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Beverage Containing Dispersible Yeast β-Glucan Decreases Cold/Flu Symptomatic Days After Intense Exercise: A Randomized Controlled Trial

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ABSTRACT

In this double-blind, randomized, placebo-controlled parallel study, we examined the effect of dairy-based beverages (250 mL/day) containing 250 mg of dispersible baker's yeast β-glucan (Wellmune) compared to a macronutrient- and calorie-matched control on upper respiratory tract infection (URTI) in marathon runners. Healthy adults running in the 2017 Austin Marathon consumed either β-glucan ($N = 132$) or control ($N = 225$) for the 45 days prior to, day of, and 45 days after the marathon (91 days total). Participants completed a daily online survey assessing compliance, training status, and URTI symptoms. URTI occurrence and severity were evaluated using the Jackson Index and confirmed by the study physician. No significant differences in average duration and number of URTI episodes were found between β-glucan and control. However, those who completed the study per protocol on the β-glucan beverage reported significantly fewer URTI symptomatic days (3.43 ± 6.44 days, max 27 days) compared to those on control beverage (3.84 ± 6.84 days, max 49 days). Total URTI severity was significantly lower for β-glucan (4.52 ± 1.61) compared to control (5.60 ± 2.23). Specifically, lower ($p < .05$) severity ratings for nasal discharge and sore throat were reported for β-glucan compared to control. Average missed postmarathon workout days due to URTI were significantly less for β-glucan (0.09 ± 0.38 days, max 2 days) compared to control (0.36 ± 1.40 days, max 10 days). Overall, consumption of dairy-based beverages containing dispersible yeast β-glucan decreased URTI symptomatic days, severity of specific URTI symptoms, and missed postmarathon workout days due to URTI, without affecting duration and number of URTI episodes.

KEYWORDS

clinical trial; human; immune; marathon; Wellmune

Introduction

β-glucan is a family of natural polysaccharides consisting of D-glucose monomers linked by a β-glycosidic bond. They are important structural elements of the cell wall and serve as energy storage in bacteria and fungi, including yeast, algae, and plants. Oat and barley β-glucans are primarily linear with large regions of (1,4)-β linkages

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separating shorter stretches of (1,3)-β structures, mushroom β-glucans have short (1,6)-β-linked branches coming off of the (1,3)-β backbone, and yeast β-glucans have (1,6)-β branches that are further elaborated with additional (1,3)-β regions (Bashir and Choi 2017). Not all β-glucans are able to modulate immune function, and the ability to do so depends mainly on the primary chemical structure of the β-glucan. Of these, those derived from fungi and yeast are known for their immunomodulating effects.

Wellmune is a commercially available (1,3)/(1,6)-β-linked glucan derived from the cell wall of a proprietary strain of yeast. It is currently incorporated into more than 100 food, beverage, and supplement products sold in more than 50 countries. Two separate clinical studies have reported a reduction in postmarathon URTI symptomatic days with Wellmune supplementation in the form of a capsule (Talbott and Talbott 2009; McFarlin et al. 2013) although the effect of this supplement on training regimen is unknown. In addition, the immunomodulating effect of Wellmune when incorporated into a food product, such as a beverage, has not been explored. The conformation of β-glucans can be modified via physical, chemical, and biological methods, which in turn modify the functionality of these β-glucans (Wang et al. 2017). Given food products undergo different processing, and that processing can affect the structure and, therefore, the function of β-glucan, it is important to understand the effect of this ingredient when incorporated into food.

