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Protective effects of fermented honeybush (*Cyclopia intermedia)* extract (HU-018) against skin aging: a randomized, double-blinded, placebo-controlled study

Sun Young Choi[a], Ji Yeon Hong[b], Eun Jung Ko[c], Beom Joon Kim[b], Sung-Woon Hong[d], Mi Hyoung Lim[d], Sung Hum Yeon[e], and Rak Ho Son[e]

[a]Department of Dermatology, Seoul Paik Hospital, Inje University College of Medicine, Seoul, Korea; [b]Department of Dermatology, Chung-Ang University College of Medicine, Seoul, Korea; [c]Department of Dermatology, Myongji Hospital, Seonam University College of Medicine, Goyang, Korea; [d]Department of Clinical Research & Medical information, Huons Co., Ltd., Gyeonggi-do, Korea; [e]Botanical Drug Research Team, Huons Co., Ltd., Gyeonggi-do, Korea

ABSTRACT

Background: Oxidative stress and photodamage resulting from ultraviolet radiation exposure play key roles in skin aging. Fermented *Cyclopia intermedia*, which is used to brew honeybush tea, exerts antioxidant and anti-wrinkle effects by inhibiting reactive oxygen species production and downregulating matrix metalloproteinase activity. **Objectives**: This randomized, double-blinded, placebo-controlled study aimed to evaluate the efficacy and safety of fermented honeybush (*Cyclopia intermedia)* extract (HU-018) for skin rejuvenation. **Methods**: 120 Korean subjects with crow's feet wrinkles were randomized to receive either low-dose extract (400 mg/day), high-dose extract (800 mg/day), or placebo (negative control, only dextran) for 12 weeks. Wrinkles were evaluated using JANUS® and PRIMO pico®. Skin elasticity, hydration and transepidermal water loss were measured. **Results**: Global skin wrinkle grade was significantly improved in both low-dose and high-dose groups compared to placebo group, as well as for skin hydration and elasticity. Both the low- and high-dose groups showed significantly decreased TEWL compared to the placebo group. There were no adverse effects during the entire study period. **Conclusion**: Our data indicate that HU-018 is effective for improving skin wrinkles, elasticity, and hydration. Therefore, daily supplementation with fermented honeybush could be helpful for protecting against skin aging.

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Fermented *Cyclopia intermedia*; honeybush; skin aging

Introduction

Skin aging is usually classified as either chronological or photo-induced aging. Chronological aging, otherwise referred to as intrinsic aging, occurs inevitably throughout the skin by genetically programmed processes that occur as the body ages. Photo-induced aging, otherwise known as extrinsic aging, results mainly from chronic sun exposure. Oxidative stress and photodamage related to ultraviolet (UV) radiation exposure play key roles in skin aging (1,2).

Aging skin changes due to gradual physiologic decline (3). Age-related loss of normal dermal collagen and elasticity fibers occurs, and age-related epidermal thinning is accompanied by a decrease in the water content of the stratum corneum (4–7). UV radiation exposure accelerates skin damage by causing oxidative stress and decreasing the collagen content, which results from increased matrix metalloproteinase (MMP) activity and the inhibition of collagen synthesis (8,9). Therefore, age-related changes in the skin manifest as wrinkles, laxity, dryness, roughness, and inelasticity.

Fermented *Cyclopia intermedia* is used to brew honeybush tea, an herbal tea indigenous to South Africa. Honeybush is a flowering plant similarity to rooibos, and is found only in the cape region of South Africa (10,11). *Cyclopia intermedia* has been shown to exert antioxidant effects by inhibiting reactive oxygen species (12,13); moreover, fermented *C. intermedia* has demonstrated anti-wrinkle effects by suppressing collagen degradation in both *in vitro* and *in vivo* studies (14,15). Therefore, here we aimed to evaluate the effect of fermented honeybush (*C. intermedia)* extract (HU-018) on skin aging properties—including wrinkles, elasticity, and hydration—in a randomized, double-blinded, placebo-controlled trial.

