Randomized Phase II Clinical Trials of Wellmune WGP® for Immune Support During Cold and Flu Season

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ABSTRACT

Beta-glucan from oats and barley may decrease cardiovascular risk factors. Beta-glucan from some kinds of mushrooms may have as similar effect while modulating the immune system. This pilot trial examined whether beta-glucan derived from *Saccharomyces cerevisiae* can favorably decrease the risk of or symptomology associated with upper respiratory illness. Forty healthy adult subjects (18 to 65 years of age) were enrolled in a 12-week, randomized, double-blind, placebo-controlled, parallel-group trial conducted during the cold/flu season. The treatment arm compared Wellmune WGP® (WGP) gluco polysaccharide (beta-glucan) (500 mg/d) vs a placebo (500 mg rice flour). Cold/flu symptoms were evaluated by medical staff within 24 hours of onset. There were no significant differences in the incidence of symptomatic respiratory infections (SRI's) among the study groups. However, none of subjects in the WGP group missed work or school due to colds, while subjects with colds in the placebo group missed an average of 1.38 days (Intent to Treat: (0.00 ± 0.00 vs. 1.38 ± 1.25; p = 0.026). Quality of Life, assessed by the Physical Component Summary score (SF36v-2), improved significantly in the WPG group vs the placebo group after 90 days as compared to baseline (Intent to Treat: 0.8 ± 5.5 vs. -1.9 ± 2.8; p = 0.042). The WGP group had a significantly lower average fever score than the placebo group (Per Protocol: 0.00 ± 0.00 vs. 3.50 ± 3.42; p = 0.042). No adverse events were detected and no safety concerns were presented. This preliminary study suggests 1,3-1,6 beta-glucan from

Saccharomyces cerevisiae may modulate the immune system and reduce some risks associated with upper respiratory influenza infections.

INTRODUCTION

The common cold, typically caused by human parainfluenza viruses, remains one of the most frustrating of medical illnesses, given its incidence and prevalence. The common cold has significant effects on health, well-being, and productivity. Each cold experienced by a working adult results in an average of 8.7 lost work hours, and 1.2 lost work hours due to attending to sick children.[1] The economic burden of lost productivity due to colds is approximately $25 billion annually, with lost productivity from missed work days comprising the majority of the financial burden.[2] There are no reliable interventions currently available that significantly protect against influenza infections or prevent the occurrence of this illness. There have been several clinical trials evaluating a variety of dietary supplements for the prevention and treatment of both experimentally induced and naturally occurring colds. Many of those interventions included Echinacea,[3-13] vitamin C,[14-18] probiotics,[19] ginseng,[20] vitamin E, [21,22] and zinc. [20,23-36] Other studies indicate no dietary supplement consistently reduces the risk of the common cold. Some studies suggest vitamin E and ginseng may reduce the incidence of common colds,[20,21] while other investigations report no favorable effects of vitamin E on upper respiratory tract infection.[22] Zinc, from zinc acetate, is reported to reduce the symptom and severity of common colds in healthy adults,[29] while other reports suggest the absence of any effect.[32,33] These apparent discrepancies are due to various study limitations across the literature, such as potential differences in product identity and dose, and small sample size and low statistical power, or lack of a clinical effect. Another possibility may be genetic variations and immunocompetencies among study subjects.

Biological response modifiers such as beta-glucan, enhance the innate immune response without inducing damaging pro-inflammatory cytokines, and may represent a novel approach to protect against cold and flu pathogens. [37,38] Beta-glucans are glucose polymers derived from yeast, fungi, or from oats. *In vivo* studies suggest beta-glucans may enhance the immune system responses to infectious organisms without eliciting a pro-inflammatory cytokine response. [37,39-43] Other *in vivo* investigations report that oat-derived beta-glucan can decrease increased risk of upper respiratory tract infection as a result of stressful exercise in mice.[44,45]

In clinical trials, beta-glucan reduces postoperative infection rates and shortens intensive care unit stay duration.[46-48] One study also reported that increasing doses of beta-glucan resulted in fewer infections after surgery.[46]

Beta-glucan from a variety of dietary sources has immunomodulatory properties. The potential immunomodulatory effect of beta-glucan from *Saccharomyces cerevisiae* has not been evaluated in a structured clinical trial that assesses its efficacy on the prevention and/or treatment of the common cold in a healthy adult population. The current study aimed to determine whether the proprietary beta-glucan extract Wellmune WGP® (WGP) can reduce the incidence and/or duration/severity of respiratory illnesses in a healthy population during peak cold/flu season.

