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Influence of yeast-derived 1,3/1,6 glucopolysaccharide on circulating cytokines and chemokines with respect to upper respiratory tract infections

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ABSTRACT

Objective: Wellmune WGP is a food supplement containing a refined 1,3/1,6 glucopolysaccharide that improves the antimicrobial activity of the innate immune cells by the priming of lectin sites. This study aimed to investigate whether Wellmune decreases the frequency and severity of upper respiratory tract infection (URTI) symptoms over 90 d during the peak URTI season in healthy university students. The secondary aims included an assessment of plasma cytokine and chemokine levels.
Methods: This was a randomized, double-blinded, placebo-controlled trial lasting 90 d. One hundred healthy individuals (18–65 y old, mean age ∼21 y) were randomized to 250 mg of Wellmune once daily or to an identical rice flour-based placebo. Health was recorded daily and two or more reported URTI symptoms for 2 consecutive days triggered a medical assessment and blood collection within 24 h. The URTI symptom severity was monitored. Plasma cytokines and chemokines were measured at day 0, day 90, and during the confirmed URTI.
Results: Ninety-seven participants completed the trial (Wellmune, $n = 48$; placebo, $n = 49$). The Wellmune tended to decrease the total number of days with URTI symptoms (198 d, 4.6%, versus 241 d, 5.5% in the control group, $P = 0.06$). The ability to "breathe easily" was significantly improved in the Wellmune group; the other severity scores showed no significant difference. Cytokines and chemokines were not different between the groups at study entry or day 90, but monocyte chemotactic protein-1 was lower in the Wellmune group during the URTI.
Conclusion: Wellmune may decrease the duration and severity of URTI. Larger studies are needed to demonstrate this.

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Introduction

Upper respiratory tract infection (URTI) is the most frequent infectious disease in humans, with an average of two to four episodes per year in adulthood and 6 to 10 episodes per year in childhood [1,2]. Often referred to as the "common cold," there are 100 to 400 viruses that have been implicated in the onset of symptoms such as a runny nose, a sore throat, nasal congestion, fever, and headache [3,4]. The common cold is usually self-limiting but carries a risk of secondary bacterial infection and morbidity and has an enormous impact on socioeconomic performance [5,6]. According to data from the USA, there are approximately 500 million non–influenza-related URTI episodes per year, with an estimated annual economic impact of $40 billion [5]. Therefore, strategies to decrease the frequency and severity of URTI symptoms and to decrease physician attendance would have a highly beneficial impact on health and socioeconomic performance. The control of infectious disease often has been targeted by vaccine approaches facilitating an adaptive immune response. Efforts to create a vaccine against the common cold have failed thus far and remain a distant possibility because of the heterogeneity of causal viruses that are also capable of seasonal mutation [3]. Non-prescription medications

such as decongestants and cough suppressors may decrease the severity of some cold symptoms but do not decrease the frequency or duration of illness, and some have been associated with undesirable side effects [7–9]. Various nutritional and herbal supplements such as zinc, vitamin C, and Echinacea have shown promise, yet studies have suggested that no supplement confers a reliable and clinically relevant protection against URTI symptoms [10–14].

The innate immune system is essential for the initial detection and control of invading viruses and bacteria and for the subsequent activation of adaptive immunity. Rapid and non-specific recognition occurs by pathogen-associated molecular patterns and complement binding [15]. Novel strategies have focused on the biological response modifiers of the innate immune system to support resistance to viral and bacterial infection. This approach is highly appealing because it has the benefit of potentially conferring non-specific protection to a wide variety of pathogens without the need for a diagnosis of the specific causal virus to determine a treatment strategy and may confer an ability to prevent and treat infection. Wellmune WGP contains a highly refined 1,3/1,6 glucopolysaccharide (also referred to as 1,3/1,6 β-glucan) derived from the cell wall of baker's yeast (*Saccharomyces cerevisiae*). This glucopolysaccharide has previously demonstrated an ability to increase the antimicrobial response of human innate immune cells in vitro [16–19] and increase the survival in animals challenged with a variety of pathogens in vivo [20–22]. A mechanism of action has been defined for 1,3/1,6 glucopolysaccharide to increase the immune response by a priming of complement receptor-3 (also known as CD11b/CD18), which is found on innate immune cells such as neutrophils, macrophages, and natural killer cells. Complement receptor-3 interacts with the complement protein (C3b) that is bound to pathogenic targets and to non-self carbohydrate structures such as 1,3/1,6 glucopolysaccharide, in a process capable of inducing phagocytosis [23,24]. Therefore, priming innate immune cells with 1,3/1,6 glucopolysaccharide has the potential to improve the antimicrobial activity against opsonized foreign challenges [24].

