



**Figure S1. Comparative assay of the effects of LAB strains on IL-10 production in human monocytes.** Human monocytes were treated with KW3110 or strains A-D (10  $\mu\text{g}/\text{mL}$ ) for 24 h and IL-10 levels in the supernatants were measured by ELISA. Values indicate means  $\pm$  SEM.  $n = 3$ . Statistical differences were analyzed by ANOVA followed by Tukey's test (\*\*,  $P < 0.01$ ).

**Table S1. Subjective symptoms of eye fatigue and related visual conditions.**

Symptoms	KW3110						Placebo					
	week 0		week 4		week 8		week 0		week 4		week 8	
Ocular fatigue sensation	48.33 ± 23.53	42.20 ± 21.04	40.45 ± 20.56 #	50.05 ± 23.26	44.90 ± 22.62	40.00 ± 21.46 ##						
Change from week-0 value		-6.13 ± 22.69	-7.88 ± 23.40 #		-5.15 ± 18.11	-10.05 ± 19.80 ##						
Blurred vision	41.55 ± 22.28	36.25 ± 22.62	37.40 ± 21.94	46.98 ± 24.49	39.58 ± 25.00	36.60 ± 21.79 ##						
Change from week-0 value		-5.30 ± 22.94	-4.15 ± 19.28		-7.40 ± 24.03	-10.38 ± 18.72 ##						
Ocular pain	29.03 ± 24.32	27.03 ± 21.86	28.85 ± 23.84	34.48 ± 25.13	28.73 ± 22.05	30.30 ± 23.29						
Change from week-0 value		-2.00 ± 20.17	-0.18 ± 19.21		-5.75 ± 22.67	-4.18 ± 18.97						
Dry eyes	46.00 ± 26.22	39.10 ± 22.71 #	37.23 ± 24.54 ##	50.53 ± 25.02	41.68 ± 25.27 ##	42.13 ± 22.30 #						
Change from week-0 value		-6.90 ± 20.23 #	-8.78 ± 19.78 ##		-8.85 ± 20.63 ##	-8.40 ± 20.88 #						
Heavy eyes	36.80 ± 25.45	32.58 ± 23.09	34.93 ± 24.18	42.65 ± 24.28	38.10 ± 25.65	38.18 ± 24.92						
Change from week-0 value		-4.23 ± 24.25	-1.88 ± 22.41		-4.55 ± 21.36	-4.48 ± 22.24						

Table S1. (continued)

Symptoms	KW3110						Placebo					
	week 0		week 4		week 8		week 0		week 4		week 8	
Sandy eyes	29.68 ± 23.37		26.65 ± 22.56		30.50 ± 25.10		36.65 ± 25.78		29.35 ± 23.15		30.08 ± 22.61	
	Change from week-0 value			-3.03 ± 17.35		0.83 ± 18.92				-7.30 ± 23.27		-6.58 ± 27.06
Eye redness	28.45 ± 21.88		26.58 ± 21.56		29.30 ± 21.98		33.28 ± 21.16		23.83 ± 20.95 <sup>###</sup>		24.10 ± 19.54 <sup>#</sup>	
	Change from week-0 value <sup>\$</sup>			-1.88 ± 20.34		0.85 ± 17.71 <sup>*</sup>				-9.45 ± 20.81 <sup>###</sup>		-9.18 ± 22.30 <sup>#</sup>
Dazzled vision	27.35 ± 20.52		25.30 ± 20.40		28.23 ± 22.53		35.80 ± 24.16		27.15 ± 22.88 <sup>#</sup>		29.10 ± 21.34	
	Change from week-0 value			-2.05 ± 16.54		0.88 ± 21.55				-8.65 ± 21.57 <sup>#</sup>		-6.70 ± 21.99
Double vision	28.38 ± 23.11		24.70 ± 20.28		27.13 ± 21.99		34.98 ± 23.99		28.20 ± 24.37		29.13 ± 22.68	
	Change from week-0 value			-3.68 ± 17.97		-1.25 ± 19.94				-6.78 ± 21.89		-5.85 ± 22.30
Faded vision	32.90 ± 22.59		30.00 ± 21.59		32.28 ± 22.84		39.73 ± 25.90		29.40 ± 25.19 <sup>###</sup>		30.18 ± 22.43 <sup>#</sup>	
	Change from week-0 value <sup>\$</sup>			-2.90 ± 18.44		-0.63 ± 18.10				-10.33 ± 21.21 <sup>###</sup>		-9.55 ± 22.41 <sup>#</sup>

Table S1. (continued)