Intensive physical activity is often used as a model of increased susceptibility to URTI, as supported by several marathon study surveys. Ultramarathoners and marathoners reported greater number of incidence of URTI symptoms compared to control (nonrunning household members or marathon drop-outs) (Peters and Bateman 1983; Nieman et al. 1990; Robson-Ansley et al. 2012). In addition, several studies have demonstrated that athletes (professional and recreational) are at an increased risk of infections during periods of heavy training (Chubak et al. 2006; Moreira et al. 2007). Suggested mechanisms behind the increase in infection following strenuous physical activity include depression of natural killer cell function (Pedersen and Ullum 1994), impaired cell-mediated immunity due to decreases in the expression of toll-like receptors, and increasing production of stress hormones and proinflammatory cytokines, leading to a state of inflammation (Gleeson and Bishop 2013), imbalanced immunity response by an enhanced release of proinflammatory cytokines followed by anti-inflammatory cytokines (Nieman et al. 2001), and suppression of cellular immunity, leading to increased susceptibility to infections (Suzuki et al. 2002). Other nonexercise factors, such as psychological stress and anxiety, nutritional deficiencies, and increased exposure to infectious pathogens common in large gatherings of people, have also been suggested as reasons for the increased susceptibility to infection in marathoners (Campbell & Turner 2018).

In this study, we investigated the effect of Wellmune incorporated into a UHT-processed diary-based beverage on URTI occurrence and severity and its impact on training regimen of individuals undergoing intense exercise stress (i.e., marathon training).

Methods

Study design

The screening and intervention for this randomized, double-blind, controlled, parallel study were conducted between October 2016 and April 2017. The study was designed

as a three-arm study to compare dispersible yeast β-glucan and soluble yeast β-glucan with a placebo control. Participants were randomized to receive one of the three products: 250 mL/d dairy-based beverages containing 250 mg dispersible yeast β-glucan, 250 mg soluble yeast β-glucan, or 0 mg yeast β-glucan (control). Only findings from the dispersible yeast β-glucan and control groups are reported herein, and the soluble yeast β-glucan will be reported in a future publication.

Study products were sent to participants as prepackaged, aseptic, sealed 250 mL Tetra Pak cartons in two shipments, one prior to the start of the intervention period for consumption during the first half of the intervention period and another prior to the start of the marathon for consumption during the second half of the intervention period. Participants were instructed to consume a 250 mL serving of study product each day over a 91-day intervention period, which included the 45 days prior to the marathon, the day of the marathon, and the 45 days after the marathon. All products were matched for appearance and taste. Throughout the intervention, participants were required to complete a Daily Health Log and other questionnaires to assess their health and training status and to capture incidence of URTI and URTI symptoms. To minimize wastage of study product, participants who failed to complete the Daily Health Log for $\geq$19 days ($<$ 80% compliance) during the first half of the intervention period were discontinued from the study prior to the second shipment of study product.

A statistician generated a block randomization list for intervention sequence using the SAS PROC PLAN with a 5:3:3 (control:dispersible:soluble) allocation ratio. Each randomization number on the list corresponded to one of the three blinded study product codes. A randomization number was manually assigned in sequential order by study staff to each eligible participant who completed the online screening survey, the online informed consent document, and the marathon registration process. Participants, study staff, and outcome assessor were blinded to the intervention assignments.

Participants

The study protocol and relevant documents were approved by an institutional review board (IntegReview, Austin, TX) prior to initiation of the trial, and participants provided informed consent and authorization for disclosure of protected health information before enrolling in the study. This study was conducted consistent with appropriate Good Clinical Practice Guidance, the Declaration of Helsinki (2006), and the United States 21 Code of Federal Regulations. Eligible participants were healthy men and women, 18–65 years of age, who were registered to participate in the 2017 Austin Full Marathon. Participants were required to complete an online screening survey and medical history questionnaire to rule out conditions that may affect the outcome of the study, including clinically important immune-compromising (e.g., HIV, chronic hepatitis, and/or chronic mononucleosis) disorders. Participants were also excluded if they smoked, were unwilling to refrain from taking medications and supplements that may affect the immune system, or had known allergy, sensitivity or intolerance to the study products.

Procedures

Participants completed an online Daily Health Log, which included questions on study product consumption, training/exercise frequency and intensity, muscle soreness or joint pain, changes in medication/supplementation, and URTI symptoms. Compliance was calculated from the online Daily Health Log, which included the question "Did you consume your beverage in its entirety today?" Participants were assumed to not have consumed the study product if they failed to complete the online Daily Health Log.