Previous randomized, double-blinded, placebo-controlled clinical trials of 1/3,1/6 glucopolysaccharide have demonstrated an increased resistance to postoperative infection [25] and a decreased frequency of URTI symptoms in moderately stressed individuals [26] and in physically challenged groups such as marathon runners during the 4-wk period after a race [27]. A significant improvement in psychological mood state has also been noted [26,27]. However, further studies are required to evaluate the efficacy of 1,3/1,6 glucopolysaccharide on infection. In the present study, we tested the hypothesis that 1,3/1,6 glucopolysaccharide (in the form of Wellmune WGP, a commercially available product with generally recognized as safe recognition [28]) can decrease the frequency, duration, and severity of URTI symptoms over a 90-d period during the winter months. We also monitored plasma cytokine and chemokine profiles.

Materials and methods

Study design, subjects and sample collection

The study was a double-blind, randomized placebo-controlled trial of 1/3,1/6 glucopolysaccharide (in the form of Wellmune WGP, Biothera, Inc., Eagen, Minnesota, USA; 250 mg/d, $n = 50$ subjects) versus rice flour as a placebo ($n = 50$ subjects). Previous research in marathon runners did not show a significant difference in outcomes with 250 versus 500 mg/d [27]; therefore, the lower dose was selected for this study. The study was approved by the Berkshire research ethics committee and all subjects gave written informed consent before their participation. Subjects were medical students at the University of Southampton

School of Medicine; this population has regular contact with patients and staff in hospitals and clinical environments and is susceptible to lifestyle stress and examination pressure, factors known to impair the immune system and to potentially increase susceptibility to infection [29]. Potential subjects were recruited by invitation and volunteers were assessed against the inclusion and exclusion criteria (see below) during a clinic visit at the Wellcome Trust Clinical Research Facility, Southampton General Hospital over a 2-wk period in January 2010, within the peak season for URTI. Assessment appointments were given to the first 150 volunteers on a first-come first-served basis with the aim of recruiting 100 subjects. Subjects with current URTI symptoms were not allowed to start the trial until an assessment could be completed after the resolution of symptoms.

The inclusion criteria were an age 18 to 65 y, general good health, an agreement to all study visits and procedures, be living in a community dwelling, and had at least one self-reported cold in the previous 12 mo. The exclusion criteria were a current respiratory illness, currently taking immune-modifying medications (including steroids, antibiotics, immunosuppressants, or immune-modifying dietary supplements), a known immune or autoimmune disorder (including the human immunodeficiency virus, ankylosing spondylitis, chronic fatigue syndrome, Crohn's disease, ulcerative colitis, vitiligo, and psoriasis), diabetes, use of an immunosuppressive medication within the previous 5 y, a low body mass index (<18 kg/m^2), having an eating disorder, a history of tuberculosis, previous splenectomy, untreated or unstable hypothyroidism, active renal disease (abnormal estimated glomerular filtration rate), liver disease (two times the normal reference range) or active asthma requiring treatment other than bronchodilators, and a recent (<3 mo) or current involvement in any clinical trial.

The blinded randomization of subjects to Wellmune WGP or placebo occurred by a random block allocation sequence produced by the University of Southampton Research Design Service. Subjects self-administered one capsule of Wellmune WGP or placebo before breakfast each morning for 90 d. Compliance was checked at days 30, 60, and 90, with six or more missed capsules in any 30-d period leading to exclusion from the trial owing to a protocol violation. Subjects received a daily health log to record the presence or absence of URTI symptoms (see below).

Blood was taken for routine hematology (full blood cell count) and biochemistry (urea, electrolytes, and liver function tests) and for the measurement of cytokine and chemokine concentrations at day 0 and at day 90.