Symptoms	KW3110						Placebo					
	week 0		week 4		week 8		week 0		week 4		week 8	
Unfocused vision	28.70 ± 21.59		28.88 ± 22.39		30.20 ± 23.54		38.40 ± 26.54		29.28 ± 25.14 <sup>##</sup>		30.85 ± 22.17 <sup>#</sup>	
	Change from week-0 value <sup>§</sup>		0.18 ± 19.69 <sup>*</sup>		1.50 ± 21.07				-9.13 ± 21.24 <sup>##</sup>		-7.55 ± 23.61 <sup>#</sup>	
Stiffness of waist or shoulder	52.85 ± 25.65		44.63 ± 22.81 <sup>##</sup>		43.53 ± 28.04 <sup>#</sup>		50.38 ± 22.64		41.83 ± 23.62 <sup>#</sup>		44.03 ± 22.06	
	Change from week-0 value		-8.23 ± 16.09 <sup>##</sup>		-9.33 ± 23.50 <sup>#</sup>				-8.55 ± 23.30 <sup>#</sup>		-6.35 ± 24.36	
Stuffy head	33.93 ± 23.43		32.08 ± 22.43		31.98 ± 25.72		37.85 ± 22.46		32.43 ± 23.48		34.55 ± 21.91	
	Change from week-0 value		-1.85 ± 14.43		-1.95 ± 22.72				-5.43 ± 21.47		-3.30 ± 25.88	
Headache	28.30 ± 25.28		23.83 ± 22.71		25.23 ± 23.54		29.08 ± 22.92		25.83 ± 21.82		24.33 ± 20.87	
	Change from week-0 value		-4.48 ± 18.96		-3.08 ± 19.29				-3.25 ± 18.81		-4.75 ± 20.04	
Frustration	28.53 ± 24.70		26.23 ± 22.88		25.28 ± 23.08		32.13 ± 24.39		26.93 ± 21.45		25.23 ± 21.18	
	Change from week-0 value		-2.30 ± 21.71		-3.25 ± 18.93				-5.20 ± 18.10		-6.90 ± 22.91	

**Table S1. (continued)**

Data are expressed as mean  $\pm$  SD. Comparisons of each value between two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate. Comparisons of changes in value from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA, followed by LSD test (\$,  $P < 0.05$ ; main effects of ingestion) (\*,  $P < 0.05$ ; effects of ingestion at each time point). Within-group comparisons between week 0 and week 4 or 8 were performed by repeated-measures ANOVA followed by LSD test (#,  $P < 0.05$ ; ##,  $P < 0.01$ ).

**Table S2. Effects of KW3110 on HFC-1 values.**

HFC-1 (Hz)	KW3110			Placebo		
	week 0	week 4	week 8	week 0	week 4	week 8
	48.34 ± 5.41	48.45 ± 4.60	47.55 ± 5.00	48.07 ± 5.39	47.44 ± 5.63	47.08 ± 5.36
Change from week-0 value		0.11 ± 4.18	-0.78 ± 4.04		-0.63 ± 3.23	-0.99 ± 3.16

Data are expressed as mean ± SD. Comparisons of HFC-1 values between the two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate. Comparisons of changes in HFC-1 values from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA. Within-group comparisons between week 0 and week 4 or 8 were performed by repeated-measures ANOVA.

**Table S3. Effects of KW3110 on miosis rates.**

Miosis rate (%)	KW3110			Placebo		
	week 0	week 4	week 8	week 0	week 4	week 8
	35.66 ± 10.51	34.06 ± 12.52	34.55 ± 10.57	34.97 ± 11.74	37.17 ± 13.29	35.60 ± 11.07
Change from week-0 value		-1.60 ± 11.00	-1.12 ± 9.91		2.20 ± 13.00	0.63 ± 13.23

Data are expressed as mean ± SD. Comparisons of miosis rates between the two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate. Comparisons of changes in miosis rates from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA. Within-group comparisons between week 0 and week 4 or 8 were performed by repeated-measures ANOVA.

**Table S4. Influence of Uchida–Kraepelin workload on CFF values, HFC-1 values, and miosis rates at week 0.**

Parameters		KW3110	Placebo	<i>p</i> Values
		Mean ± SD	Mean ± SD	
CFF (Hz)	Before load	34.32 ± 1.79	35.33 ± 3.14	0.0814
	After load	33.71 ± 2.11	34.18 ± 3.58	0.4756
	After rest	33.48 ± 2.31	33.66 ± 3.35	0.7815
	Variation <sup>a</sup>	-0.61 ± 1.23	-1.15 ± 1.19	0.0498
	Variation <sup>b</sup>	-0.23 ± 1.27	-0.52 ± 1.44	0.3397
HFC-1 (Hz)	Before load	48.34 ± 5.41	48.07 ± 5.39	0.8267
	After load	48.97 ± 8.05	48.39 ± 4.80	0.6937
	After rest	47.70 ± 5.00	48.20 ± 4.86	0.6520
	Variation <sup>a</sup>	0.63 ± 6.78	0.31 ± 2.96	0.7847
	Variation <sup>b</sup>	-1.27 ± 6.91	-0.18 ± 4.20	0.3989
Miosis rate (%)	Before load	35.66 ± 10.51	34.97 ± 11.74	0.7812
	After load	33.06 ± 11.14	38.90 ± 11.20	0.0219
	After rest	33.13 ± 10.66	35.63 ± 11.85	0.3235
	Variation <sup>a</sup>	-2.61 ± 10.86	3.93 ± 10.27	0.0071
	Variation <sup>b</sup>	0.07 ± 8.82	-3.27 ± 10.76	0.1331

Data are expressed as mean ± SD. Comparisons between two groups were performed by unpaired Student's *t*-test. Before load, value recorded before Uchida–Kraepelin workload; after load, value recorded after Uchida–Kraepelin workload; after rest, value recorded after rest; variation <sup>a</sup>,



difference in each value between before and after Uchida–Kraepelin workload, variation <sup>b</sup>, difference in each value between after Uchida–Kraepelin workload and after rest.

