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Baker's Yeast Beta-Glucan Decreases Episodes of Common Childhood Illness in 1 to 4 Year Old Children during Cold Season in China

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Abstract

Infections are common in early childhood and create a large economic burden on both the healthcare system and individual family. To solve this problem, we evaluated the ability of baker's yeast beta glucan (BYBG) to reduce the number of episodes of common childhood illness in 174 Chinese children with 1 to 4 years old in a 12 week randomized, double-blinded, placebo controlled study. We found that children in BYBG group experienced less common childhood infectious illness episodes during the study compared to the placebo group and BYBG were well tolerated for the children with 1 to 4 years old.

Keywords: Yeast; Beta-glucan; Healthcare; Susceptibility

Introduction

Infections, especially upper respiratory tract infections (URTI) are common in early childhood because of their narrower airways, developing lungs and immune systems [1]. The overall incidence of acute respiratory infection in the children less than 5 years old was observed to be 2.5 episodes per child per year, of which, 2.2 episodes per year per child were URTI [2]. According to a survey conducted in China, there were 3.1 episodes of common cold per year per child fewer than 7 years old and most occurred during the autumn and winter months [3]. The incidence of common cold episodes was twice as high for children under 4 years compared to children between 4 and 7 years [3]. URTI in children creates a large economic burden on both the healthcare system and individual family, including lost work hours due to parents attending to the sick child [4,5]. In addition to the drugs or vaccines, there are many foods and dietary supplement ingredients intended to improve children's health status and immune function to decrease their susceptibility to common childhood illness, but the level of supporting evidence needs to be further substantiated with well-designed clinical research [6].

Baker's yeast β-glucan (BYBG) has been shown to have immuno-modulatory effects and to reduce the incidence of URTI symptoms in adults in previous studies [7-10]. There are significantly fewer studies on the effects of BYBG on the physical health status of young children. BYBG is a naturally occurring β-1,3/1,6 glucan purified from the cell wall of *Saccharomyces cerevisiae*. It is widely approved for use in food, beverage and dietary supplement products in Asia, Europe, North and South America. In 2010, the Chinese Ministry of Health approved BYBG as a novel food ingredient. Additionally, in 2012 BYBG was approved as nutrient supplement added when added to toddler formula and milk powder intended for young children by the No. 6 announcement of the Ministry of Health in China.

The immuno-modulatory effect of BYBG and reduced URTI incidence has been demonstrated in adults [7-10] and this study was intended to evaluate similar benefits for children. There are significantly fewer studies on the effects of BYBG on the physical health of young children and additional support is prudent. This study was designed to evaluate the effect of BYBG on the incidence of infectious illnesses in children between 12 to 48 months in China during cold season.

Materials and Methods

Study design

This study was a randomized, double-blinded, placebo controlled study completed in Beijing, China. It was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Changping Women's and Children's Hospital research ethics committee. The parent or legal guardian of subjects gave written informed consent before their participation. The study was conducted from November 2013 to April 2014. Potential subjects were screened against inclusion and exclusion criteria (see below) during an initial meeting with the investigator. According to the recommendation of CFDA, we chose about one-third dosage of adults (250 mg every day in previous studies [7-10]), 75 mg as the high dosage and half of high dosage, 35 mg as low dosage in our study. The blinded randomization of enrolled subjects was 1:1:1 to two treatment groups (35 mg or 75 mg of BYBG per day) or placebo group, according to a randomly generated coding allocation produced by the statistical staff.

Study population

The inclusion criteria included healthy children from 12 to 48 months of age (≥ 12 months to ≤ 48 months) enrolled in daycare at Beijing Changping Maternal and Child Health Hospital with a medical history of upper respiratory tract infection of at least two URTI episodes in the previous three months. The exclusion criteria were:

- History of severe infectious diseases (i.e., pneumonia, septicemia, urinary tract infection).

- History of cardiac, liver or kidney diseases, endocrine and metabolism system diseases, hematological diseases and peripheral and central nervous system diseases.
- Family history of inherited diseases.
- Current use of immune-potentiator or immune-suppressive agents within the last three months.
- Current use of any product therapy or supplement that might affect the safety of the product user or complicate the study results.
- Any medical condition or disease that might affect the safety of the product user or make the study results complicated, or a history of allergy to food especially dairy products.