MATERIALS AND METHODS

Protocol

A randomized, double-blind, placebo-controlled, parallel-group trial compared beta-glucan extract Wellmune WGP®

Table 1. Inclusion and Exclusion Criteria

Criteria	
Inclusion criteria	Age ≥18 and ≤ 65 Generally healthy BMI > 25 kg/m2 and ≤ 40 kg/m2 at screening Agree to all study visits and visit procedures Females must agree to use appropriate birth control methods during the study Community dwelling At least 1 self-reported cold in the last 12 months prior to screening
Exclusion criteria	Cigarette smoking Current respiratory illness Temperature > 38.3°C at screening Immune modifying medications: Anti-inflammatory agents, Antibiotics, Steroids Subjects with any history of immune system disorder or auto-immune disorder including but not limited to the following: • AIDS, HIV, • Ankylosing Spondylitis, Chronic Fatigue Syndrome, CREST Syndrome, Crohn's Disease, Dermatomyositis, Fibromyalgia, Grave's Disease, Hashimoto's Thyroiditis, Lupus, Myasthenia Gravis, Pernicious Anemia, Polyarteritis Nodosa, Primary Biliary Cirrhosis, Psoriasis, Reynaud's Disease, Rheumatoid Arthritis, Sarcoidosis, Scleroderma, Sjögren's Syndrome, Temporal Arthritis, Ulcerative Colitis, and Vitiligo Use of any immunosuppressive drugs in the last 5 years (Steroids, Biologics, etc.) History of Splenectomy History of Tuberculosis Diabetes (Type I and II) Untreated Hypothyroidism Active Liver Disease with liver function tests > 2X upper limit of normal (ULN) Active Renal Disease with Cr > 1.5 ULN Active Asthma requiring ongoing treatment Weight loss of ? 20 pounds in the last 3 months Untreated or unstable Hypothyroidism Abnormal physical examination Subjects with active eating disorder including anorexia nervosa, bulimia, and/or obsessive compulsive eating disorders

(WGP) and placebo in healthy community-dwelling subjects. Wellmune WGP, a registered trademark of Biothera, is a functional ingredient for foods, beverages and supplements that is derived from a proprietary strain of yeast (*Saccharomyces cerevisiae*) . The entire study was conducted at the Miami Research Associates (Miami, FL) facilities. This study was approved by the Copernicus Group, an Independent Review Board located in Cary, North Carolina.

All subjects who were taking immune-modifying dietary supplements prior to enrollement underwent a 4-week washout phase prior to randomization. Subjects were then randomly assigned to trail groups in which they were blinded to intervention. During the 90-day intervention period, subjects consumed 500 mg/d of beta-glucan or a rice-flour placebo. Subjects were evaluated by the medical staff within 24 hours of cold onset.

Endpoints were measured at the onset of symptoms of a respiratory infection, and twice daily for seven days. Endpoints measured were changes from baseline in: number of symptomatic res-

Table 2. Baseline Characteristics

Variables	Subject Demographics WGP 3–6 (*n* = 21) Total (%)	 Placebo (*n* = 19) Total (%)	 *p*-value
Age (years)	30.3 ± 11.4	36.4 ± 16.2	0.248
Sex:			
Female	14 (67)	14 (74	0.736
Male	7 (33)	5 (26)	
Race:			
Asian	1 (5)	0 (0)	1.000
Caucasian	18 (86)	19 (100)	
Other	1 (5)	0 (0)	
Unknown	1 (5)	0 (0)	
Hispanic:			
No	5 (24)	6 (32)	0.727
Yes	16 (76)	13 (68)	
Consent Language:			
English	21 (100)	19 (100)	