**Table S5. Subjective symptom of fatigue.**

Symptom	KW3110			Placebo		
	week 0	week 4	week 8	week 0	week 4	week 8
	44.20 ± 21.28	39.90 ± 18.67	40.23 ± 21.58	47.43 ± 15.75	46.25 ± 18.25	38.18 ± 17.77 <sup>##</sup>
Change from week-0 value		-4.30 ± 25.63	-3.98 ± 25.73		-1.18 ± 17.37	-9.25 ± 16.77 <sup>##</sup>

Data are expressed as mean ± SD. Comparisons of values between the two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate. Comparisons of changes in value from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA. Within-group comparisons between week 0 and week 4 or 8 were performed by repeated-measures ANOVA followed by LSD test (<sup>##</sup>,  $P < 0.01$ ).

Table S6. Profile of mood states.

Parameters	KW3110			Placebo		
	week 0	week 4	week 8	week 0	week 4	week 8
TMD	44.73 ± 6.80	42.53 ± 6.52 <sup>#</sup>	41.55 ± 5.64 <sup>##</sup>	45.63 ± 6.78	45.38 ± 8.53	43.13 ± 6.77 <sup>#</sup>
	Change from week-0value	-2.20 ± 5.37 <sup>#</sup>	-3.18 ± 6.18 <sup>##</sup>		-0.25 ± 8.59	-2.50 ± 5.86 <sup>#</sup>
AH	44.13 ± 5.64	42.70 ± 5.78	40.73 ± 4.27 <sup>##</sup>	46.08 ± 7.89	45.28 ± 10.13	43.60 ± 8.58
	Change from week-0 value	-1.43 ± 6.02	-3.40 ± 6.22 <sup>##</sup>		-0.80 ± 10.69	-2.48 ± 8.28
CB	44.08 ± 7.30	41.83 ± 6.53 <sup>#</sup>	39.38 ± 6.28 <sup>##</sup>	44.53 ± 7.28	43.08 ± 8.55	40.68 ± 8.16 <sup>##</sup>
	Change from week-0value	-2.25 ± 7.24 <sup>#</sup>	-4.70 ± 7.96 <sup>##</sup>		-1.45 ± 6.58	-3.85 ± 5.76 <sup>##</sup>
DD	45.75 ± 6.46	43.58 ± 4.78 <sup>*,##</sup>	42.65 ± 4.32 <sup>##</sup>	46.08 ± 6.62	46.43 ± 8.00	44.43 ± 5.10
	Change from week-0 value <sup>\$</sup>	-2.18 ± 4.76 <sup>##</sup>	-3.10 ± 5.34 <sup>##</sup>		0.35 ± 8.17	-1.65 ± 5.11
FI	47.08 ± 8.40	44.50 ± 9.14 <sup>#</sup>	42.95 ± 7.99 <sup>##</sup>	45.98 ± 6.83	45.35 ± 8.70	43.03 ± 7.86 <sup>#</sup>
	Change from week-0 value	-2.58 ± 8.34 <sup>#</sup>	-4.13 ± 8.19 <sup>##</sup>		-0.63 ± 9.45	-2.95 ± 8.95 <sup>#</sup>

Table S6. (continued)

Parameters	KW3110			Placebo		
	week 0	week 4	week 8	week 0	week 4	week 8
TA	46.85 ± 8.11	42.53 ± 7.55 <sup>##</sup>	42.38 ± 8.37 <sup>##</sup>	46.83 ± 9.03	45.40 ± 10.06	42.58 ± 9.45 <sup>##</sup>
	Change from week-0 value	-4.33 ± 7.49 <sup>##</sup>	-4.48 ± 8.12 <sup>##</sup>		-1.43 ± 9.54	-4.25 ± 7.18 <sup>##</sup>
VA	53.05 ± 10.29	51.43 ± 11.97	48.68 ± 10.94 <sup>##</sup>	50.70 ± 8.41	48.10 ± 9.95 <sup>#</sup>	47.95 ± 10.55 <sup>#</sup>
	Change from week-0 value	-1.63 ± 9.75	-4.38 ± 9.51 <sup>##</sup>		-2.60 ± 7.47 <sup>#</sup>	-2.75 ± 8.60 <sup>#</sup>
F	54.83 ± 10.75	51.60 ± 13.65 <sup>#</sup>	47.98 ± 13.91 <sup>##</sup>	50.93 ± 9.58	45.80 ± 11.87 <sup>##</sup>	44.60 ± 11.24 <sup>##</sup>
	Change from week-0 value	-3.23 ± 10.90 <sup>#</sup>	-6.85 ± 11.41 <sup>##</sup>		-5.13 ± 10.67 <sup>##</sup>	-6.33 ± 9.95 <sup>##</sup>

Data are expressed as mean ± SD. Comparisons of each value between the two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate, followed by LSD test (\$,  $P < 0.05$ ; main effects of ingestion) (\*,  $P < 0.05$ ; effects of ingestion at each time point). Comparisons of changes in each value from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA. Within-group comparisons between week 0 and week 4 or 8 were performed by ANOVA with subjects and times as fixed factors followed by LSD test (<sup>#</sup>,  $P < 0.05$ ; <sup>##</sup>,  $P < 0.01$ ). TMD, total mood disturbance; TA, tension-anxiety; DD, depression–dejection; AH, anger-hostility; VA, vigor-activity; FI, fatigue-interia; CB, confusion-bewilderment; F, friendliness.

