87 ± 8.65
Day 64	526.29 ± 37.66	515.44 ± 68.02	492.98 ± 52.61	491.19 ± 44.31	257.46 ± 18.14	252.23 ± 14.43	250.16 ± 20.11	254.14 ± 8.54
Day 71	544.66 ± 41.26	532.41 ± 69.48	507.16 ± 57.15	505.40 ± 42.48	258.77 ± 19.63	256.98 ± 13.08	253.92 ± 17.91	257.81 ± 8.87
Day 78	558.39 ± 40.71	546.69 ± 70.60	519.89 ± 60.31	520.76 ± 47.54	261.86 ± 20.38	258.85 ± 15.95	258.05 ± 19.73	259.67 ± 8.99
Day 85	573.36 ± 44.74	559.04 ± 74.11	531.01 ± 61.23	534.14 ± 48.61	266.93 ± 20.97	263.25 ± 16.15	262.08 ± 20.86	262.35 ± 10.30
Day 91	583.10 ± 45.14	596.31 ± 78.13	540.59 ± 60.80	543.34 ± 51.12	267.03 ± 21.13	265.87 ± 14.67	261.79 ± 19.43	264.88 ± 8.43

B. Mean body weight gain of rats receiving astaxanthin over 13-week period

Mean Body Weights (g, Mean \pm SD)								
Study Day	Male				Female			
	Vehicle Control 0 mg/kg/day	Low-dose 6 mg/kg/day	Mid-dose 12 mg/kg/day	High-dose 24 mg/kg/day	Vehicle Control 0 mg/kg/day	Low-dose 6 mg/kg/day	Mid-dose 12 mg/kg/day	High-dose 24 mg/kg/day
Number of animals	10	10	10	10	10	10	10	10
Day 1-8	59.65 \pm 6.48	59.89 \pm 11.98	56.38 \pm 7.43	54.39 \pm 6.30	21.96 \pm 5.25	21.89 \pm 6.89	17.13 \pm 7.36	21.28 \pm 3.99
Day 8-15	57.51 \pm 8.02	55.61 \pm 10.33	53.06 \pm 8.60	53.02 \pm 7.90	14.12 \pm 5.14	15.33 \pm 5.38	13.11 \pm 6.73	17.53 \pm 3.74
Day 15-22	51.80 \pm 6.23	49.23 \pm 11.53	49.25 \pm 10.25	47.13 \pm 8.68	13.35 \pm 5.66	13.67 \pm 4.35	15.68 \pm 4.08	11.77 \pm 5.55
Day 22-29	41.69 \pm 5.98	42.85 \pm 12.21	40.78 \pm 10.84	39.60 \pm 7.37	9.27 \pm 4.54	11.01 \pm 4.81	12.80 \pm 3.24	13.67 \pm 6.55
Day 29-36	36.85 \pm 6.76	31.55 \pm 7.05	30.65 \pm 6.43	29.76 \pm 6.76	15.44 \pm 4.80	12.42 \pm 5.40	10.75 \pm 3.99	9.46 \pm 7.04
Day 36-43	28.32 \pm 5.00	28.78 \pm 3.93	25.46 \pm 6.23	25.32 \pm 4.35	6.33 \pm 3.02	9.61 \pm 3.23	7.69 \pm 4.25	12.45 \pm 4.63*
Day 43-50	27.55 \pm 4.25	23.16 \pm 7.20	19.95 \pm 6.02	21.60 \pm 6.78	6.11 \pm 5.67	4.44 \pm 4.78	6.80 \pm 5.19	1.93 \pm 4.53
Day 50-57	22.98 \pm 5.41	27.19 \pm 6.13	20.53 \pm 3.70	21.25 \pm 4.22	5.24 \pm 5.64	4.39 \pm 5.77	4.44 \pm 2.76	3.85 \pm 4.47
Day 57-64	17.69 \pm 7.01	14.15 \pm 6.46	15.16 \pm 5.05	16.63 \pm 5.52	8.91 \pm 4.27	6.11 \pm 5.55	4.97 \pm 4.02	7.27 \pm 5.53
Day 64-71	18.37 \pm 5.62	16.97 \pm 4.82	14.18 \pm 5.77	14.21 \pm 4.55	1.31 \pm 4.97	4.75 \pm 2.68	3.76 \pm 5.62	3.67 \pm 4.57
Day 71-78	13.73 \pm 3.26	14.28 \pm 4.67	12.73 \pm 5.88	15.36 \pm 6.87	3.09 \pm 5.56	1.87 \pm 6.71	4.13 \pm 4.61	1.86 \pm 2.55
Day 78-85	14.97 \pm 5.47	12.35 \pm 6.13	11.12 \pm 4.42	13.38 \pm 4.03	5.07 \pm 5.35	4.40 \pm 4.93	4.03 \pm 4.48	2.68 \pm 3.73
Day 85-91	9.74 \pm 3.74	10.27 \pm 6.94	9.58 \pm 3.06	9.20 \pm 5.64	0.10 \pm 4.65	2.62 \pm 6.67	-0.29 \pm 4.49	2.53 \pm 3.73
Day 1-91	400.85 \pm 44.38	386.28 \pm 77.95	358.63 \pm 61.13	360.85 \pm 53.01	110.30 \pm 19.14	112.51 \pm 15.20	105.00 \pm 17.95	109.95 \pm 9.17