	Morphometry and Vital Signs WGP 3–6 (*n* = 21) Total (%)	 Placebo (*n* = 19) Total (%)	 *p*-value
Height (cm)	167.4 ± 9.7	166.8 ± 10.1	0.851
Weight (kg)	66.3 ± 11.8	70.2 ± 14.9	0.486
BMI (kg/m^2)	23.6 ± 2.5	25.1 ± 4.3	0.258
Body temperature (°F)	98.16 ± 0.48	98.22 ± 0.60	0.531
Heart Rate (beats/minute)	81.7 ± 16.6	72.5 ± 10.7	0.098
SBP (mm Hg)	112.3 ± 12.9	112.7 ± 8.0	0.919
DBP (mm Hg)	71.8 ± 10.8	74.1 ± 6.2	0.433
Flu Vaccine:			
No	14 (67)	15 (79)	0.488
Yes	7 (33)	4 (21)	

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

piratory infections (SRIs) that each subject had during the study, total days of duration of each subject's SRIs, average days of duration of each subject's SRIs, symptom-days total for each SRI symptom based on a self-report daily diary, and average symptom-day total for each subject that included categories SRIs into Colds, Flu, or Pharyngitis. Other endpoints included safety data through laboratory (CBC, kidney, and liver function) and physical testing.

Subjects

Subjects were screened in January and February of 2006. Subjects were recruited from existing patient populations, physician referrals, subject databases, and community-based local advertising. Approximately 65 potential candidates were telephone screened and 42 were called in for a screening visit (Figure 1). Exclusion and inclusion criteria are provided in Table 1. Out of the 42 potential subjects, two screened subjects did not

Table 3. Symptomatic Respiratory Episodes

	Intent-to-Treat Population			Per-Protocol Population		
	WGP 3–6 (*n* = 17) Total (%)	Placebo (*n* = 16) Total (%)	*p*-value Total (%)	WGP 3–6 (*n* = 14) Total (%)	Placebo (*n* = 13) Total (%)	*p*-value
Any Colds During the Study?						
No	11 (65)	11 (69)	1.000	9 (64)	9 (69)	1.000
Yes	6 (35)	5 (31)		5 (36)	4 (31)	
Number of Colds	0.41 ± 0.62	0.44 ± 0.73	0.948	0.43 ± 0.65	0.46 ± 0.78	0.953
Average Durationof a Cold	12.9 ± 12.4	7.5 ± 2.0	0.592	13.5 ± 13.8	7.5 ± 2.0	0.902
Average Number of Missed Days of School or Work per Cold	0.00 ± 0.00*	1.38 ± 1.25	0.026	0.00 ± 0.00*	1.38 ± 1.25	0.042
Number of SRI Episodes	0.41 ± 0.62	0.44 ± 0.73	0.948	0.43 ± 0.65	0.46 ± 0.78	0.953
Number of Cold Episodes	0.29 ± 0.59	0.38 ± 0.72	0.866	0.36 ± 0.63	0.46 ± 0.78	0.832
Number of Flu Episodes	0.059 ± 0.243	0.000 ± 0.00	0.363	0.00 ± 0.00	0.00 ± 0.00	
Number of Pharyngitis Episodes	0.059 ± 0.243	0.000 ± 0.00	0.363	0.071 ± 0.0267	0.00 ± 0.00	0.374
Number of URI Episodes	0.00 ± 0.00	0.063 ± 0.250	0.332	0.00 ± 0.00	0.00 ± 0.00	
Total Duration ofSRI Episodes	5.1 ± 9.9	3.0 ± 6.2	0.580	5.4 ± 10.7	3.7 ± 6.8	0.862
Total Missed Days of School or Work per Subject	0.00 ± 0.00	0.50 ± 1.10	0.071	0.00 ± 0.00	0.62 ± 1.19	0.068

*p < 0.05

meet the inclusion/exclusion criteria: one subject had abnormal laboratory results, and another was listed as ineligible in the database.

The remaining 40 healthy community-dwelling adults (28 females, 12 males) between the ages of 18 and 65 were enrolled into the study. There were 12 early terminations: one subject withdrew consent, and 11 subjects were lost to follow-up. The remaining 28 subjects finished the study without protocol deviations. One subject completed all scheduled visits, but was excluded because of inadequate compliance. Subject baseline characteristics are displayed in Table 2. Subjects who qualified based on their screening visit, received $50 for the screening visit, and $50 for completion of each study visit. Total compensation was up to $300 per subject.