**Table S7. Performance during Uchida–Kraepelin workload.**

Parameters	KW3110			Placebo		
	week 0	week 4	week 8	week 0	week 4	week 8
Total workload	114.48 ± 31.96	120.32 ± 33.12 <sup>##</sup>	119.94 ± 36.95 <sup>#</sup>	107.76 ± 29.79	111.00 ± 28.08	111.02 ± 29.21
Change from week-0 value		5.84 ± 9.12 <sup>##</sup>	5.46 ± 12.93 <sup>#</sup>		3.24 ± 13.35	3.26 ± 13.38
Average workload	57.24 ± 15.98	60.16 ± 16.56 <sup>##</sup>	59.97 ± 18.48 <sup>#</sup>	53.88 ± 14.90	55.50 ± 14.04	55.51 ± 14.60
Change from week-0 value		2.92 ± 4.56 <sup>##</sup>	2.73 ± 6.47 <sup>#</sup>		1.62 ± 6.68	1.63 ± 6.69
Primacy effect rate	1.12 ± 0.09	1.11 ± 0.11	1.13 ± 0.12	1.11 ± 0.09	1.11 ± 0.08	1.11 ± 0.09
Change from week-0 value		-0.01 ± 0.09	0.01 ± 0.09		0.00 ± 0.11	0.00 ± 0.10
Upset rate	0.33 ± 0.14	0.34 ± 0.16	0.35 ± 0.20	0.30 ± 0.09	0.34 ± 0.16	0.35 ± 0.17 <sup>#</sup>
Change from week-0 value		0.01 ± 0.11	0.02 ± 0.16		0.04 ± 0.16	0.05 ± 0.15 <sup>#</sup>
Correct answer rate	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.02	0.99 ± 0.01 <sup>#</sup>	0.99 ± 0.01
Change from week-0 value		0.00 ± 0.01	0.00 ± 0.01		0.00 ± 0.01 <sup>#</sup>	0.00 ± 0.02

Table S7. (continued)

Parameters		KW3110			Placebo		
		week 0	week 4	week 8	week 0	week 4	week 8
Total correct answer rate		0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.02	0.99 ± 0.01 <sup>#</sup>	0.99 ± 0.01
	Change from week-0 value		0.00 ± 0.01	0.00 ± 0.01		0.00 ± 0.01 <sup>#</sup>	0.00 ± 0.02
Break effect rate		1.07 ± 0.05	1.04 ± 0.06 <sup>#</sup>	1.04 ± 0.08	1.08 ± 0.06	1.12 ± 0.33	1.05 ± 0.10
	Change from week-0 value		-0.03 ± 0.07 <sup>#</sup>	-0.03 ± 0.10		0.04 ± 0.33	-0.03 ± 0.10
Break growth rate		0.07 ± 0.05	0.04 ± 0.06 <sup>#</sup>	0.04 ± 0.08	0.08 ± 0.06	0.12 ± 0.33	0.05 ± 0.10
	Change from week-0 value		-0.03 ± 0.07 <sup>#</sup>	-0.03 ± 0.10		0.04 ± 0.33	-0.03 ± 0.10

Data are expressed as mean ± SD. Comparisons of each value between the two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate. Comparisons of changes in each value from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA. Within-group comparisons between week 0 and week 4 or 8 were performed by repeated-measures ANOVA followed by LSD test (<sup>#</sup>,  $P < 0.05$ ; <sup>##</sup>,  $P < 0.01$ ).

**Table S8. Circulatory parameters.**

Parameters		KW3110		Placebo	
		before	after	before	after
		ingestion period	ingestion period	ingestion period	ingestion period
SBP (mmHg)		112.73 ± 9.90	115.02 ± 11.12	113.52 ± 15.62	115.91 ± 14.20
	Change from value at Scr		2.29 ± 9.59		2.38 ± 8.26
DBP (mmHg)		72.19 ± 8.36	74.05 ± 9.00	72.73 ± 11.99	73.83 ± 11.14
	Change from value at Scr		1.86 ± 7.60		1.09 ± 6.09
Pulse rate (bpm)		70.10 ± 9.58 **	71.23 ± 9.58	76.05 ± 11.12	77.65 ± 13.31
	Change from value at Scr		1.13 ± 8.60		1.60 ± 13.30

Data are expressed as mean ± SD. Comparisons of each value after the ingestion period between the two groups were performed by two-way repeated-measures ANCOVA with the value before the ingestion period as a covariate. Comparisons of each value before the ingestion period and changes in each value from the value before the ingestion period between the two groups were performed by unpaired Student's *t*-test (\*\*,  $P < 0.01$ ). Within-group comparisons between the values recorded before and after the ingestion period were performed by paired Student's *t*-test. Scr, screening.