Participants who reported experiencing any cold or flu symptoms on the online Daily Health Log were instructed to complete the Jackson Index score, which included the following symptoms: nasal discharge, nasal obstruction, sneezing, sore throat, malaise, headache, cough, and chilliness. Symptoms were rated using the published Jackson Index scoring system on a 4-point scale: 0 = absent (symptom not present in previous 24 h), 1 = mild, 2 = moderate, and 3 = severe (Jackson et al. 1958). Categorization of an URTI episode was based on published criteria (Jackson et al. 1958; Tiralongo et al. 2016), and each episode report was reviewed and confirmed by the study physician. Specifically, potential URTI episodes were identified by participants reporting $\geq$2 consecutive days of symptoms and indicating they had a cold/flu on the Daily Health Log questionnaire and were either confirmed by a total Jackson Index score of $\geq$14 or, if the total Jackson Score was $<$14, confirmed by the study physician following assessment of symptoms. In addition, when participants reported $\geq$2 consecutive days of symptoms but indicated they did not have a cold/flu and had a total Jackson Index score of $<$14, URTI was confirmed by the presence of $\geq$3 days of nasal discharge. If none of these requirements were fulfilled, the symptoms/episode was categorized either as a nonconfirmed URTI or an "other" (e.g., allergies).

Statistical analyses

Power calculations were performed in SAS for Windows (version 9.4; Cary, NC) using data from a previous study that investigated an encapsulated Wellmune in marathon runners (McFarlin et al. 2013). To reject the null hypothesis of equal means with a 90% power, when the population mean difference is $\mu1-\mu2 = 1.30 - 2.30 = -1.00$ with standard deviations of 1.74 for group 1 (active) and 2.25 for group 2 (control), and with a nominal significance level (alpha) of .025 using a two-sided two-sample unequal-variance z test, with a Hochberg correction for multiplicity (Chow at al. 2008; Julious 2010; Machin et al. 1997; Zar 1984), the required samples sizes per group were 87 (active) and 145 (control) evaluable participants. Since there were two active groups and one control group, the total number of evaluable participants was $87 + 87 + 145 = 319$. An attrition of 36% was used to estimate the dropout rate, resulting in the minimum total number of 500 participants to be randomized.

The primary outcome variable was the average duration of confirmed URTI episodes (one episode defined as $\geq$2 consecutive symptom days). Differences among groups were analyzed using a two-sided Wilcoxon rank sum test, and the Hochberg procedure was used to control for multiplicity. Secondary outcomes included total number of confirmed URTI symptom days, total number of confirmed URTI episodes, missed days of premarathon training due to confirmed URTI, and missed days of postmarathon

workouts due to confirmed URTI, analyzed using two-sided, two-sample zero-inflated Poisson model, severity of confirmed URTI analyzed using two-sided, two-sample unequal-variance z test, days to starting postmarathon workouts analyzed using log-rank test, and frequency or intensity of workouts postmarathon analyzed using two-sided Wilcoxon rank sum test. Unless otherwise stated, tests of significance were two-sided and performed at a 5% significance level. Missing data were not imputed; thus, only observed data were analyzed. Data are presented as mean ± standard deviation (SD) unless otherwise stated.

Primary analysis was completed for the intent-to-treat (ITT) population, which included all participants who were randomized into the study and completed at least one Daily Health Log. In addition, analyses were conducted for the per-protocol (PP) population, which included only participants who finished the intervention, completed at least 80% of the daily questionnaires, and consumed at least 80% of the study product. The ITT and PP populations were identified prior to locking the database, and the scientific investigators and statisticians remained blinded to the intervention sequence until after the completion of all statistical analyses. Results for the PP population are reported herein, with reference to the findings in the ITT population when qualitative differences were noted only.