Materials and methods

Study design

In this 12-week, randomized, double-blinded, placebo-controlled trial, subjects were randomly assigned to one of three treatment regimens: low-dose extract (HU-018 400 mg/day), high-dose extract (HU-018 800 mg/day), or placebo (negative control, only dextran). Participants were assigned to the regimens at a 1: 1: 1 ratio using a computer-generated randomization schedule. The study protocol conformed to the guidelines of the Declaration of Helsinki and the Korea Good Clinical Practice guidelines. This study was approved by the institutional review board of Chung-Ang University Hospital (Protocol no. C2015137(1595)).

CONTACT Beom Joon Kim beomjoon@unitel.co.kr Department of Dermatology, Chung-Ang University Hospital 224-1 Heukseok-dong, Dongjak-ku, Seoul 156-755, South Korea.

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Subjects

One hundred twenty healthy Korean subjects were enrolled in this study. Subjects were required to be between 35 and 60 years old and to have moderate to severe crow's feet wrinkles. We used the global skin wrinkle grade, which evaluated wrinkles on a scale of zero to nine, suggested in 'Guideline for Efficacy Evaluation of Functional Cosmetics' published by Korean Ministry of Food and Drug Safety. The inclusion criteria included crow's feet wrinkles higher than score 3. The exclusion criteria included a history of any cutaneous disease including infectious or eczematoid dermatitis on the face, another systemic disease, pregnancy and lactation. Subjects with a history of tissue augmentation or botulinum toxin injection within the previous 6 months, laser therapy or chemical peeling within the previous month, immunosuppressive therapy including corticosteroids within the last 3 months, and hypersensitivity or allergy to dietary supplements were also excluded. All subjects voluntarily participated in the study and provided written informed consent after a full explanation of the risks and benefits of the procedure.

Preparation of fermented honeybush extract powder (HU-018)

Honeybush (*C. intermedia*) was purchased from Rooibos Ltd. (Western Cape, South Africa; www.rooibosltd.co.za); lactic acid bacterium (*Streptococcus thermophilus*) was purchased from Lallemand Health Solutions Inc. (Montreal, Canada; www.lallemand-health-solutions.com). For the preparation of honeybush extract, honeybush was extracted twice with water under reflux and then filtered. For use in the clinical trial, capsules were filled with 100 mg HU-018, 200 mg HU-018, or dextran.

Interventions

All subjects were randomized to receive low dose (HU-018 400 mg/day), high dose (HU-018 800 mg/day), or placebo (negative control, only dextran) twice a day. Forty subjects were included in each group. The entire period of supplement administration was 12 weeks.

Efficacy and safety evaluation

For efficacy and safety evaluation, all subjects were instructed to visit every 4 weeks. Measurements of skin properties including wrinkles, elasticity, and hydration were performed in triplicate at baseline (0 weeks), 4 weeks, 8 weeks, and 12 weeks by the same blinded investigator.

To evaluate the degree of skin wrinkles on the crow's feet, the global skin wrinkle grade (0: no wrinkles, 9: maximum wrinkles) was assessed using a JANUS® instrument (PSI Co., Ltd., Korea). The blinded investigator graded the score on each side of the crow's feet. To evaluate the volume of skin wrinkles on the crow's feet, a GFM PROMOS pico® system (GFM, Berlin, Germany) was used. Average roughness (Ra) and eye wrinkle volume were measured on each side of the crow's feet. Skin elasticity was measured on each side of the cheek using a Cutometer CM580® instrument (Courage+Khazaka electronic GmbH, Cologne, Germany). The R2 value (skin redeformation) was measured, which reflects the general elasticity of skin; values close to 1 indicate highly elastic skin. Skin hydration and transepidermal water loss were measured on each side of the cheek using a Corneometer® (Courage+Khazaka electronic GmbH, Cologne, Germany) and a Tewameter® (Courage+Khazaka electronic GmbH, Cologne, Germany), respectively. Both the investigator and the subject assessed the Global Aesthetic Improvement Scale (GAIS) score (1 = much improved; 2 = improved; 3 = no change; 4 = worse; 5 = much worse) at every visit.

All adverse events occurring during the entire study period were recorded in a safety evaluation. For each adverse event, the degree of symptoms and relationship with the test product were evaluated to determine the most appropriate action and whether or not the participant should continue to participate. For evaluation of systemic abnormalities, laboratory tests including complete blood count, chemistry battery, lipid battery, and urine analysis were performed at baseline and at 12 weeks.