**Table S9. Urinalysis.**

Parameters	Reference range	KW3110				Placebo			
		before		after		before		after	
		Ingestion period		ingestion period		Ingestion period		ingestion period	
		In	Out	In	Out	In	Out	In	Out
Protein	-	42	1	38	5	37	6	41	2
Glucose	-	43	0	43	0	43	0	42	1
Urobilinogen	±	43	0	43	0	43	0	41	2
Bilirubin	-	43	0	43	0	43	0	43	0
pH	5.0-7.5	41	2	42	1	41	2	43	0
Occult blood	-	39	4	39	4	34	9	37	6
Ketone body	-	43	0	43	0	42	1	43	0

Data are expressed as the number of subjects whose parameters were inside or outside the reference ranges. Comparisons between the two groups were performed by  $\chi^2$  test. Within-group comparisons between values recorded before and after the ingestion period were performed by McNemar test. In, inside reference range; Out, outside reference range.



**Table S10. Peripheral blood analysis.**

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
WBC (/ $\mu$ L)	3300-9000	Change from value at Scr	5825.58 $\pm$ 1457.18	5695.35 $\pm$ 1148.70	5581.40 $\pm$ 1269.09	5846.51 $\pm$ 1285.51
				-130.23 $\pm$ 1162.41		265.12 $\pm$ 1141.40
RBC ( $\times 10^4$ / $\mu$ L)	Male: 430-570 Female: 380-500	Change from value at Scr	460.72 $\pm$ 48.59	464.07 $\pm$ 45.14	447.14 $\pm$ 38.73	448.60 $\pm$ 40.30
				3.35 $\pm$ 22.96		1.47 $\pm$ 17.14
Hb (g/dL)	Male: 13.5-17.5 Female: 11.5-15.0	Change from value at Scr	13.69 $\pm$ 1.80	13.86 $\pm$ 1.72	13.33 $\pm$ 1.62	13.41 $\pm$ 1.67
				0.17 $\pm$ 0.62		0.08 $\pm$ 0.71
Ht (%)	Male: 39.7-52.4 Female: 34.8-45.0	Change from value at Scr	42.57 $\pm$ 4.33	42.89 $\pm$ 4.05	41.50 $\pm$ 3.97	41.51 $\pm$ 4.14
				0.32 $\pm$ 1.81		0.01 $\pm$ 1.80
Plt ( $\times 10^4$ / $\mu$ L)	14.0-34.0	Change from value at Scr	27.95 $\pm$ 6.55	28.15 $\pm$ 6.85	30.75 $\pm$ 6.55	30.60 $\pm$ 6.80
				0.20 $\pm$ 3.10		-0.15 $\pm$ 2.87

**Table S10. (continued)**

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
MCV (fL)	85-102	Change from value at Scr	92.56 ± 5.56	92.65 ± 5.11 0.09 ± 2.17	92.88 ± 4.86	92.63 ± 5.06 -0.26 ± 2.41
MCH (pg)	28.0-34.0	Change from value at Scr	29.73 ± 2.37	29.87 ± 2.36 0.14 ± 0.70	29.79 ± 2.35	29.87 ± 2.28 0.09 ± 1.14
MCHC (%)	30.2-35.1	Change from value at Scr	32.08 ± 1.24	32.24 ± 1.25 0.16 ± 0.64	32.04 ± 1.25	32.24 ± 1.13 0.20 ± 0.87
Neutrophil rate (%)	40.0-75.0	Change from value at Scr	61.04 ± 8.31	60.74 ± 7.27 -0.30 ± 6.26	58.95 ± 7.68	60.10 ± 8.43 1.15 ± 6.78
Lymphocyte rate (%)	18.0-49.0	Change from value at Scr	30.62 ± 7.48	30.46 ± 6.09 -0.16 ± 5.91	32.79 ± 7.16	31.38 ± 7.99 -1.40 ± 6.10

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
Monocyte rate (%)	2.0-10.0	Change from value at Scr	5.26 ± 1.42	5.21 ± 1.13	4.73 ± 1.14	4.78 ± 1.21
				-0.05 ± 1.14		0.05 ± 1.17
Eosinophil rate (%)	0.0-8.0	Change from value at Scr	2.43 ± 2.35	2.84 ± 2.28	2.82 ± 2.01	3.07 ± 2.46
				0.41 ± 2.42		0.25 ± 1.63
Basophil rate (%)	0.0-2.0	Change from value at Scr	0.64 ± 0.50	0.75 ± 0.45	0.71 ± 0.46	0.67 ± 0.49
				0.10 ± 0.37		-0.04 ± 0.38
Neutrophils (/μL)	-	Change from value at Scr	3633.81 ± 1299.09	3502.98 ± 986.83	3333.25 ± 1047.81	3566.33 ± 1089.72
				-130.83 ± 978.72		233.08 ± 1012.05
Lymphocytes (/μL)	-	Change from value at Scr	1712.99 ± 329.63	1692.58 ± 321.12	1791.45 ± 453.90	1789.20 ± 481.25
				-20.41 ± 342.70		-2.25 ± 282.40