Results

Participants

A total of 370 participants were randomized to the control and dispersible yeast β-glucan groups and were included in the ITT analysis (Supplemental Figure 1). Of these, 21 in the control group and 18 in the dispersible yeast β-glucan group failed to complete at least one Daily Health Log and did not contribute any outcome data. Participants who failed to complete the Daily Health Log for ≥19 days prior to the marathon were categorized as lost to follow-up if they were unresponsive to emails or phone calls ($n = 45$) or noncompliant ($n = 27$), and discontinued from the study. Four participants ($n = 2$ per group) reported adverse effects, which included upset stomach, dizziness, muscle soreness, and itchy throat after consumption of the dispersible β-glucan beverage and nausea and lower leg cramps after consumption of the control beverage. Of the 236 participants who completed the study in its entirety, 34 were excluded from the PP population due to noncompliance. Average compliance for the PP population was 93.3% and 93.4% (range of 80–100%) in the control and dispersible yeast β-glucan groups, respectively. Participants in the control and dispersible yeast β-glucan groups were similar in age (18–66 years) with near-equal distributions of females to males (Table 1).

URTI days and episodes

No differences in the number of confirmed URTI episodes or the average duration of confirmed URTI episodes between β-glucan and control groups were found; however, in the PP population, participants consuming the dispersible yeast β-glucan beverage reported an average of 11% fewer URTI symptomatic days (range of 0–27 days)

Table 1. Demographics.

Variable	Control ($N = 133$)	β-Glucan ($N = 69$)
Sex		
Sex (% female)	68 (51.1%)	34 (49.3%)
Age (y)	39.2 ± 10.2	37.4 ± 10.3
Race		
White	104 (78.2%)	56 (81.2%)
Black or African American	4 (3.0%)	2 (2.9%)
American Indian/Alaskan Native	2 (1.5%)	1 (1.4%)
Asian or Pacific Islander	13 (9.8%)	5 (7.2%)
Multiracial Origin	6 (4.5%)	1 (1.4%)
Other	4 (3.0%)	3 (4.3%)
Not Provided	0 (0.0%)	1 (1.4%)

Values are expressed as mean ± standard deviation for quantitative data and N (%) for categorical data and are for the per-protocol (PP) population.

Table 2. Upper respiratory tract infection outcomes.

	Control ($N = 133$)	β-Glucan ($N = 69$)	p value
Duration of URTI episodes	2.99 ± 4.43	2.80 ± 4.84	.5304
Total symptomatic days	3.84 ± 6.84	3.43 ± 6.44	.0346
Total number of URTI episodes	0.52 ± 0.71	0.38 ± 0.60	.1647

All values are expressed as mean ± standard deviation. Results shown here are from the per-protocol (PP) population. Duration of URTI episodes was analyzed using two-sided Wilcoxon rank sum test using Hochberg procedure for multiplicity. Total symptomatic days and total number of URTI episodes were analyzed using two-sided, two-sample zero-inflated Poisson model. One URTI episode is defined as ≥2 symptomatic days. URTI = upper respiratory tract infection.

compared to those consuming the control beverage (range of 0–49 days; Table 2). By contrast, the number of URTI symptom days was significantly higher in the dispersible yeast β-glucan group (4.28 ± 8.27 days, range of 0–62 days) compared to control (3.38 ± 6.56 days, range of 0–49 days) in the ITT sample.

URTI severity

Total severity of URTI was significantly lower in the dispersible yeast β-glucan group compared to the control group in the PP population (Table 3). Consistent with this, severity ratings for nasal discharge and sore throat were lower in the dispersible yeast β-glucan group compared to the control group in the PP population. These were not significantly different in the ITT population.

Exercise activities

There were no significant differences between the dispersible yeast β-glucan and control groups for number of missed days of marathon training due to URTI in the PP population (Table 4). Number of missed days of postmarathon workout due to URTI was significantly lower in the dispersible yeast β-glucan group (range of 0–2 days) compared to the control group (range of 0–10 days) in the PP population. There were no significant differences between groups in the number of days it took participants to resume workouts after completion of the marathon and intensity of their postmarathon workouts in the PP population.

Table 3. Jackson index rating.