Products Tested

Forty subjects were randomly assigned to WGP (Wellmune WGP® beta-glucan) derived from *Saccharomyces cerevisiae* (250 mg) or a sensory-identical placebo

Table 4. Symptom Severity from Diary

	Intent-to-Treat Population (ITT)			Per-Protocol Population (PP)		
	WGP 3–6 (*n* = 17)	Placebo (*n* = 16)	*p*-value WGP 3–6	WGP 3–6 (*n* = 14)	Placebo (*n* = 13)	*p*-value
Total Tiredness	6.9 ± 12.3	6.8 ± 13.2	0.611	6.4 ± 12.1	8.3 ± 14.3	0.954
Total Stuffy Nose	8.8 ± 15.6	7.6 ± 15.1	0.642	7.3 ± 13.2	9.4 ± 16.4	1.000
Total Runny Nose	8.1 ± 15.5	7.1 ± 12.9	0.580	6.4 ± 13.0	8.7 ± 13.9	0.954
Total Scratchy/Sore Throat	8.8 ± 18.9	7.1 ± 14.6	0.674	9.2 ± 20.4	8.8 ± 15.8	0.954
Total Headache	3.1 ± 5.7	3.9 ± 7.6	0.963	3.4 ± 6.2	4.8 ± 8.2	0.810
Total Muscle Ache	3.5 ± 6.5	2.8 ± 6.6	0.565	3.6 ± 6.9	3.4 ± 7.3	0.850
Total Earache	1.12 ± 3.87	0.38 ± 1.50	0.357	1.2 ± 4.3	0.5 ± 1.7	0.625
Total Fever	0.6 ± 2.4	1.6 ± 4.3	0.295	0.0 ± 0.0	2.0 ± 4.8	0.068
Total Sneezing	6.1 ± 10.9	5.2 ± 10.1	0.658	4.9 ± 8.6	6.4 ± 10.9	0.977
Total Hoarse Voice	8.2 ± 19.3	5.7 ± 12.0	1.000	8.3 ± 20.8	7.0 ± 13.1	0.659
Total Cough Frequency	7.7 ± 15.7	6.3 ± 11.6	0.783	7.5 ± 16.3	7.7 ± 12.5	0.928
Total Cough Intensity	6.8 ± 14.1	6.1 ± 11.3	0.872	6.9 ± 15.1	7.5 ± 12.2	0.928
Total Phlegm / Mucous	8.1 ± 14.1	8.9 ± 17.9	0.740	7.7 ± 14.1	11.0 ± 19.4	0.954
Total Sleeplessness	5.3 ± 9.7	4.6 ± 9.1	0.854	5.9 ± 10.5	5.6 ± 9.9	0.952

containing rice flour. The intervention subjects consumed two capsules (total=500mg beta-glucan) once daily, 30 minutes before breakfast. The Intent-to-Treat (ITT) population consisted of 33 subjects (17 in the WGP group, and 16 in the placebo group) and defined as only those who received at least one dose of investigational product and returned for at least one visit after baseline. The Per-Protocol (PP) population consisted of 27 subjects (14 in the WGP 3–6 group, and 13 in the placebo group) who completed all visits, and had 80% compliance with the prescribed amount of product.

Baseline

At Visit 1 (Screening), subjects provided informed consent. Assessments at this visit were demographic and anthropomorphic, physical examination, vital signs, urine pregnancy test (females) medical history, current medication history, Quality of Life *via* the SF36v-2 questionnaire, and standard blood panel (CBC, kidney, and liver function).

Supplementation and Follow-up

At Visit 2 (Randomization, Day 0), subjects who met the inclusion/exclusion criteria were randomized and dispensed a 4-week supply of study product or placebo. Randomization was determined by atmospheric noise entropy (www.Random.org). Block randomization was utilized to insure uniform allocation of WGP and placebo. At Visit 3 (Day 30), subjects returned for blood draws, vital signs measurements, Quality of Life via the SF36v-2 questionnaire, interim medical history, compliance assessment, and adverse events review. Participants were then dispensed another 4-week supply of study product or placebo. These same procedures were completed at Visit 4 (Day 60) and Visit 5 (Day 90).