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
Monocytes (/μL)	-	Change from the value at Scr	303.39 ± 104.52	295.78 ± 83.12 -7.60 ± 71.63	263.33 ± 81.69	275.02 ± 83.43 11.69 ± 87.77
Eosinophils (/μL)	-	Change from value at Scr	139.90 ± 135.12	161.33 ± 133.57 21.43 ± 139.96	155.50 ± 115.01	178.36 ± 150.22 22.86 ± 90.77
Basophils (/μL)	-	Change from value at Scr	35.50 ± 25.40	42.67 ± 25.19 <sup>#</sup> 7.17 ± 20.75 <sup>#</sup>	37.86 ± 22.47	37.60 ± 26.82 -0.26 ± 18.49
AST (U/L)	10-40	Change from value at Scr	20.09 ± 4.82	20.28 ± 6.29 0.19 ± 3.92	19.58 ± 5.27	18.98 ± 6.40 -0.60 ± 5.07
ALT (U/L)	5-45	Change from value at Scr	17.09 ± 6.83	17.40 ± 8.75 0.30 ± 5.61	18.40 ± 10.78	16.95 ± 9.90 -1.44 ± 7.40

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
γ-GTP (U/L)	Male: ≤80 Female: ≤30	Change from value at Scr	28.40 ± 23.13	29.02 ± 23.79	21.67 ± 13.32	21.05 ± 12.57
				0.63 ± 13.08		-0.63 ± 5.80
ALP (U/L)	100-325	Change from value at Scr	173.37 ± 44.40	174.84 ± 61.10	180.72 ± 63.69	175.77 ± 59.42
				1.47 ± 28.72		-4.95 ± 20.40
LDH (U/L)	120-240	Change from value at Scr	170.26 ± 23.97	170.12 ± 25.08	173.28 ± 24.49	175.28 ± 24.25
				-0.14 ± 10.28		2.00 ± 16.77
LAP (U/L)	Male: 45-81 Female: 37-61	Change from value at Scr	49.16 ± 11.32	49.63 ± 11.17	49.33 ± 6.77	49.14 ± 7.41
				0.47 ± 4.51		-0.19 ± 3.69
Total bilirubin (mg/dL)	0.2-1.2	Change from value at Scr	0.86 ± 0.31	0.84 ± 0.27	0.80 ± 0.30	0.78 ± 0.27
				-0.02 ± 0.29		-0.02 ± 0.26

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
Direct bilirubin (mg/dL)	0.0-0.2	Change from value at Scr	0.07 ± 0.05	0.07 ± 0.05	0.06 ± 0.05	0.07 ± 0.05
				0.00 ± 0.05		0.01 ± 0.06
Indirect bilirubin (mg/dL)	0.2-1.0	Change from value at Scr	0.79 ± 0.28	0.77 ± 0.24	0.74 ± 0.26	0.71 ± 0.25
				-0.01 ± 0.27		-0.03 ± 0.23
Cholinesterase (U/L)	Male: 234-493 Female: 200-452	Change from value at Scr	314.23 ± 69.36	316.30 ± 74.74	298.70 ± 65.30	301.79 ± 65.42
				2.07 ± 21.09		3.09 ± 19.27
Total protein (g/dL)	6.7-8.3	Change from value at Scr	6.97 ± 0.43	7.10 ± 0.34 <sup>#</sup>	7.02 ± 0.44	7.08 ± 0.37
				0.13 ± 0.35 <sup>#</sup>		0.06 ± 0.34
Urea nitrogen (mg/dL)	8.0-20.0	Change from value at Scr	12.52 ± 3.09	12.71 ± 2.99	12.33 ± 2.69	12.60 ± 2.61
				0.19 ± 2.74		0.27 ± 2.36

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
Creatinine (mg/dL)	Male: 0.61-1.04	Change from value at Scr	0.70 ± 0.14	0.69 ± 0.14	0.65 ± 0.12	0.65 ± 0.13
	Female: 0.47-0.79			-0.01 ± 0.05		0.00 ± 0.05
Uric acid (mg/dL)	Male: 3.8-7.0	Change from value at Scr	5.04 ± 1.34 *	4.86 ± 1.24	4.46 ± 1.31	4.40 ± 1.33
	Female: 2.5-7.0			-0.18 ± 0.59		-0.06 ± 0.52
CK (U/L)	Male: 60-270	Change from value at Scr	103.40 ± 56.42	108.95 ± 60.69	108.14 ± 63.92	107.14 ± 53.81
	Female: 40-150			5.56 ± 49.40		-1.00 ± 48.77
Na (mEq/L)	137-147	Change from value at Scr	139.95 ± 1.91	139.84 ± 2.02	139.95 ± 1.50	139.91 ± 1.38
				-0.12 ± 1.43		-0.05 ± 1.51
K (mEq/L)	3.5-5.0	Change from value at Scr	4.43 ± 0.45	4.37 ± 0.34	4.30 ± 0.38	4.31 ± 0.33
				-0.06 ± 0.45		0.00 ± 0.37