Statistical analysis

Statistical analyses were performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). To determine the significance of differences within groups, the paired *t*-test was used. To determine the significance of differences between groups, one-way analysis of variance (ANOVA) was used. Data are presented as mean ± standard deviation. *P*-values < 0.05 were considered statistically significant.

Results

A total of 120 Korean subjects were enrolled and randomized in this study. Since five subjects were withdrawn, 115 subjects (low-dose group: $n = 39$, high-dose group: $n = 38$, and placebo group: $n = 38$) completed the study. The mean subject age was 51.33 ± 4.59 years in low-dose group, 49.70 ± 5.79 years in high-dose group, and 50.40 ± 5.31 years in placebo group. Only female subjects were enrolled.

The global skin wrinkle grade was significantly improved in treatment groups at 4, 8, and 12 weeks. Statistically significantly different changes were observed from baseline between low-dose group and placebo group, and between high-dose group and placebo group, but there were no significantly different changes from baseline between low-dose and high-dose groups at 12 weeks. The global skin wrinkle grades are shown in Table 1 and dermoscope images of crow's feet from representative subjects are shown in Figure 1. Serial PRIMOS lite® images of crow's feet areas at baseline, 4 weeks, 8 weeks, and 12 weeks are shown in Figure 2, which demonstrates gradual improvement of skin wrinkles over time, with the most significant change in placebo group.

The percentages (%) of change in Ra and eye wrinkle volume were also calculated. Ra was decreased by 71.43 ± 16.95 (%) in the low-dose group, 71.60 ± 21.23 (%) in the high-dose group, and 54.26 ± 24.51 (%) in the placebo

Table 1. Global skin wrinkle grade as measured using a JANUS® instrument.

	Low dose	High dose	Control	*P*-value#
Baseline (week 0)	6.34 ± 1.63	5.79 ± 1.79	6.46 ± 1.77	0.2331
Week 4	6.12 ± 1.71	5.50 ± 1.86	6.40 ± 1.80	0.5099
Week 8	5.88 ± 1.67	5.27 ± 1.84	6.41 ± 1.80	0.0567
Week 12	5.57 ± 1.58	5.01 ± 1.75	6.43 ± 1.80	0.0003**
Difference (week 0–week 4)	−0.22 ± 0.41	−0.29 ± 0.39	−0.06 ± 1.33	
P-value##	0.0037**	0.0001**	0.7981	
Difference (week 0–week 8)	−0.46 ± 0.50	−0.51 ± 0.51	−0.04 ± 1.34	
P-value##	<0.0001**	<0.0001**	0.8488	
Difference (week 0–week 12)	−0.76 ± 0.45	−0.77 ± 0.43	−0.03 ± 1.34	
P-value##	<0.0001**	<0.001**	0.8987	

#: compared between groups; *p*-value by one-way ANOVA
##: compared within groups; *p*-value by the paired *t*-test
* $p < 0.05$, ** $p < 0.005$

group at 12 weeks. There were statistically significantly different changes between low-dose group and placebo group, and between high-dose group and placebo group at 12 weeks. Eye wrinkle volume was decreased by 28.69 ± 17.69 (%) in low-dose group, 27.79 ± 25.08 (%) in high-dose group, and 0.14 ± 22.06 (%) in placebo group at 12 weeks. There were statistically significant differences between low-dose group and placebo group, and between high-dose group and placebo group at 8 weeks and 12 weeks (Table 2).

The skin elasticity (R2 value) was significantly increased in the treatment groups at 8 weeks and 12 weeks. There were statistically significant differences between low-dose group and placebo group, and between high-dose group and placebo group, but there were no significant differences between low-dose and high-dose groups at 8 weeks and 12 weeks. The R2 values are shown in Table 3.