At any stage within the 90-d trial, participants who reported two or more URTI symptoms for 2 consecutive days as defined in the daily health log contacted the study team. This triggered a same-day telephone interview and a face-to-face medical assessment was completed within 24 h. The medical assessment involved a confirmation of URTI symptoms, nose and throat swabs for H1N1 polymerase chain reaction analysis, and another blood sample to monitor cytokine and chemokine concentrations during the symptomatic phase of the URTI episode.

During each day of a confirmed URTI episode, participants also completed the Wisconsin Upper Respiratory Tract Infection Severity Score–21 (WURSS-21) to assess the severity of URTI symptoms from the first day of symptoms until their resolution (see below).

Daily health log

Participants were provided with daily health logs covering days 0 to 30, 31 to 60, and 61 to 90. Participants were instructed to complete a score according to the presence or absence of symptoms and to return the diary at the end of the 30-d period in stamped addressed envelopes. Categories were 1 (no health problems today), 2 (cold symptoms, e.g., runny nose, blocked nose, sore throat, coughing, sneezing, and/or colored discharge), 3 (flulike symptoms, e.g., fever, headache, general aches and pains, fatigue and weakness, and/or chest discomfort), and 4 (gastrointestinal symptoms, e.g., nausea, vomiting, and diarrhea). These categories are in accordance with previous URTI research [4,30]. The presence of two or more symptoms for 2 consecutive days prompted the participants to make immediate contact with the study team. Symptom patterns were then medically assessed to confirm the URTI and blood and H1N1 swab samples collected.

Wisconsin Upper Respiratory Tract Infection Severity Score–21

After confirmation (as above) of the URTI, participants were provided with a WURSS-21 form and instructed to complete the 21 questions; the form includes a specific symptom severity scale (from 0, "do not have this symptom," to 7, "severe") and the severity of impact on activities of daily living such as the ability to sleep well. A form was completed for each symptomatic day of the URTI for each confirmed episode. The WURSS-21 score is a validated tool for URTI symptom severity that has been used in many published peer-reviewed studies [31]. The WURSS-21 forms were posted to the central location with the health log data.

Measurement of chemokine and cytokine concentrations

Plasma was prepared from fresh blood collected into heparin and then stored at −80°C until analysis. A range of cytokines (interleukin [IL]-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, tumor necrosis factor [TNF]-α, TNF-β, and interferon-γ) and chemokines (macrophage inflammatory protein [MIP]-1β, granulocyte colony-stimulating factor, monokine induced by Interferon gamma, and monocyte chemotactic protein-1 [MCP-1]) were measured from plasma using Flow-Cytomix Multiplex kits (eBioscience, Hatfield, UK) according to the manufacturer's instructions. The limits of detection ranged from 0.9 to 20.8 pg/mL. Any value lower than the limit of detection was assigned half the value of the lowest detectable standard.

Statistical analysis

Data were initially entered into Excel (Microsoft, Redmond, WA, USA) and transferred to SPSS (SPSS Inc., Chicago, IL, USA). The chi-square test was used for between-group comparisons of the total number of days of cold and flu symptoms. The Mann–Whitney U test was used for between-group comparisons of data from the WURSS-21 assessment and the plasma chemokine and cytokine concentrations. The median differences and the 95% confidence intervals were generated by the software CIA (Southampton, UK). In all cases, $P < 0.05$ was taken to indicate statistical significance.

Results

Subject characteristics

One hundred male and female subjects 18 to 65 y old were recruited into the study from the Southampton University Medical School. Ninety-nine participants were 18 to 30 y old and one participant was 50 y old. Table 1 lists the characteristics of subjects in each group at study entry. There were no differences between the two groups in any of these characteristics. Figure 1 shows the flow of subjects through the study. Fifty subjects were randomized to each arm of the study. Three subjects were excluded as protocol violators ($n = 1$ in the placebo group, $n = 2$ in the Wellmune group). None of the excluded participants reported side effects from the study supplementation. Few side effects from the placebo or