*: $p \leq 0.05$ (compared to vehicle control group)

Table S4.

Mean food consumption of rats receiving astaxanthin over 13-week period

Mean Food Consumption (g/day, Mean \pm SD)								
Study Day	Male				Female			
	Vehicle Control 0 mg/kg/day	Low-dose 6 mg/kg/day	Mid-dose 12 mg/kg/day	High-dose 24 mg/kg/day	Vehicle Control 0 mg/kg/day	Low-dose 6 mg/kg/day	Mid-dose 12 mg/kg/day	High-dose 24 mg/kg/day
Number of cages	5	5	5	5	5	5	5	5
Day	24.88 \pm	24.62 \pm 1.03	23.01 \pm	23.27 \pm	15.71 \pm	16.51 \pm	15.78 \pm	15.90 \pm
1-8	1.64		0.82	0.90	0.66	0.88	0.84	0.76
Day 8-15	27.98 \pm	27.86 \pm 1.49	25.76 \pm	26.33 \pm	16.22 \pm 0.68	16.72 \pm	16.39 \pm	16.24 \pm
	1.50		1.34	1.05		0.85	0.92	0.64
Day 15-22	29.82 \pm	29.77 \pm 1.82	27.21 \pm	27.35 \pm	16.31 \pm	17.38 \pm	16.65 \pm	16.32 \pm
	1.84		1.98	1.55	0.60	1.53	0.83	0.55
Day 22-29	29.36 \pm	29.56 \pm 2.42	26.56 \pm	27.20 \pm	16.79 \pm 0.62	17.98 \pm	17.00 \pm	16.68 \pm
	1.17		2.13	1.91		0.95	0.79	0.84
Day 29-36	28.97 \pm	28.83 \pm 2.39	25.74 \pm	26.75 \pm	17.20 \pm 0.43	17.61 \pm	17.01 \pm	16.51 \pm
	1.49		1.65	2.00		1.24	0.72	0.71
Day 36-43	29.26 \pm	29.13 \pm 2.37	26.11 \pm	26.89 \pm	16.65 \pm 0.53	17.42 \pm	16.73 \pm	16.97 \pm
	2.11		1.67	1.74		1.23	0.63	1.11
Day 43-50	29.56 \pm 2.59	29.34 \pm 2.49	25.50 \pm	25.79 \pm	16.96 \pm	17.55 \pm	16.90 \pm	16.20 \pm
			2.14	2.02	1.02	1.66	0.85	0.70
Day 50-57	28.69 \pm	28.64 \pm 1.75	25.36 \pm	26.29 \pm	16.62 \pm 0.69	16.80 \pm	16.15 \pm	15.89 \pm
	1.64		1.95*	1.91		0.90	0.58	1.01
Day 57-64	27.23 \pm	26.99 \pm 2.04	24.33 \pm	25.22 \pm	16.15 \pm	16.50 \pm	15.78 \pm	15.37 \pm
	2.13		1.57	1.82	0.61	0.78	0.77	1.21
Day 64-71	26.63 \pm	26.81 \pm 3.04	23.38 \pm	24.80 \pm	15.80 \pm 0.95	16.39 \pm	15.83 \pm	15.00 \pm
	2.41		1.96	1.77		0.92	0.85	1.62
Day 71-78	26.43 \pm 2.40	26.55 \pm 2.09	23.96 \pm	25.39 \pm	15.85 \pm 1.09	15.71 \pm	15.41 \pm	15.07 \pm
			2.10	1.79		1.46	1.06	1.27
Day 78-85	26.09 \pm 2.83	25.49 \pm 1.96	22.68 \pm	24.34 \pm	15.98 \pm 0.68	15.92 \pm	15.78 \pm	14.95 \pm
			1.63	2.12		1.15	0.83	1.00
Day 85-91	27.63 \pm	27.41 \pm 2.68	24.06 \pm	25.80 \pm	15.92 \pm 0.55	16.10 \pm	15.51 \pm	15.68 \pm
	3.09		1.70	1.89		1.10	0.82	1.46

