

Table S1. Time-dependent changes in questionnaire scores.

Questionnaire	Probability for each factor			Treatment	Scores		
	Treatment	Time	Time x Treatment		Week 0	Week 12	Week 24
STAI state anxiety	0.786	< 0.001	0.670	CP2305	37.1 ± 1.6	34.2 ± 1.5	45.9 ± 1.7
				Placebo	35.8 ± 1.6	35.1 ± 1.9	43.4 ± 2.2
STAI trait anxiety	0.014 *	0.699	0.093	CP2305	41.8 ± 1.8	37.7 ± 1.6	39.9 ± 1.2
				Placebo	39.7 ± 1.8	38.2 ± 1.8	40.8 ± 2.2
HADS anxiety	0.072	0.007	0.397	CP2305	4.8 ± 0.5	4.6 ± 0.5	5.5 ± 0.6
				Placebo	4.3 ± 0.5	5.4 ± 0.7	5.6 ± 0.7
HADS depression	0.071	0.003	0.800	CP2305	5.8 ± 0.5	5.0 ± 0.6	7.0 ± 0.8
				Placebo	5.2 ± 0.6	6.3 ± 0.8	6.7 ± 0.7
GHQ-28 total	0.615	0.013	0.667	CP2305	4.1 ± 0.7	3.6 ± 0.6	5.0 ± 0.6
				Placebo	3.7 ± 0.6	3.1 ± 0.6	4.9 ± 0.8
GHQ-28 depression	0.022 *	0.545	0.249	CP2305	0.06 ± 0.04	0.00 ± 0.00	0.03 ± 0.03
				Placebo	0.07 ± 0.07	0.22 ± 0.12	0.66 ± 0.12
PSQI global score	0.041 *	0.542	0.143	CP2305	4.2 ± 0.4	4.1 ± 0.5	3.9 ± 0.4
				Placebo	3.4 ± 0.3	3.9 ± 0.4	4.1 ± 0.5

Data are shown as the means ± SEM.

\*Significant different between CP2305 and placebo groups ( $p < 0.05$  by repeated-measures ANOVA).

Table S2. Time-dependent changes in salivary stress markers.

Parameters	Probability for each factor			Treatment	Values		
	Treatment	Time	Time x Treatment		Week 0	Week 12	Week 24
Chromogranin A (pmol/mg protein)	0.039 *	0.001	0.056	CP2305	21.0 ± 2.8	13.8 ± 2.2	10.8 ± 2.1
				Placebo	15.2 ± 2.9	10.5 ± 2.2	12.5 ± 2.2
cortisol (µg/dL)	0.086	< 0.001	0.716	CP2305	0.14 ± 0.02	0.28 ± 0.03	0.28 ± 0.03
				Placebo	0.14 ± 0.02	0.18 ± 0.03	0.26 ± 0.03

Data are shown as the means ± SEM. \*Significant different between CP2305 and placebo groups ( $p < 0.05$  by repeated-measures ANOVA).

Table S3. Time-dependent changes in stool properties and bowel habits.

Questionnaire	Probability for each factor			Treatment	Scores		
	Treatment	Time	Time x Treatment		Week 0	Week 12	Week 24
Frequency of bowel movement	0.965	0.533	0.987	CP2305	9.6 ± 0.7	9.5 ± 0.8	9.4 ± 1.0
				Placebo	9.2 ± 0.8	9.2 ± 1.1	9.1 ± 0.7
Output	0.677	0.356	0.833	CP2305	25.3 ± 2.4	25.4 ± 2.3	24.2 ± 2.1
				Placebo	26.0 ± 3.1	25.0 ± 4.0	24.6 ± 2.5
Form	0.546	0.011	0.791	CP2305	4.0 ± 0.1	4.0 ± 0.1	3.7 ± 0.1
				Placebo	4.0 ± 0.1	3.6 ± 0.2	3.7 ± 0.2
Color	0.002 *	0.320	0.079	CP2305	3.5 ± 0.1	3.6 ± 0.2	3.6 ± 0.1
				Placebo	3.6 ± 0.1	3.2 ± 0.1	3.3 ± 0.1

Data are shown the means ± SEM.

\*Significant different between CP2305 and placebo groups ( $p < 0.05$  by repeated-measures ANOVA).

Table S4. Gender-stratified analysis of salivary cortisol.

Parameters	Probability for each factor			Treatment	Values ( $\mu\text{g/dL}$ )		
	Treatment	Time	Time x Treatment		Week 0	Week 12	Week 24
Women	0.251	0.016	0.645	CP2305	$0.14 \pm 0.03$	$0.26 \pm 0.06$	$0.29 \pm 0.08$
				Placebo	$0.11 \pm 0.02$	$0.13 \pm 0.02$	$0.21 \pm 0.05$
Men	0.208	< 0.001	0.926	CP2305	$0.14 \pm 0.02$	$0.28 \pm 0.04$	$0.28 \pm 0.04$
				Placebo	$0.15 \pm 0.03$	$0.21 \pm 0.03$	$0.28 \pm 0.03$

Data are shown as the means  $\pm$  SEM. Probability for each factor was analyzed using two-way ANOVA with repeated measures.