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
Cl (mEq/L)	98-108	Change from value at Scr	101.47 ± 1.68	101.72 ± 1.76 0.26 ± 1.63	101.74 ± 1.60	101.93 ± 1.71 0.19 ± 1.78
Ca (mg/dL)	8.4-10.4	Change from value at Scr	9.09 ± 0.36	9.11 ± 0.39 0.02 ± 0.34	9.06 ± 0.26	9.06 ± 0.37 0.00 ± 0.34
Inorganic phosphorus (mg/dL)	2.5-4.5	Change from value at Scr	3.27 ± 0.57	3.14 ± 0.50 -0.13 ± 0.55	3.27 ± 0.58	3.28 ± 0.44 0.01 ± 0.49
Fe (µg/dL)	Male: 50-200 Female: 40-180	Change from value at Scr	100.23 ± 55.63	98.05 ± 41.99 -2.19 ± 51.95	94.84 ± 42.05	96.86 ± 44.80 2.02 ± 42.44
Amylase (U/L)	40-122	Change from value at Scr	80.44 ± 24.11	80.56 ± 23.88 0.12 ± 12.89	78.67 ± 22.46	77.51 ± 20.83 -1.16 ± 11.41



Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
Total cholesterol (mg/dL)	120-219	Change from value at Scr	201.72 ± 31.97	205.67 ± 39.37 3.95 ± 19.59	210.93 ± 35.55	214.44 ± 36.52 3.51 ± 17.11
HDL-cholesterol (mg/dL)	Male: 40-85 Female: 40-95	Change from value at Scr	67.05 ± 17.64	66.86 ± 18.20 -0.19 ± 4.78	69.56 ± 18.65	71.53 ± 19.32 1.98 ± 6.69
LDL-cholesterol (mg/dL)	65-139	Change from value at Scr	117.26 ± 29.33	120.91 ± 34.66 3.65 ± 15.59	124.70 ± 32.13	127.26 ± 35.88 2.56 ± 14.89
TG (mg/dL)	30-149	Change from value at Scr	96.23 ± 71.46	101.44 ± 69.54 5.21 ± 37.58	89.26 ± 78.89	86.47 ± 49.73 -2.79 ± 60.92
Glucose (mg/dL)	70-109	Change from value at Scr	81.35 ± 6.55	82.77 ± 7.98 1.42 ± 5.93	83.44 ± 7.58	85.05 ± 8.23 1.60 ± 8.50

Table S10. (continued)

Parameters	Reference range		KW3110		Placebo	
			before	after	before	after
			Ingestion period	ingestion period	Ingestion period	ingestion period
HbA1c (%)	4.6-6.2	Change from value at Scr	5.24 ± 0.22	5.27 ± 0.21	5.30 ± 0.26	5.33 ± 0.26
				0.03 ± 0.21		0.04 ± 0.17
Glycoalbumin (%)	12.3-16.5	Change from value at Scr	13.71 ± 1.13	13.79 ± 1.26	13.94 ± 1.24	13.93 ± 1.12
				0.08 ± 0.60		-0.01 ± 0.68

Data are expressed as mean ± SD. Comparisons of each value after the ingestion period between the two groups were performed by two-way repeated-measures ANCOVA with the value before the ingestion period as a covariate. Comparisons of each value before the ingestion period and changes in each value from the value before the ingestion period between the two groups were performed by unpaired Student's *t*-test (\*,  $P < 0.05$ ). Within-group comparisons between the values recorded before and after the ingestion period were performed by paired Student's *t*-test (#,  $P < 0.05$ ).

**Table S11. Ophthalmic analysis.**

Parameter	KW3110								Placebo							
	Scr		week 0		week 4		week 8		Scr		week 0		week 4		week 8	
Eyesight (average of both eyes)	0.61 ± 0.54		0.55 ± 0.51		0.59 ± 0.57		0.63 ± 0.58		0.57 ± 0.53		0.54 ± 0.52		0.54 ± 0.49		0.52 ± 0.48	
	Change from week-0 value				-0.02 ± 0.27		0.02 ± 0.43						-0.03 ± 0.20		-0.05 ± 0.20	
Eyesight (dominant eye)	0.61 ± 0.53		0.55 ± 0.51		0.60 ± 0.59		0.68 ± 0.84		0.57 ± 0.53		0.56 ± 0.52		0.53 ± 0.49		0.51 ± 0.48	
	Change from week-0 value				-0.01 ± 0.32		0.07 ± 0.78						-0.05 ± 0.24		-0.07 ± 0.22	
Eyesight (non-dominant eye)	0.61 ± 0.58		0.56 ± 0.53		0.58 ± 0.57		0.58 ± 0.54		0.57 ± 0.56		0.53 ± 0.54		0.55 ± 0.51		0.53 ± 0.50	
	Change from week-0 value				-0.04 ± 0.26		-0.03 ± 0.24						-0.02 ± 0.22		-0.04 ± 0.25	
Eyesight (right eye)	0.63 ± 0.55		0.55 ± 0.52		0.62 ± 0.61		0.59 ± 0.53		0.56 ± 0.52		0.54 ± 0.51		0.52 ± 0.48		0.51 ± 0.47	
	Change from week-0 value				-0.01 ± 0.29		-0.04 ± 0.20						-0.04 ± 0.24		-0.05 ± 0.20	

Table S11. (continued)