	Control ($N = 133$)	β-Glucan ($N = 69$)	p value[2]
Total score	5.60 ± 2.23	4.52 ± 1.61	.0184
Nasal discharge	1.38 ± 0.47	1.07 ± 0.31	.0008
Nasal obstruction	0.93 ± 0.59	0.94 ± 0.48	.8955
Sneezing	0.73 ± 0.56	0.76 ± 0.50	.7948
Sore throat	0.64 ± 0.53	0.28 ± 0.27	< .0001
Malaise	0.49 ± 0.61	0.32 ± 0.41	.1453
Headache	0.43 ± 0.46	0.39 ± 0.43	.7673
Cough	0.77 ± 0.62	0.58 ± 0.60	.1981
Chilliness	0.23 ± 0.37	0.18 ± 0.27	.4703

All values are expressed as mean ± standard deviation. Results shown here are from the per-protocol (PP) population; p values obtained from two-sided, two-sample unequal-variance z test.

Table 4. Exercise-related outcomes.

	Control ($N = 133$)	β-Glucan ($N = 69$)	P value
Missed days of premarathon training due to URTI	0.43 ± 1.10	0.29 ± 0.96	0.5702
Missed days of postmarathon workout due to URTI	0.36 ± 1.40	0.09 ± 0.38	0.0054
Days to resuming postmarathon workout	3.52 ± 3.19	3.57 ± 4.74	0.7007
Intensity of postmarathon workout	5.94 ± 0.96	5.77 ± 1.19	0.8252

All values are expressed as mean ± standard deviation. Results shown here are from the per-protocol (PP) population. Missed days of marathon training and missed days of postmarathon workout due to URTI were analyzed using two-sided, two-sample zero-inflated Poisson model. Days to resuming postmarathon workout was analyzed using log-rank test. Intensity of postmarathon workout was analyzed using two-sided Wilcoxon rank sum test. Intensity was measured using an 11-point scale whereby 0 = extremely easy and 10 = extremely hard. URTI = upper respiratory tract infection.

Discussion

To the best of our knowledge, this randomized, controlled study is the first report of the effect of dispersible yeast β-glucan incorporated into a pasteurized beverage on URTI in marathon runners. Study results indicate that dispersible yeast β-glucan beverage consumption prior to and after a marathon decreased the number of symptomatic URTI days and severity of URTI symptoms, without affecting duration and number of URTI episodes. Consumption of dispersible yeast β-glucan beverage also decreased the number of missed postmarathon workout days without affecting premarathon training and intensity of postmarathon workouts.

Previous studies have investigated the effects of dispersible yeast β-glucan as an encapsulated supplement on URTI postmarathon and reported beneficial effects. Marathon runners who consumed 250 mg/day or 500 mg/day of encapsulated dispersible yeast β-glucan for 28 days after completing a marathon reported fewer URTI symptoms (Talbott and Talbott, 2009) and tended to experience fewer cold symptomatic days compared to those who were on the control (0 mg β-glucan) (McFarlin et al. 2013). Similarly, we observed decreases in URTI symptomatic days and URTI severity following consumption of dispersible yeast β-glucan before and after a marathon. The results suggest that the structural characteristics of the dispersible yeast β-glucan important for priming the immune system are still present and accessible following incorporation into a food matrix and undergoing additional processing (e.g., pasteurization). However, the extent to which these characteristics are affected by food manufacturing is unknown, and additional study is warranted to compare the immunomodulating properties of dispersible yeast β-glucan before and after incorporation into a food product.

In addition to a reduction in URTI symptomatic days, participants in the dispersible yeast β-glucan group reported fewer missed days of postmarathon workout due to URTI, without any changes in premarathon training. None of the previous studies on dispersible yeast β-glucan in marathon runners (Talbott and Talbott, 2009; McFarlin et al. 2013) have assessed the effect of the supplement on exercise regimen. Our observations suggest that dispersible yeast β-glucan may improve postevent workout, possibly by reducing the occurrence and severity of URTI symptoms that would otherwise prevent exercise activities. Indeed, the rate of infection is associated with training volume in elite athletes (Martensson et al. 2014), whereby greater occurrence of infection is related to less training. Additional study is needed to investigate the relationship between URTI and exercise activities in recreationally active individuals, either in preparation for or following a sporting event.