Skin hydration was significantly increased in both treatment groups at 4, 8, and 12 weeks. There were statistically

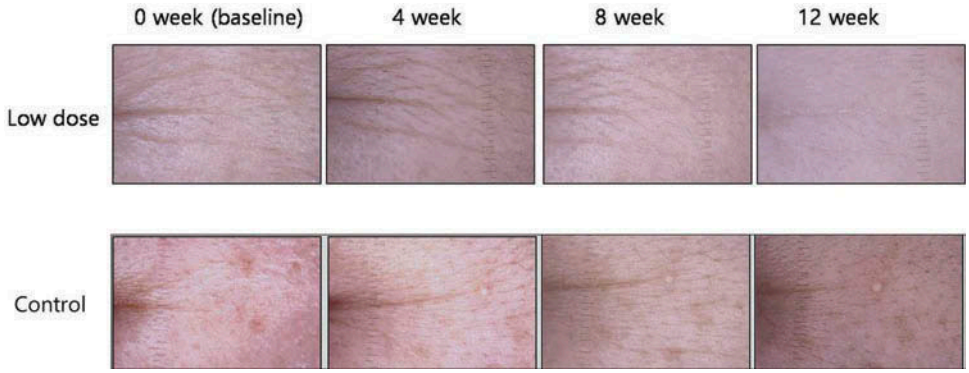

Figure 1. Dermoscope images of the left crow's foot of representative subjects in the low-dose and control groups at baseline (0 weeks), 4 weeks, 8 weeks, and 12 weeks.

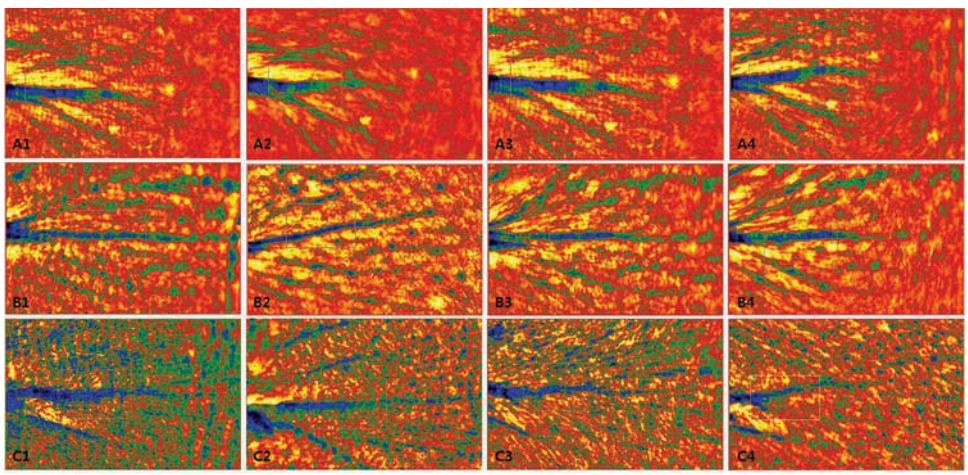

Figure 2. PRIMOS lite® images of the left crow's feet of representative subjects in the (A) control, (B) low-dose, and (C) high-dose groups at (1) baseline, (2) 4 weeks, (3) 8 weeks, and (4) 12 weeks. While the control group showed consistent wrinkles, the treatment groups showed gradual improvement of the crow's feet wrinkles, with more significant changes in the high-dose group.

Table 2. Percentages (%) of change in Ra and eye wrinkle volume as measured using a PRIMOSlite® instrument.

		Low dose	High dose	Control	*P*-value#
Ra (%)	Week 4	−34.66 ± 35.44	−36.05 ± 32.18	−31.82 ± 38.94	0.8816
	Week 8	−54.44 ± 22.66	−46.29 ± 34.34	−46.48 ± 24.37	0.3846
	Week 12	−71.43 ± 16.95	−71.60 ± 21.23	−54.26 ± 24.51	0.0009**
Eye wrinkle Volume (%)	Week 4	−10.26 ± 19.46	−9.79 ± 21.91	0.10 ± 25.26	0.1015
	Week 8	−15.01 ± 19.88	−13.01 ± 26.34	−2.54 ± 23.78	0.0046**
	Week 12	−28.67 ± 17.69	−27.79 ± 25.08	−0.14 ± 22.06	<.0001**

#: compared between groups; *p*-value by one-way ANOVA
* $p < 0.05$, ** $p < 0.005$

Table 3. Skin elasticity (R2 value) as measured using a Cutometer®.