Test samples and compliance

The BYBG treatment samples contained Wellmune® (manufactured by Kerry, Inc. Beloit, WI USA) as the source of BYBG along with maltodextrin and sugar. The placebo contained only sugar and maltodextrin. All samples were prepared by Kerry and packaged in single serve packets with 5 g contents which were dissolved in warm water prior to consumption. Each child needed to consume one packet (BYBG treatment or placebo) once daily for 12 weeks.

Assessments

This study aimed to evaluate the health status of children in different groups. The health status of the children was assessed as the proportion of subjects that experienced any confirmed common childhood infectious illness episodes, which determined by the investigator based on a study diary maintained by subject's parent or legal guardian and medical records (original materials including clinic visits, outpatient records, laboratory tests, use of prescription drugs, etc.) during the study. The study diary was used to record symptoms in the following categories: respiratory system; urinary system; digestive system; aches; general symptom; any other symptoms. Secondary endpoints included the duration and number of episodes of upper respiratory tract infection (URTI) and duration and number of episodes of all common childhood infectious illness symptoms. Safety was evaluated by monitoring adverse events, physical examination and vital signs of subjects.

Statistical Analyses

The statistical analyses were conducted using SAS 9.1.3. All randomized subjects who received at least one dose of yeast BYBG or placebo and had at least once efficacy evaluation after baseline were included into the FAS statistical analysis. All subjects who received at least one dose of yeast β-glucan/placebo and had at least one safety evaluation were included into the analysis of safety. Results are described as mean ± SD (standard deviation). For qualitative variables the results are described as frequency (percentage). The primary endpoints of the three groups were compared using the Cochran-Mantel-Haenszel test. When $P < 0.05$, comparisons between either two groups were conducted by ANCOVA. The secondary endpoints of three groups were compared with ANCOVA. A P-value less than or equal to 0.05 was considered as statistically significant. The safety parameters including the incidence, the severity and type of AEs, physical examination and vital signs of the product users were analyzed.

Results

Study population

Of 174 subjects enrolled, 152 subjects completed the study (Figure 1). Of 22 subjects whose participation was terminated, there were 4 subjects who received yeast β-glucan/placebo and had efficacy evaluation after base-line; these 156 subjects represent the full analysis set and were included in the FAS efficacy analysis. Figure 1 shows the flow of subjects in the study. A total of 73 boys and 83 girls were included. The mean (± SD) of age was 28.86 (± 11.75) months. The mean (± SD) of height was 90.22 (± 12.36) centimeters. The mean (± SD) of weight was 13.86 (± 3.35) kilograms. All the subjects have upper respiratory tract infection history in the past three months. All relevant characteristics in the three groups were comparable (Table 1).

Variables	Statistics	75 mg BYBG (n = 51)	35 mg BYBG (n = 53)	Placebo (n = 52)
Age (months)	N	51	53	52
	Mean (SD)	29.7 (12)	29.6 (11)	27.3 (11)
Gender				
Male	N (%)	20 (39%)	26 (49%)	27 (52%)
Female	N (%)	31 (61%)	27 (51%)	25 (48%)
Height(cm)	Mean (SD)	91 (13)	91 (12)	88 (12)
Weight(kg)	Mean (SD)	14.0 (3.5)	14.4 (3.6)	13.3 (2.9)
Days with childhood infectious symtoms*	Mean (SD)	17.1 (5.0)	16.1 (3.5)	16.7 (3.7)
Episodes of childhood infectious disease*	Mean (SD)	2.5 (0.6)	2.3 (0.5)	2.3 (0.5)
Days with URTI symptoms*	Mean (SD)	15.3 (5.1)	15.0 (3.27)	15.6 (3.33)
Episodes of URTI*	Mean (SD)	2.1 (0.46)	2.1 (0.27)	2.1 (0.27)

Table 1: Demographics and baseline characteristics (FAS). *In three months previous to start of trial.