*: $p \leq 0.05$ (compared to vehicle control group)

Table S5.

Ophthalmologic examinations of rats receiving astaxanthin over 13-week period

Gender	Dose (mg/kg/day)	Ophthalmologic Examination (N/N) ¹	
		Before study	Before necropsy (Day 91)
Male	0	0/10	0/10
	6	0/10	0/10
	12	0/10	0/10
	24	0/10	0/10
Female	0	0/10	0/10
	6	0/10	0/10
	12	0/10	0/10
	24	0/10	0/10

¹ N/N: Number of animals with ophthalmologic abnormality/Total number of animals**Table S6.**

A. Absolute organ weight of rats receiving astaxanthin over 13-week period

Parameters		Organs Weights (gram, Mean ± SD)						
Group	Vehicle	Low-dose	Mid-dose	High-dose	Vehicle	Low-dose	Mid-dose	High-dose
	Control	6	12	24	Control	6	12	24
	0	mg/kg/day	mg/kg/day	mg/kg/day	0	mg/kg/day	mg/kg/day	mg/kg/day
	mg/kg/day	mg/kg/day						
Gender	Male				Female			
Number of animals	10	10	10	10	10	10	10	10
Adrenals	0.04955 ± 0.00546	0.05224 ± 0.00982	0.05446 ± 0.00564	0.05437 ± 0.00810	0.06268 ± 0.00862	0.05650 ± 0.00702	0.06074 ± 0.00816	0.06012 ± 0.00631
	0.01462 ± 0.00304	0.01265 ± 0.00325	0.01368 ± 0.00192	0.01479 ± 0.00070	0.01555 ± 0.00223	0.01525 ± 0.00240	0.01534 ± 0.00231	0.01581 ± 0.00182
Brain	2.239 ± 0.107	2.132 ± 0.139	2.235 ± 0.059	2.209 ± 0.147	2.014 ± 0.071	1.971 ± 0.052	1.985 ± 0.107	2.025 ± 0.062
	1.609 ± 0.181	1.632 ± 0.203	1.550 ± 0.170	1.523 ± 0.154	0.912 ± 0.084	0.884 ± 0.062	0.872 ± 0.090	0.895 ± 0.082
Heart	0.311 ± 0.060	0.289 ± 0.119	0.350 ± 0.063	0.316 ± 0.084	0.211 ± 0.066	0.241 ± 0.043	0.232 ± 0.067	0.228 ± 0.050