	Low dose	High dose	Control	*P*-value#
Baseline (week 0)	0.62 ± 0.08	0.66 ± 0.08	0.68 ± 0.10	0.0351*
Week 4	0.67 ± 0.08	0.68 ± 0.07	0.67 ± 0.10	0.0263*
Week 8	0.70 ± 0.06	0.71 ± 0.07	0.67 ± 0.07	0.0002**
Week 12	0.74 ± 0.07	0.76 ± 0.07	0.66 ± 0.08	<0.0001**
Difference (week 0–week 4)	0.05 ± 0.07	0.01 ± 0.07	−0.00 ± 0.08	
P-value##	0.0008**	0.2144	0.7590	
Difference (week 0–week 8)	0.07 ± 0.08	0.05 ± 0.07	−0.00 ± 0.07	
P-value##	<0.0001**	0.0002**	0.7853	
Difference (week 0–week 12)	0.12 ± 0.07	0.10 ± 0.06	−0.02 ± 0.08	
P-value##	<0.0001**	<0.0001**	0.1772	

#: compared between groups; *p*-value by one-way ANOVA
##: compared within groups; *p*-value by the paired *t*-test
* $p < 0.05$, ** $p < 0.005$

significant differences between low-dose group and placebo group, and between high-dose group and placebo group, but there were no significant differences between low-dose and high-dose groups at 4, 8, and 12 weeks. Skin hydration values are shown in Table 4.

The amount of TEWL was significantly decreased in both treatment groups at 8 and 12 weeks. There were statistically significant differences between low-dose group and placebo group, and between high-dose group and placebo group, but there were no significant differences between low-dose and high-dose groups at 12 weeks. The TEWL values are shown in Table 5.

The investigator-assessed GAIS scores showed significant changes at 4, 8, and 12 weeks between the groups. However,

Table 4. Skin hydration as measured using a Corneometer®.

	Low dose	High dose	Control	*P*-value#
Baseline (week 0)	54.85 ± 11.08	58.97 ± 12.77	63.88 ± 10.95	0.0076
Week 4	60.68 ± 10.33	62.51 ± 12.90	60.37 ± 9.38	<0.0001**
Week 8	66.25 ± 8.29	65.02 ± 8.88	58.14 ± 8.01	<0.0001**
Week 12	71.84 ± 7.70	72.08 ± 6.55	53.43 ± 7.53	<0.0001**
Difference (week 0–week 4)	5.38 ± 7.54	3.54 ± 6.49	−3.51 ± 10.66	
P-value##	<.0001**	0.0027**	0.0633	
Difference (week 0–week 8)	11.40 ± 8.94	6.05 ± 9.95	−5.74 ± 9.10	
P-value##	<0.0001**	0.0010**	0.0008**	
Difference (week 0–week 12)	16.99 ± 11.44	13.11 ± 13.37	−10.45 ± 9.35	
P-value##	<0.0001**	<0.0001**	<0.0001**	

#: compared between groups; *p*-value by one-way ANOVA
##: compared within groups; *p*-value by the paired *t*-test
* $p < 0.05$, ** $p < 0.005$

Table 5. Transepidermal water loss as measured using a Tewameter®.

	Low dose	High dose	Control	*P*-value#
Baseline (week 0)	16.12 ± 5.69	16.31 ± 8.80	15.61 ± 11.35	0.9457
Week 4	11.76 ± 2.81	14.96 ± 10.21	14.53 ± 6.20	0.2501
Week 8	10.92 ± 3.99	11.69 ± 5.22	13.70 ± 4.85	0.3452
Week 12	8.87 ± 2.71	8.38 ± 2.03	13.92 ± 3.82	0.0149*
Difference (week 0–week 4)	−4.36 ± 5.16	−1.35 ± 10.66	−1.08 ± 10.00	
P-value##	<0.0001**	0.4580	0.5328	
Difference (week 0–week 8)	−5.20 ± 5.27	−4.62 ± 9.87	−1.91 ± 12.93	
P-value##	<0.0001**	0.0091*	0.3945	
Difference (week 0–week 12)	−7.25 ± 6.19	−7.93 ± 8.68	−1.70 ± 12.67	
P-value##	<0.0001**	<0.0001**	0.4402	

#: compared between groups; *p*-value by one-way ANOVA
##: compared within groups; *p*-value by the paired *t*-test
* $p < 0.05$, ** $p < 0.005$

Table 6. Investigator-assessed and subject-assessed Global Aesthetic Improvement Scale (GAIS) scores.