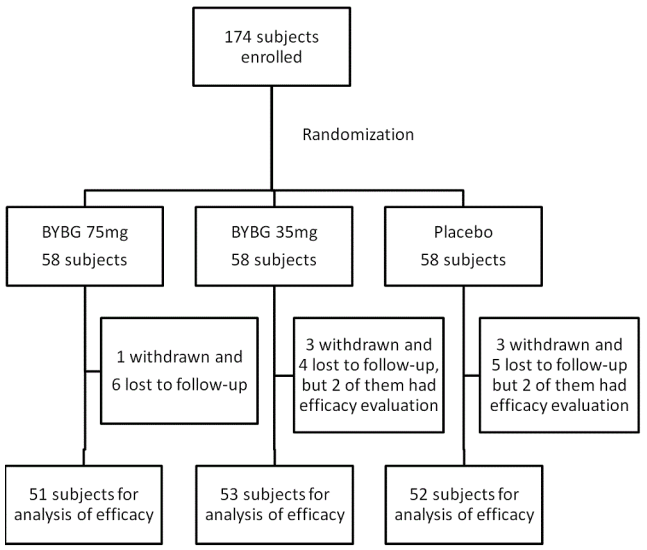

Figure 1: Flow diagram of the study.

Incidence of one or more episodes of infectious illness during the study

During the 12-week study, the mean (± SD) of administration of β-glucan/placebo according to the protocol was 80 (± 6) days. During the 12-week course of the study 85% of children in the placebo group experienced one or more episodes of infectious illness. By contrast, children in either of the two BYBG treatment groups (47% in BYBG 75 mg/d group, 32% in BYBG 35 mg/d group) experienced a significantly reduced incidence of infectious illness (Figure 2). There was no significant difference in infectious illness episodes between either BYBG treatment groups (P=0.6314) (Figure 2).

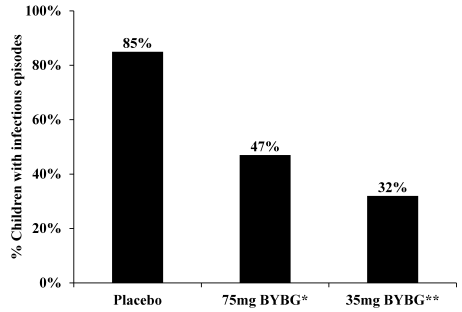

Figure 2: The proportion of subjects with common childhood infectious episodes during the study. The subjects received yeast β-glucan at the indicated dose or placebo for 12 weeks. All infections during the study were recorded. Both BYBG groups were significantly different from placebo (*75 mg $p < 0.001$ and **35 mg $p < 0.0001$) and there was no significant difference between the two BYBG groups.

Duration and number of URTI episodes

The duration and number of episodes of all infectious illness experienced in the three months prior to starting the study was similar among all study participants. During 12-week study period BYBG was observed to decrease the both the duration and number of URTI episodes compared to children in the placebo group. The average URTI duration in the placebo group was 8.9 days compared with 3.5 and 2.9 days in the 75 mg/d and 35 mg/d BYBG groups respectively ($P < 0.0001$). Similarly, the average number of URTI episodes in the placebo group was 1.5, compared to 0.7 and 0.5 in the BYBG 75 mg/d and 35 mg/d treatment groups respectively ($P < 0.0001$). No difference in either URTI duration or episode incidence was observed between either BYBG treatment groups (Figure 3).

Duration and number of all infectious illness episodes

A total of 153 episodes of common childhood illness in 94 children were recorded during this study (BYBG 75 mg/d: 27 children, BYBG 35 mg/d: 22 children, placebo: 45 children). This included 135 URTI episodes in 83 children, 16 episodes of bronchitis in 9 children, one episode of pyrexia and one episode of diarrhea. The average day with common childhood illnesses symptoms in the placebo group was 9.9 days. This was significantly longer than the average days with common childhood illnesses symptoms in either BYBG treatment group (75 mg/d group: 3.6 days, $P < 0.0001$ or /d group: 4.7 days, $P < 0.001$). The average number of incidents of all common childhood illnesses in the placebo group was 1.6 episodes during the study, significantly more than BYBG 75 mg/d (0.7 episodes, $P < 0.0001$) or BYBG 35 mg/d (0.7 episodes, $P < 0.0001$). There was no difference in number of common childhood illness episodes between either BYBG treatment groups (Figure 4).

Safety

All reported adverse events (AE) were mild to moderate and no serious adverse events (SAE) were reported during the study. Only 1 AE (mild vomiting) in the BYBG 35 mg/d group was considered to have a doubtful relationship with the study product and the rest were determined to be not related to the investigational product. All results of the physical examinations that were done in the baseline and visits were normal and there was no clinically significant difference in the vital signs among the three groups.