Parameter	KW3110				Placebo			
	Scr	week 0	week 4	week 8	Scr	week 0	week 4	week 8
Eyesight (left eye)	0.60 ± 0.56	0.55 ± 0.52	0.56 ± 0.56	0.67 ± 0.84	0.59 ± 0.56	0.54 ± 0.55	0.57 ± 0.52	0.53 ± 0.50
Change from week-0 value			-0.04 ± 0.29	0.08 ± 0.79			-0.02 ± 0.22	-0.06 ± 0.26
Intraocular pressure (average of both eyes) (mmHg)	\$ 13.93 ± 2.44	13.86 ± 2.38	13.44 ± 2.88 *	13.97 ± 2.75	14.67 ± 2.73	14.44 ± 2.79	14.94 ± 2.76	15.06 ± 3.10
Change from week-0 value \$			-0.49 ± 1.98	0.03 ± 2.07			0.26 ± 1.84	0.39 ± 1.89
Intraocular pressure (dominant eye) (mmHg)	\$\$ 13.89 ± 2.84	14.21 ± 3.16	13.47 ± 3.50	14.07 ± 3.25	14.71 ± 2.97	14.35 ± 2.99	15.05 ± 2.97	15.26 ± 3.71
Change from week-0 value \$\$			-0.43 ± 2.47	0.18 ± 2.36			0.34 ± 2.15	0.54 ± 2.48
Intraocular pressure (non-dominant eye) (mmHg)	13.98 ± 2.49	13.51 ± 2.39	13.42 ± 2.74 *	13.86 ± 2.58	14.63 ± 2.73	14.53 ± 2.84	14.82 ± 2.99	14.87 ± 2.80
Change from week-0 value			-0.56 ± 2.06	-0.12 ± 2.28			0.19 ± 2.27	0.23 ± 2.10

Table S11. (continued)

Parameter	KW3110				Placebo			
	Scr	week 0	week 4	week 8	Scr	week 0	week 4	week 8
Intraocular pressure (right eye) (mmHg)	13.76 ± 2.58	14.26 ± 2.75	13.26 ± 2.81 *	14.00 ± 2.58	14.77 ± 2.88	14.40 ± 2.95	14.98 ± 3.08	14.81 ± 3.22
Change from week-0 value			-0.50 ± 2.16	0.24 ± 2.30			0.22 ± 2.25	0.05 ± 2.15
Intraocular pressure (left eye) (mmHg)	14.11 ± 2.76	13.47 ± 2.84	13.63 ± 3.43	13.93 ± 3.25	14.58 ± 2.82	14.49 ± 2.89	14.89 ± 2.88	15.31 ± 3.34 #
Change from week-0 value			-0.48 ± 2.39	-0.18 ± 2.33			0.31 ± 2.17	0.73 ± 2.39 #

Data are expressed as mean ± SD. Comparisons of each value between the two groups were performed by two-way repeated-measures ANCOVA with the week-0 value as a covariate, followed by LSD test (\$,  $P < 0.05$ ; main effects of ingestion) (\*,  $P < 0.05$ ; effects of ingestion at each time point). Comparisons in changes of each value from the week-0 value between the two groups were performed by two-way repeated-measures ANOVA. Within-group comparisons between week 0 and week 4 or 8 were performed by repeated-measures ANOVA followed by LSD test (#,  $P < 0.05$ ).



**Table S12. (continued)**

Symptoms	KW3110						Placebo					
	week 0		week 4		week 8		week 0		week 4		week 8	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Pollakiuria	0	43	0	43	0	43	1	42	0	43	0	43
Hot flashes	0	43	0	43	0	43	0	43	0	43	0	43
Sleep deprivation	1	42	0	43	0	43	1	42	0	43	1	42
Dry mouth	0	43	0	43	0	43	0	43	0	43	0	43
Others	0	43	1	42	0	43	1	42	0	43	1	42

Data are expressed as the number of subjects who answered “Yes” or “No” to each question. The comparisons between two groups were performed by a  $\chi^2$  test. The within-group comparisons between week 0 and week 4 or 8 were performed by a McNemar test.

**Table S13. Primer sequences used for quantitative real-time RT-PCR.**

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
<i>GAPDH</i>	AGGCTAGCTGGCCCGATTTTC	TGGCAACAATATCCACTTTACCAGA
<i>p53</i>	CATCCTCACCATCATCACAC	CTCCATCCAGTGGTTTCTTC
<i>p21</i>	CGATGGAACCTTCGACTTTGT	AGGCACAAGGGTACAAGA
<i>IL-6</i>	CTCCAGAACAGATTTGAGAGTAG	GCGCAGAATGAGATGAGTT
<i>IL-8</i>	CTCTTGGCAGCCTTCCT	AGACAGAGCTCTCTTCCATC
<i>IL-1<math>\beta</math></i>	CTGTCCTGCGTGTTGAAAGATG	TTCTGCTTGAGAGGTGCTGATG
<i>ZO-1</i>	GAAGCTGATGGTGTGGATAG	GTCTGGTTTGGACACTAAGG
<i>claudin-1</i>	GATGAGGTGCAGAAGATGAG	GGACAGGAACAGCAAAGTAG