All subjects were contacted by phone at weeks 2, 6, and 10 to assess compliance. In addition, subjects' compliance with the prescribed amount of product was determined by the returned pill-count method at the 30-, 60-, and 90-day visits, and expressed as a fraction.

Table 5. Adverse Events (MedDRA coded)

	Number of Subjects		
	WGP 3–6	Placebo	*p*-value
Ear and labyrinth disorders	0	1	1.000
Eye disorders	1	0	1.000
Gastrointestinal disorders	1	1	1.000
General disorders and administration site conditions	1	0	1.000
Infections and infestations	9	5	0.296
Injury, poisoning and procedural complications	0	2	0.485
Musculoskeletal and connective tissue disorders	1	0	1.000
Nervous system disorders	1	3	0.601
Psychiatric disorders	1	1	1.000
Respiratory, thoracic and mediastinal disorders	1	1	1.000
Surgical and medical procedures	1	0	1.000
All Events	11	9	0.728

Subjects were instructed to page a member of the study team as soon as they felt symptoms of a respiratory illness. Subjects were examined by a qualified member of the study team within 24 hours of the onset of any SRI. The examination focused on SRI history, physical examination, standardized diagnosis (Clinical Diagnostic Criteria), baseline symptoms, and blood analysis. These subjects were provided symptom diaries, and instructed on their use. At 7 to 10 days following the SRI baseline visit, subjects returned for the following evaluations: SRI history, physical examination, collection of symptom diaries, and blood analysis.

Adverse Events

Self-report adverse events (AEs) were listed, Medical Dictionary for Regulatory Activities (MedDRA) encoded, grouped by general type of event (e.g., gastrointestinal, neurological, cardiac, or dermatologic), and cross-tabulated by event type and product dosing level. Potential differences in AE patterns between products were tested by the Fisher's Exact test. Significance was assigned at $p < 0.05$.

Sample Size

There appears to be a dearth of information on the prevention or treatment of upper respiratory tract infections that included 1-3,1-6 beta glucan. Limited information on the use of dietary supplements directed to cold/flu prevention indicated that community-based trials had sample sizes ranging from 126 to 668 subjects. The duration of these studies ranged from 30 days to several years. Inoculation and severity trials tended to have smaller sample sizes. Given the lack of data to calculate an effect size, the current investigation was undertaken as a pilot study intended to provide critical data for future studies. Power calculations based on the cold/flu literature supported a sample size of 40.

Statistical Analysis

The primary endpoint changes from baseline values were analyzed using a repeated measures analysis of variance (ANOVA). Two approaches to the analysis were performed. Analysis of the primary efficacy endpoints were performed in Intent-to-Treat (ITT) patients as well as Per-Protocol (PP) patients. The Intent-to-Treat analysis was considered primary. All data were transferred

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Infections and infestations	9	5	0.296
Injury, poisoning and procedural complications	0	2	0.485
Musculoskeletal and connective tissue disorders	1	0	1.000
Nervous system disorders	1	3	0.601
Psychiatric disorders	1	1	1.000
Respiratory, thoracic and mediastinal disorders	1	1	1.000
Surgical and medical procedures	1	0	1.000
All Events	11	9	0.728

into the '**R'** statistical system version 2.5.1 (*R* foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org) for subsequent statistical analysis. Specially-created R programs were used to generate the descriptive tables and statistical tests. For the Intent-to-Treat efficacy analysis, missing efficacy endpoints were imputed with the last available value (last observation carried forward (LOCF) imputation). All descriptive data are expressed as mean ± SD. Significance level was set at $p < 0.05$.

RESULTS

There were no significant differences between the treatment and placebo groups in the number of SRI episodes (6 vs. 5, WGP and placebo, respectively, p = 1.00), number of SRI's *per* subject (0.41 WGP vs. 0.44 placebo, p = 0.948), or number of subjects with SRI (Table 3). There were no significant differences between the groups in the duration of SRI episodes, or in the total daily symptom score of SRI's for seven days after the onset of symptoms. None of the WGP subjects missed work or school due to colds, while subjects in the placebo group with colds missed an average of 1.38 days. This was statistically significant in both the ITT and PP populations (p = 0.026 and p = 0.042, respectively).