Discussion

BYBG is a naturally occurring β 1,3/1,6 glucan purified from the cell wall of Saccharomyces cerevisiae that is a known biological response modifier (BRM) [11]. It is one of many microbe associated molecular patterns (MAMPs) which are recognized by the human immune system's pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs),and C-type lectin receptors (CLRs). These receptors are expressed in distinct patterns mainly on cells of the immune and epithelial systems. When PRRs recognize a MAMP, defined intracellular signaling pathways are activated. Both secretion of so called "level 1" cytokines and in some cases activation of cellular effector functions are the result of MAMP detection by PRRs [12,13].

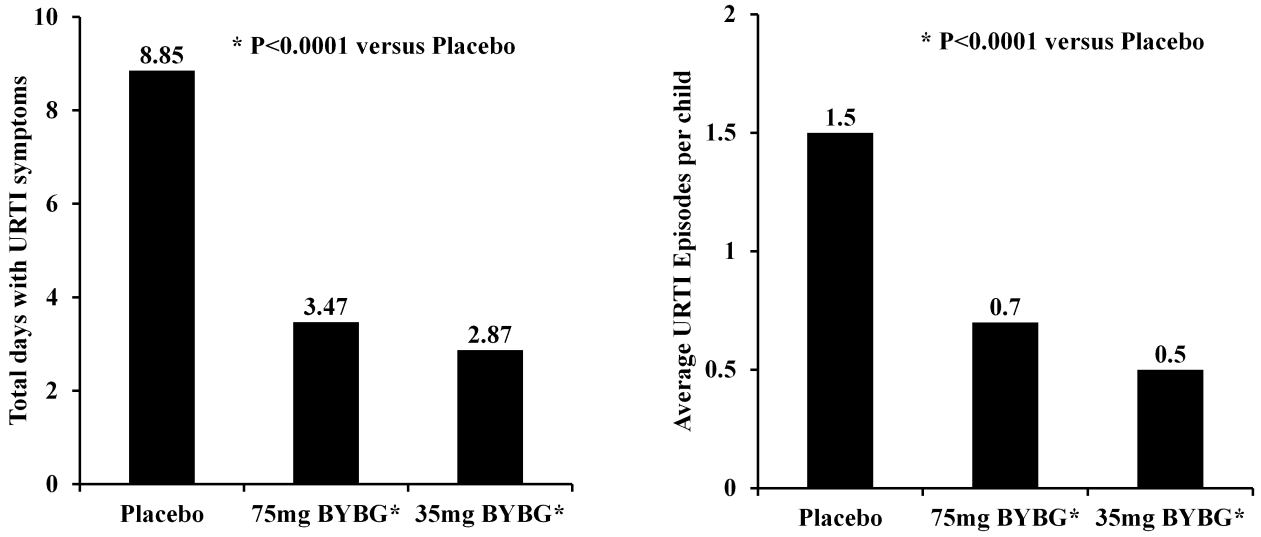

Figure 3: Total duration and incidence of URTI in FAS. After enrollment, subjects received BYBG or placebo at the indicated dose for 12 weeks. Both BYBG groups had significantly fewer ($p < 0.0001$) URTI episodes and total days with URTI symptoms than the placebo group. There was no significant difference between the two BYBG groups for either measure.