Liver	16.431 ± 2.811	14.985 ± 3.182	13.959 ± 2.310	13.951 ± 2.038	6.813 ± 0.477	7.428 ± 1.029	7.441 ± 1.160	7.147 ± 0.484
Spleen	0.860 ± 0.124	0.775 ± 0.201	0.729 ± 0.113	0.745 ± 0.137	0.470 ± 0.088	0.474 ± 0.040	0.477 ± 0.087	0.494 ± 0.094
Kidneys	3.555 ± 0.336	3.422 ± 0.494	3.316 ± 0.453	3.419 ± 0.370	1.745 ± 0.171	1.815 ± 0.154	1.831 ± 0.158	1.904 ± 0.109
Testes	3.596 ± 0.307	3.448 ± 0.309	3.493 ± 0.205	3.532 ± 0.194	NA	NA	NA	NA
Epididymides	1.321 ± 0.139	1.288 ± 0.077	1.272 ± 0.063	1.288 ± 0.078	NA	NA	NA	NA
Prostate and Seminal	3.471 ± 0.364	3.476 ± 0.379	3.443 ± 0.365	3.595 ± 0.144	NA	NA	NA	NA
Ovary/Oviduct	NA	NA	NA	NA	0.11430 ± 0.01402	0.12051 ± 0.01612	0.11556 ± 0.02036	0.11830 ± 0.01136
Uterus/Cervix	NA	NA	NA	NA	0.809 ± 0.359	0.737 ± 0.313	0.583 ± 0.181	0.720 ± 0.252

B. Estrus Cycle of female rats receiving astaxanthin over 13-week period

Entrus Cycle Stages (Number of rats)				
Group	Proestrus	Estrus	Metestrus	Diestrus
1	7	0	3	0
2	6	1	3	0
3	7	1	2	0
4	7	1	2	0

C. Relative organ weights (organ-to-terminal body weight) of rats receiving astaxanthin over 13-week period

Parameters		Organs Weights/Terminal Body Weight Ratio (% , Mean ± SD)						
Group	Vehicle	Low-dose	Mid-dose	High-dose	Vehicle	Low-dose	Mid-dose	High-dose
	Control	6	12	24	Control	6	12	24
	0	mg/kg/day	mg/kg/day	mg/kg/day	0	mg/kg/day	mg/kg/day	mg/kg/day
	mg/kg/day				mg/kg/day			
Gender	Male				Female			
Number of animals	10	10	10	10	10	10	10	10
Adrenals	0.00888 ± 0.00097	0.00956 ± 0.00127	0.01061 ± 0.00091*	0.01051 ± 0.00163*	0.02486 ± 0.00339	0.02273 ± 0.00284	0.02474 ± 0.00310	0.02422 ± 0.00260
Pituitary	0.00262 ±	0.00230 ±	0.00266 ±	0.00286 ±	0.00615 ±	0.00614 ±	0.00624 ±	0.00637 ±