		Low dose	High dose	Control	*P*-value[#]
Investigator	Week 4	2.29 ± 0.58	2.46 ± 0.66	3.15 ± 0.44	<0.0001**
	Week 8	2.24 ± 0.65	2.37 ± 0.69	3.12 ± 0.48	<0.0001**
	Week 12	1.97 ± 0.52	1.97 ± 0.59	3.00 ± 0.35	<.0001**
Subject	Week 4	2.53 ± 0.56	2.80 ± 0.53	2.82 ± 0.58	0.0575
	Week 8	2.56 ± 0.61	2.60 ± 0.55	2.71 ± 0.58	0.5624
	Week 12	2.38 ± 0.55	2.46 ± 0.66	2.59 ± 0.66	0.3908

#: compared between groups; *p*-value by one-way ANOVA
* $p < 0.05$, ** $p < 0.005$

there were no significant differences in the subject-assessed GAIS scores between the groups (Table 6).

There were no severe adverse effects during the entire study period, nor were there any abnormal, serious, or delayed systemic symptoms or signs related to the test product during its application period.

Discussion

Cyclopia intermedia, also referred to as honeybush, is a popular traditional herbal tea in its native South Africa and has a growing worldwide market. *Cyclopia* plants are rich in polyphenols including xanthones, flavones, isoflavones, flavanones, and soumestans (16–18). Of these various polyphenols, hesperidin has been shown to be an active marker compound of fermented *C. intermedia* extracts. Hesperidin is a bioactive flavonoid characterized by its antioxidant and antimutagenic properties. Many studies have demonstrated that hesperidin exerts diverse positive effects including antimicrobial activity, anti-carcinogenic activity, anti-melanogenic activity, and UV protective activity (19–22). Based on its biological effects, hesperidin is a popular active cosmetic ingredient of various anti-wrinkle and whitening products(23). Therefore, we focused on the potential of *C. intermedia*, a source of hesperidin, as an effective anti-aging dietary supplement.

Fermented *C. intermedia* has been shown to suppress the expression of inflammatory mediators induced by UVB irradiation in human keratinocytes. Moreover, fermented *C. intermedia* was shown to downregulate the expression of MMPs by inhibiting UVB-induced activation of Mitogen-activated protein kinase (MAPK) signaling in human keratinocytes(14). Oral supplements of fermented *C. intermedia* extract (HU-018) reduced the length and depth of skin wrinkles in a mouse model of UVB-induced photoaging, as assessed by replica image analysis. The anti-wrinkle effects in UVB-irradiated mice were also confirmed histologically, which showed that collagen tissue breakdown was suppressed(15). Therefore, we evaluated the anti-aging effect of oral supplementation of fermented *C. intermedia* extract in a randomized, double-blinded, placebo-controlled trial. Additionally, we aimed to confirm the optimal dose of the oral supplement of fermented *C. intermedia* extract.

Daily supplements of either low-dose (HU-018 400 mg/day) or high-dose (HU-018 800 mg/day) extract reduced skin wrinkle severity, roughness, and volume. Daily supplements of HU-018 also improved skin elasticity and enhanced skin moisture. The high-dose supplement was not more effective in improving any of the skin properties than the low-dose supplement. Therefore, our data indicate that daily supplementation of 400 mg HU-018 is sufficient to achieve anti-aging effects.

The underlying mechanism by which the HU-018 supplement improved skin wrinkles, elasticity, and hydration was not investigated in this clinical trial. However, based on previous *in vivo* and *in vitro* studies, we hypothesize that the HU-018 supplement may positively affect collagen degradation. The well-known antioxidant activity of polyphenols, which are abundant in *C. intermedia* (particularly hesperidin), may help mediate its protective effects against skin aging.

In conclusion, our randomized, double-blinded, placebo-controlled study demonstrated that oral supplements of fermented *C. intermedia* extract produced significant anti-aging effects. Therefore, fermented *C. intermedia* extract has potential as a dietary supplement protective against skin aging.

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None

Conflicts of interest

Some of the authors have declared conflicts of interest.

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