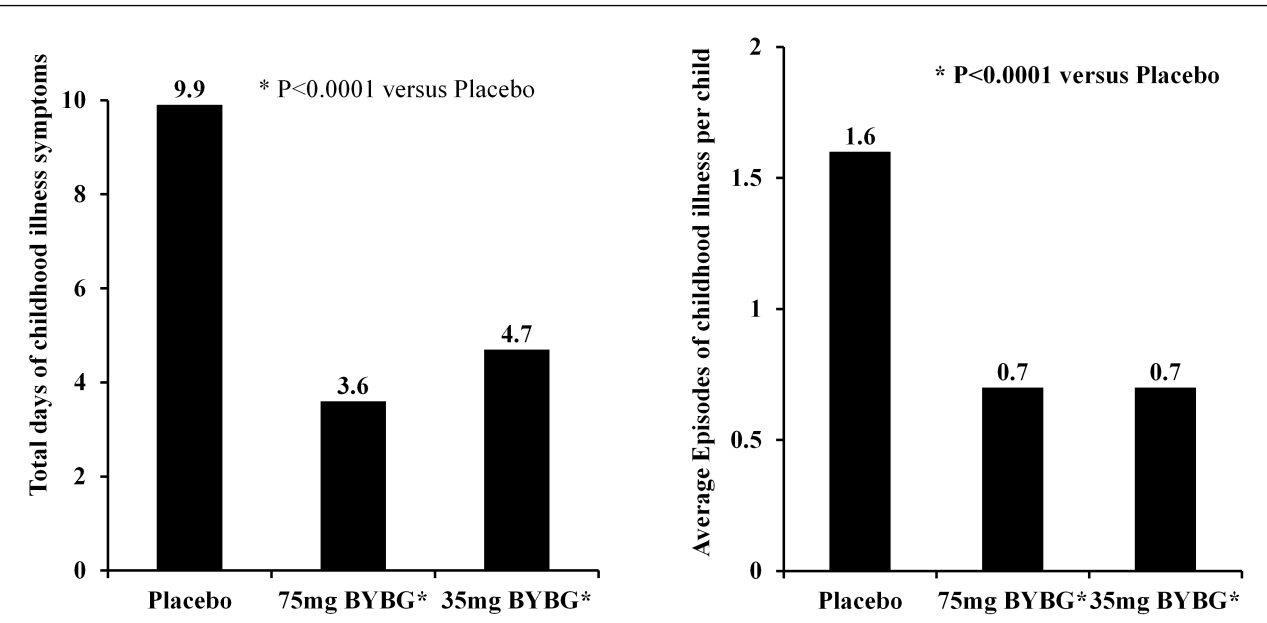

Figure 4: Duration and total number of episodes of all infectious illness in FAS. After enrollment, subjects received BYBG or placebo at the indicated dose for 12 weeks. Both BYBG groups had significantly fewer ($p < 0.0001$) common childhood illness episodes and total days with common childhood illness symptoms than the placebo group ($p < 0.0001$). There was no significant difference between the two BYBG groups for either measure.

Research conducted over the past 10 years has suggested that supplementing a healthy diet with BYBG may have beneficial effects on the human immune system. This has been demonstrated in previous studies as a reduction in the incidence of URTI symptoms in adults supplemented with BYBG [7-10]. Talbott et al. [10] reported that after 2 weeks of BYBG supplementation in stressed, otherwise healthy adults, only 8-10% of subjects reported URTI symptoms while 32% of the placebo group reported URTI symptoms. Auinger et al reported β-glucan could reduce the number of symptomatic common cold infections by 25% as compared to placebo in the people with at least three colds in the last 6 months [14]. Additionally, in three separate studies in children between the ages of 3 and 12 years [15-17], BYBG

supplementation resulted in a reduced incidence and duration of acute respiratory infection (ARI). Richter et al reported that the production of lysozyme, CRP and calprotectin significantly increased in glucan-treated children from 8 to 12 years old [16].

This study was designed to answer the question of whether supplementing a normal diet with BYBG in children aged 1-4 year in a daycare in China would have a similar beneficial effect on the health status of the children during the cold/flu season. Here we report that BYBG supplementation during a 12-week study improved the health status of the children in the treatment group as measured by a reduction in incidence and duration of infectious illness compared to placebo. Eighty-five percent of children in the placebo group reported one or more episode of infectious illness during the 12-week study compared with only 47% and 32% of children in the BYBG supplementation groups. Further, the incidence and duration of URTI in the BYBG supplementation groups was significantly lower than in the placebo group. Two doses (75 mg/d and 35 mg/d) of BYBG were evaluated in this trial for safety and efficacy and no difference in any outcome or safety parameter was observed. Both doses were well tolerated. Therefore we suggest that the 35 mg/d dose is sufficient for children between 12 and 48 months of age to observe optimal benefit during the cold and flu season. Since this study was limited to a single-center trial in Beijing, future work should expand the study population into other larger districts to confirm the result of the study. Additionally, future trials would benefit from evaluating some biomarkers of immune status as further evidence of efficacy. In the pediatric population this presents some challenges including enrollment barriers when invasive techniques are used (i.e., blood collection), but options for investigation of biomarkers in non-invasively collected body fluids (saliva, urine, feces) could be explored. Combining monitoring infection status with an immune biomarker would strengthen future studies in this area. However, despite these limitations of the study we believe that BYBG supplementation in children could decrease the incidence and severity of infectious illness during the cold/flu season, alleviating some of the burden on parents of caring for sick children.

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