	0.00052	0.00042	0.00033	0.00023	0.00067	0.00097	0.00093	0.00075
Brain	0.40285 ±	0.39495 ±	0.43780 ±	0.42716 ±	0.80089 ±	0.79440 ±	0.80995 ±	0.81632 ±
	0.03701	0.04166	0.04396	0.03516	0.06253	0.06009	0.06083	0.04561
Heart	0.28755 ±	0.29980 ±	0.30143 ±	0.29365 ±	0.36170 ±	0.35526 ±	0.35401 ±	0.36036 ±
	0.01735	0.02230	0.02158	0.02386	0.03100	0.02071	0.01535	0.03169
Thymus	0.05601 ±	0.05146 ±	0.06797 ±	0.06036 ±	0.08378 ±	0.09693 ±	0.09395 ±	0.09235 ±
	0.01193	0.01675	0.00981	0.01375	0.02619	0.01699	0.02509	0.02307
Liver	2.92675 ±	2.71852 ±	2.69910 ±	2.67791 ±	2.69980 ±	2.98688 ±	3.01070 ±	2.87849 ±
	0.29745	0.26417	0.22519	0.22399	0.12228	0.40311*	0.23581*	0.19718
Spleen	0.15367 ±	0.13999 ±	0.14189 ±	0.14293 ±	0.18606 ±	0.19093 ±	0.19329 ±	0.19916 ±
	0.01694	0.02206	0.01932	0.01876	0.03330	0.02002	0.02788	0.03911
Kidneys	0.63697 ±	0.62867 ±	0.64339 ±	0.65838 ±	0.69069 ±	0.73006 ±	0.74450 ±	0.76700 ±
	0.04837	0.06658	0.04905	0.04684	0.04533	0.06278	0.03801	0.04710*
Testes	0.64700 ±	0.63801 ±	0.68479 ±	0.68349 ±	NA	NA	NA	NA
	0.07450	0.06988	0.08337	0.05478				
Epididymides	0.23708 ±	0.23939 ±	0.24985 ±	0.24891 ±	NA	NA	NA	NA
	0.02562	0.03312	0.03269	0.01691				
Prostate and	0.623 ±	0.649 ±	0.675 ±	0.697 ±	NA	NA	NA	NA
Seminal	0.065	0.127	0.101	0.067				
Ovary/	NA	NA	NA	NA	0.04548 ±	0.04855 ±	0.04696 ±	0.04765 ±
Oviduct					0.00670	0.00713	0.00741	0.00455
Uterus/	NA	NA	NA	NA	0.31725 ±	0.29473 ±	0.23741 ±	0.29063 ±
Cervix					0.13315	0.12087	0.07090	0.10468

*: $p \leq 0.05$ (compared to vehicle control group)

Relative organ weight (%) = Absolute organ weight (g) / Terminal Body weight of rat on the day of sacrifice (g) x 100

D. Relative organ weight (organ-to-brain weight) of rats receiving astaxanthin over 13-week period

Parameters	Organs Weights/Terminal Body Weight Ratio (% , Mean ± SD)							
	Vehicle	Low-dose	Mid-dose	High-dose	Vehicle	Low-dose	Mid-dose	High-dose
Group	Control	6	12	24	Control	6	12	24
	0	mg/kg/day	mg/kg/day	mg/kg/day	0	mg/kg/day	mg/kg/day	mg/kg/day
	mg/kg/day				mg/kg/day			
Gender	Male				Female			
Number of animals	10	10	10	10	10	10	10	10
Adrenals	2.21728 ±	2.45088 ±	2.43692 ±	2.47264 ±	3.10798 ±	2.86499 ±	3.06796 ±	2.97251 ±
	0.26872	0.43833	0.24853	0.41776	0.37457	0.33150	0.45910	0.34334
Pituitary	0.65713 ±	0.58897 ±	0.61248 ±	0.67142 ±	0.77200 ±	0.77528 ±	0.77358 ±	0.77962 ±
	0.14793	0.13357	0.08798	0.04202	0.10760	0.13294	0.12024	0.07288
Brain	100.00000	100.00000	100.00000 ±	100.00000	100.00000	100.00000	100.00000 ±	100.00000 ±