Table 1
Characteristics of subjects according to treatment group

Variables	Wellmune WGP ($n = 50$)	Placebo ($n = 50$)
Age (y)	21.9 ± 4.8	21.3 ± 2.7
Sex		
Men	25 (50%)	25 (50%)
Women	25 (50%)	25 (50%)
Height (cm)	172.2 ± 9.4	173.3 ± 9.9
Weight (kg)	69.8 ± 10.2	69.7 ± 11.3
Body mass index (kg/m^2)	23.5 ± 2.7	23.1 ± 2.6
Systolic blood pressure (mmHg)	125 ± 13	125 ± 15
Diastolic blood pressure (mmHg)	72 ± 10	71 ± 10
Heart rate (beats/min)	76 ± 13	76 ± 13

Data are presented as mean ± SD or numbers of subjects (percentage)

Wellmune were reported and all routine hematologic, biochemistry, and liver function tests remained in the normal range in the two groups.

Self-reported days of URTI symptoms

Table 2 presents data from the daily health log, presenting the total person-days for each category in each treatment group over the course of the study period. In the two groups, most subjects scored 1 (no symptoms) on most days (approximately 95%) during the study. The total number of days with reported URTI symptoms tended to be lower in the Wellmune group (241, 5.5%, versus 198, 4.6%, $P = 0.06$).

URTI symptom severity assessed by WURSS-21

Twenty-four episodes of URTI were confirmed for assessment with the WURSS-21, with 12 URTI episodes in each group. Eleven participants in each group were confirmed as having URTI and completed the daily WURSS-21 scores for each symptomatic day. Two participants in each group developed
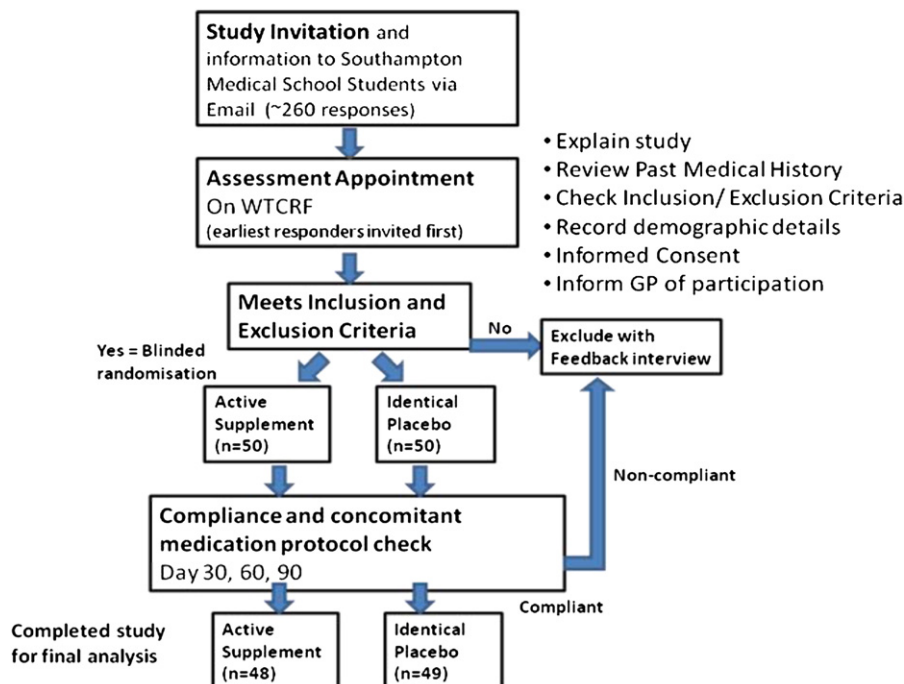

Fig. 1. Consort diagram illustrating the flow of subjects through the study. GP, general practitioner; WTCRF, Wellcome Trust Clinical Research Facility.

Table 2
Total subject-days of upper respiratory tract infection symptom according to treatment group

| | Cold and flu status | | Total |
	No cold/flu	Cold + flu	
Treatment group			
Placebo			
Count	4169	241	4410
Percentage within treatment group	94.5	5.5	100.0
Wellmune			
Count	4122	198	4320
Percentage within treatment group	95.4	4.6	100.0
Total			
Count	8291	439	8730
Percentage within treatment group	95.0	5.0	100.0

two episodes of URTI during the trial period. However, because there were at least 14 asymptomatic days between the first and second symptomatic periods, they were assessed as separate episodes. The ability to "breathe easily" was significantly better in the Wellmune group ($P < 0.05$), but there were no significant differences between the groups for any of the other components of the WURSS-21 (Table 3).