SRI symptoms are shown in Table 4. None of the WGP subjects presented a fever, whereas the subjects in the control group became febrile (2.0 ± 4.8) in the PP group (p = 0.068). There was no significant effect of WGP on fever in the ITT analysis (0.6 ± 2.4 in WGP subjects and 1.6 ± 4.3 in the placebo group; p = 0.295). There were no other apparent trends or significant differences in any other SRI symptom between the two treatment groups (Table 4).

The WGP group exhibited a significantly greater "General Health" summary score over the 90 days (58.7 ± 7.0 vs. 52.0 ± 14.6; p = 0.038) with a concomitant significant comparative improvement in the Physical Component Summary (WGP: 57.5 ± 4.5; Placebo: 55.5 ± 3.5; p = 0.029). There were no other significant differences between the two groups for any other 'quality of life' measures from the SF-36v2 questionnaire.

Compliance and Side Effects

Overall compliance was nearly 90% in the ITT population, and approximately 95% in the PP population. One subject

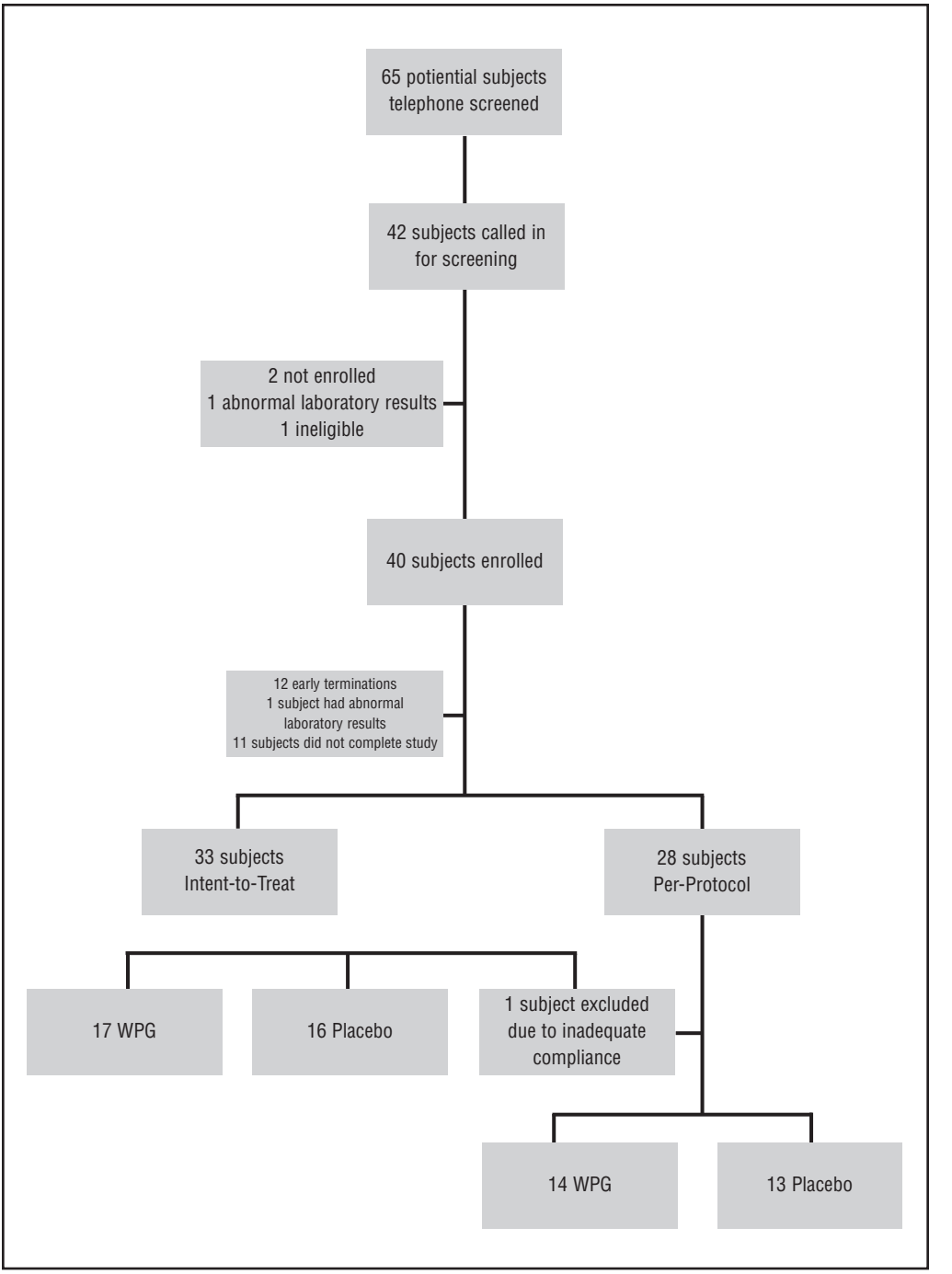

Figure 1: Flow diagram for study participants.

who had completed all scheduled visits was excluded from the PP population because of inadequate compliance.

A total of 43 adverse events (AEs) were reported by 20 subjects during this study. Twenty-two events were recorded

by 11 subjects in the WGP group, whereas 21 events among 9 control subjects were documented. All events were of mild to moderate severity. All were judged by the principal investigator to be probably not related to each other or as a consequence of the study product. None of the events contributed the subject's self-discontinuance or withdrawal from the study. The number and types of adverse events were distributed evenly between WGP and placebo groups. There was no tendency for AEs to occur more frequently in one study group vs the other ($p = 0.728$). There were no safety concerns in the study (Table 5).

DISCUSSION

This is the first clinical study to assess the efficacy of *Saccharomyces cerevisiae* derived beta-glucan on incidence, duration, and severity of SRI in a healthy, adult, community-dwelling population. Importantly, none of the subjects from the WGP group missed work or school during the 90-day study. In addition, the WGP group's physical component summary score improved more than the placebo group, and the WGP group had a significantly lower fever score. However, there were no significant differences between WGP and placebo on SRI incidence.