	± 0.00000	± 0.00000	0.00000	± 0.00000	± 0.00000	± 0.00000	0.00000	0.00000
Heart	71.93438 ± 8.09064	76.40161 ± 6.97738	69.36157 ± 7.47811	69.08830 ± 7.28754	45.27415 ± 3.78880	44.86268 ± 3.11345	43.95798 ± 4.18680	44.29964 ± 5.04055
Thymus	13.87213 ± 2.42212	13.37398 ± 5.08095	15.64278 ± 2.63502	14.28617 ± 3.73081	10.45749 ± 3.13108	12.26994 ± 2.39970	11.64525 ± 3.07804	11.24520 ± 2.32978
Liver	735.53341 ± 131.64079	699.78210 ± 131.27845	624.21273 ± 100.06107	631.59290 ± 81.93341	338.55639 ± 25.14445	376.61486 ± 49.06503	375.04653 ± 54.88274	353.33701 ± 27.64662
Spleen	38.48325 ± 5.75422	36.16696 ± 8.63830	32.65621 ± 5.21805	33.63503 ± 5.08597	23.37912 ± 4.69625	24.04074 ± 1.86449	23.97242 ± 3.87714	24.36295 ± 4.32669
Kidneys	158.97385 ± 15.29231	160.10357 ± 18.04395	148.45323 ± 20.43978	154.85288 ± 14.31550	86.59682 ± 7.46051	92.08376 ± 7.38824	92.21555 ± 5.77266	94.09488 ± 6.04684
Testes	160.81788 ± 14.61765	161.80640 ± 11.57058	156.34507 ± 9.38066	160.31247 ± 10.77010	NA	NA	NA	NA
Epididymides	58.98945 ± 5.50995	60.65638 ± 5.57287	56.95050 ± 3.19883	58.38157 ± 2.73921	NA	NA	NA	NA
Prostate and Seminal	155.361 ± 17.932	163.815 ± 22.269	154.329 ± 18.606	163.525 ± 14.414	NA	NA	NA	NA
Ovary/ Oviduct	NA	NA	NA	NA	5.67960 ± 0.72943	6.11232 ± 0.78629	5.81201 ± 0.86809	5.84633 ± 0.58486
Uterus/ Cervix	NA	NA	NA	NA	40.25734 ± 17.90657	37.68779 ± 16.87806	29.41385 ± 9.18077	35.58113 ± 12.44363

Relative organ weight (%) = Absolute organ weight (g) / Terminal Body weight of rat on the day of sacrifice (g) x 100

Table S7.

Gross necropsy of rats receiving astaxanthin over 13-week period

Male

Group	Control	Low-dose	Mid-dose	High-dose
Gross findings	Incidence ¹			
Thymus				
Discoloration, present, red	1/10	0/10	0/10	0/10
Adrenal glands				
Discoloration, present, multifocal, white	1/10	0/10	0/10	0/10
Brain				
Abnormal shape, present, cerebrum, right, depressed	1/10	0/10	0/10	0/10

¹ Incidence = number of animals with gross findings / number of animals for gross examinations (N/N).

Female

Group	Control	Low-dose	Mid-dose	High-dose
Gross findings	Incidence ¹			
Mandibular lymph node				
Discoloration, present, red	1/10	0/10	0/10	0/10
Liver				
Nodule, present, right lateral lobe	1/10	0/10	0/10	0/10

¹ Incidence = number of animals with gross findings / number of animals for gross examinations (N/N).

Table S8.

Histopathology values of rats receiving astaxanthin over 13-week period

Group		Control	Low-dose	Mid-dose	High-dose		Control	Low-dose	Mid-dose	High-dose
Histopathologic findings	S ²	Incidence ¹				S ²	Incidence ¹			
Thymus										
Congestion	P	1/10	NA	NA	0/10	P	1/10	NA	NA	0/10
Liver										
Infiltration, mononuclear cell	1	3/10	NA	NA	4/10	1	4/10	NA	NA	3/10
Fatty change, minimal	1	1/10	NA	NA	0/10	P	1/10	NA	NA	0/10
Kidneys										
Degeneration, tubular epithelial cell	1	1/10	NA	NA	1/10	1	0/10	NA	NA	1/10
Infiltration, mononuclear cell, interstitial	1	2/10	NA	NA	2/10	1	1/10	NA	NA	0/10
Mineralization, corticomedullary junction	1	0/10	NA	NA	1/10					

¹ Incidence = number of animals with histopathologic findings / Total number of animals for histopathologic examinations (N/N).

² The severity grading scheme: 1 = minimal (< 10%), 2 = mild (10–39%), 3 = moderate (40–79%), 4 = marked (80–100%), P = present.