Plasma cytokine and chemokine concentrations

The concentrations of interferon-γ, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, TNF-α, and TNF-β were rarely above the limit of detection in any plasma sample in either group. IL-1β, IL-8, MIP1-α, MIP-1β, MCP-1, granulocyte colony-stimulating factor, and MIG were detected in most samples. There were no differences in the concentration of these mediators from day 0 to day 90 according to the treatment group. Cytokines and chemokines were also measured in plasma at the time of the self-reported URTI (Table 4). A significant difference was observed in MCP-1 concentration, which was lower in the Wellmune group (median 183.8 pg/mL, 25th percentile 172.8, 75th percentile 106.7, versus 240.4 pg/mL, 25th percentile 207.2, 75th percentile 172.6, $P = 0.006$).

Potential H1N1 infection

The polymerase chain reaction analysis of the nose and throat swabs taken during the URTI episodes did not detect any positive H1N1 infection.

Discussion

Viral URTI is a leading cause of lost work and school days, with a considerable impact on health and socioeconomic performance [1,5,6]. Despite the common nature of this problem, it remains a medical challenge to decrease the frequency, duration, and severity of episodes [3]. The present study of a healthy student population taking Wellmune 250 mg/d demonstrated a tendency to a decreased number of days with cold or flu symptoms (18% less) compared with placebo ($P = 0.06$). This finding is consistent with previous clinical studies in other groups [26,27]. The relatively small number of confirmed URTI episodes was below the expected levels [1,2] and limited the likelihood of achieving statistical significance in the present study. During acute URTI, the ability to breathe easily was significantly improved in those taking Wellmune. Other symptoms did not reach statistical significance, yet the low level of background URTI symptoms makes this assessment limited. Further studies capable of capturing larger numbers of symptom days would provide further assessment of severity scores.

Wellmune was well tolerated, with similar reported side effects in the active and placebo groups. No participants exited the study because of side effects or tolerability issues.

Serum cytokine analysis demonstrated no change in profiles after 90 d of Wellmune consumption compared with placebo. The lack of an induction of inflammatory cytokines is in keeping with previous in vitro results [16]. During periods of symptomatic URTI, there were also no cytokine changes compared with placebo, but the results for the monocyte attractant MCP-1 did display a significant decrease in the Wellmune group compared with the placebo

Table 3
Wisconsin Upper Respiratory Tract Infection Severity Score–21 symptom severity scores in each treatment group

Measurement	Placebo (n = 12)	Wellmune (n = 12)	Difference (placebo versus Wellmune)	P
	Median (LQ, UQ)	Median (LQ, UQ)	Median (95% CI)	
How sick did you feel today?	2.77 (2.33, 2.94)	2.31 (1.85, 3.20)	0.31 (−0.54, 1.00)	0.729
Runny nose	2.54 (1.88, 3.00)	2.42 (1.20, 3.12)	0.13 (−0.83, 1.31)	0.707
Plugged nose	1.96 (0.67, 2.48)	1.67 (0.32, 2.00)	0.31 (−0.85, 1.44)	0.469
Sneezing	1.69 (0.60, 2.06)	0.68 (0.15, 1.46)	0.49 (−0.36, 1.47)	0.259
Sore throat	0.72 (0.00, 2.18)	2.20 (0.68, 3.22)	−1.10 (−2.40, 0.07)	0.126
Scratchy throat	0.39 (0.13, 1.60)	1.09 (0.07, 2.10)	−0.22 (−1.35, 0.44)	0.467
Cough	1.33 (0.11, 1.83)	1.87 (0.00, 2.63)	−0.32 (−1.77, 0.80)	0.520
Hoarseness	0.58 (0.00, 1.27)	0.53 (0.00, 0.92)	0.00 (−0.75, 0.67)	0.790
Head congestion	1.79 (1.00, 2.69)	0.68 (0.00, 2.27)	0.78 (−0.43, 1.78)	0.139
Chest congestion	0.06 (0.00, 0.95)	0.33 (0.00, 1.87)	0.00 (−1.33, 0.43)	0.544
Feeling tired	2.08 (1.47, 2.70)	1.67 (0.48, 3.10)	0.50 (−0.83, 1.57)	0.488
Think clearly	2.00 (1.04, 2.44)	1.15 (0.15, 2.07)	0.70 (−0.30, 1.75)	0.148
Sleep well	1.36 (0.92, 2.20)	0.99 (0.00, 2.03)	0.42 (−0.66, 1.22)	0.418
Breathe easily	1.74 (1.06, 2.29)	0.65 (0.00, 2.03)	1.00 (−0.07, 1.75)	**0.049**
Walk, climb stairs, exercise	0.75 (0.15, 2.25)	0.24 (0.00, 1.36)	0.22 (−0.11, 1.75)	0.139
Accomplish daily activities	0.88 (0.19, 1.97)	0.17 (0.00, 0.80)	0.25 (−0.11, 1.67)	0.114
Work outside home	1.55 (0.42, 2.30)	0.68 (0.00, 0.93)	0.70 (−0.25, 1.63)	0.163
Work inside home	1.08 (0.20, 1.92)	0.30 (0.00, 0.78)	0.38 (−0.29, 1.67)	0.206
Interact with others	0.75 (0.15, 1.88)	0.37 (0.00, 0.68)	0.17 (−0.28, 1.50)	0.337
Live your personal life	0.50 (0.19, 2.00)	0.37 (0.00, 0.68)	0.19 (−0.28, 1.55)	0.324
Compared with yesterday, I feel that my cold is	4.08 (3.64, 4.33)	4.00 (3.64, 4.32)	−0.02 (−0.50, 0.38)	0.885