β-Glucans are a heterogeneous group of polysaccharides found in the bran of oat and barley cereal grains, the cell wall of baker's yeast, and mushrooms (Jesenak et al. 2017). Similar to those observed for dispersible yeast β-glucan, supplementation with dispersible β-glucan derived from *Pleurotus ostreatus* (oyster mushroom; 200 mg/day for 3 months) decreased the incidence of URTI in elite athletes (Bergendiova et al. 2011). By contrast, supplementation of dispersible oat β-glucan (5.6 g/day for 2 weeks) failed to affect URTI incidence in trained male cyclists (Nieman et al. 2008). The effect of yeast β-glucan on URTI in comparison to other types of β-glucan is unknown and warrants investigation to better understand the structure–function relationship between the different β-glucans and URTI induced by strenuous exercise.

Various studies have investigated the mechanism by which β-glucans regulate the immune function. Dispersible β-glucans are not absorbed into the blood and the mechanism by which they interact with the immune system is unclear. β-Glucan may enter the matrix of Peyer's patches of the small intestinal lumen through microfold (M) cells and interact with resident macrophages and dendritic cells (Volman et al. 2008). Alternatively, the dendritic cells of the follicle-associated epithelium extend projections into the intestinal lumen that may capture β-glucan by binding to various receptors, such as dectin-1 and complement receptor 3 (CR3) (Goodridge et al. 2009). A limitation of this study is our participants were screened for immune-related disorders, but not specifically for gastrointestinal disorders, which may affect the absorption of the dispersible yeast β-glucan. An important receptor mediating the biological effects of dispersible β-glucan is dectin-1, a pattern-recognition receptor for a variety of β-glucans (Goodridge et al. 2011). It is expressed on the cells of nonspecific immunity (e.g., macrophages, neutrophils, and dendritic cells) and activates antimicrobial and inflammatory responses and plays a role in the adaptive immune immunity. Activation of dectin-1 is dependent on the solubility of the β-glucan as soluble yeast β-glucan does not induce dectin-1 signaling (Goodridge et al. 2011). Instead, studies have demonstrated binding of soluble yeast β-glucan to CR3 expressed on neutrophils and monocytes (Bose et al. 2013). In addition, supplementation with soluble yeast β-glucan decreased URTI symptomatic days in marathon runners (McFarlin et al. 2013), suggesting that soluble yeast β-glucan possesses immunomodulating properties as well. Although we did not investigate the possible mechanisms by which yeast β-glucan decreased URTI symptomatic days and severity, others have demonstrated changes in

inflammatory mediators and antibodies following dispersible yeast β-glucan supplementation (Carpenter et al. 2013; McFarlin et al. 2013; Fuller et al. 2017).

We noted differences between the analysis of the ITT and PP populations; however, the PP population is more reflective of the response in individuals who actually consumed the product. Thus, our observations suggest that dispersible β-glucan is likely to confer beneficial immunomodulating effects if taken as instructed during the preparation for, and recovery from, a strenuous exercise activity. A reason for the high attrition and noncompliance rate is the lack of personal interaction due to the online/electronic nature of the study, despite implementation of several strategies to encourage retention such as reminder emails, follow-up telephone calls, and scheduled updates on study progress. In addition, high prerace dropout rates are inherent to marathons due to such factors as injury, loss of motivation, and scheduling changes (Clough et al. 1987). Finally, while the current study suggests beneficial effects of dispersible β-glucan in marathon runners, studies are needed to investigate the effects of this beverage in other populations.

Conclusion

In conclusion, the consumption by marathon runners of a dairy-based beverage containing dispersible yeast β-glucan decreased severity ratings for specific URTI symptoms and the number of missed days of postmarathon workout due to URTI without affecting duration and number of URTI episodes. The results demonstrate that dispersible yeast β-glucan, incorporated into a food matrix, confers beneficial effects on exercise-induced URTI in marathon runners.

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Declaration of interest

EM, VNK, KMK, and DJL are employees of Biofortis, Merieux Nutrisciences. Kerry, Inc. was initially involved in study conception but had no influence on the final study design and data analysis and interpretation regarding the conclusions of this study.

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