CI, confidence interval; LQ, lower quartile; UQ, upper quartile

Table 4
Comparison of plasma cytokine and chemokine concentrations during symptomatic upper respiratory tract infection according to treatment group

Mediator (pg/mL)	Placebo group	Wellmune group	P
IL-1β	2.10 (2.10, 2.10)	2.10 (2.10, 13.77)	0.456
IL-8	13.22 (9.74, 21.16)	7.86 (2.39, 15.93)	0.296
MIP-1β	15.17 (11.24, 21.52)	18.00 (7.74, 26.45)	0.697
MCP-1	240.39 (207.18, 272.59)	183.82 (172.82, 196.97)	**0.006**
MIP-1α	918.87 (179.44, 1851.37)	627.25 (95.41, 2541.04)	0.750
G-CSF	115.26 (1.70, 608.11)	83.94 (1.70, 792.20)	0.860
MIG	217.44 (88.71, 497.75)	150.59 (115.18, 500.26)	0.972

G-CSF, granulocyte colony-stimulating factor; IL, interleukin; MCP-1, monocyte chemotactic protein-1; MIG, monokine induced by interferon gamma; MIP, macrophage inflammatory protein

Values are presented as median (25th, 75th percentiles)

group. This warrants further investigation to clarify the potential to modulate this inflammatory chemokine, which has been associated with increased viral symptom severity [30,32]. Further clinical studies could also assess the capacity to modulate innate immune functions such as natural killer cell activity and the phagocytic index in addition to data on URTI symptom patterns.

Strategies to increase the non-specific innate immune response are clinically appealing because these may improve host resistance to diverse immune challenges. This is particularly relevant to the management of viral URTI given the significant heterogeneity of viral causes, which limits vaccination development [3]. An increase of the innate immune response using yeast-derived 1/3,1/6 glucopolysaccharide may also have wider clinical potential such as a role in postoperative infection control [25] and as an adjuvant for cancer immunotherapy using monoclonal antibodies [33].

Although the present study had a larger sample and a longer trial duration compared with previous trials of Wellmune in URTI, the sample was found to be too small to identify a significant effect on URTI outcomes in this population. Identifying the sample size was hampered by the lack of accurate data for the incidence of URTI in healthy students. Further trials of Wellmune with a larger sample and including populations that are susceptible to developing URTI and its complications seem justified.

Conclusion

Wellmune WGP was well tolerated and tended to decrease the number of days with reported cold and flu symptoms ($P = 0.06$) compared with placebo. Further studies are warranted to clarify the potential role of this food supplement to increase the innate immune response and decrease the burden of viral URTI.

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