Beta-glucan from other sources appears to improve immune function in a variety of animal models, without increasing pro-inflammatory cytokines or inducing a febrile response. [37,42,49,50] Other *in vivo* models indicate that oat-derived beta-glucan, a linear molecule, can prevent increased risk of URTI as a result of stressful exercise in mice.[44,45] It appears that beta-glucan may be a powerful immune stimulator, as evidenced by its ability to activate macrophages and stimulate positive immune actions on B lymphocytes, natural killer cells, and suppressor T cells in the immune system.[51-53] Many *in vitro* studies have shown that beta-glucan significantly increases microbiocidal activity of human neutrophils and macrophages against a variety of pathogens without directly stimulating synthesis of the cytokines, IL-1 or TNF·. The exact pathway through which beta-glucans interact with the immune system is unknown. One proposed mechanism is the activation of dectin-1 pattern recognition receptor on blood peripheral mononuclear cells.[54,55]

Other dietary supplements are reported to reduce upper respiratory tract infection symptoms in humans.[14] For example, zinc acetate treatment (12.8 mg q3h 12d) reduced severity and duration of cold symptoms.[30] A highly purified beta-glucan (0.1-1.0 mg/kg bw) from *Saccharomyces cerevisiae* helped to reduce post-surgical infections and decrease intensive care unit stay length.[46-48] A more recent study reported no change in self-reported upper respiratory tract infection symptoms or the average number of sick days in endurance athletes given a beta-glucan supplement for 18 days.[56] In this report, beta-glucan was administered at 5.6 g/day in a 600 ml beverage containing Gatorade® and Oatvantage®, a 54% oat beta-glucan concentrate. Subjects ingested the supplements in two 300 mL doses each day before their first and last meals on an empty stomach. Nieman et al [56] also reported no changes in natural killer cell activity, polymorphonuclear respiratory burst activity, phytohemagglutinin-stimulated lymphocyte proliferation, plasma interleukin 6 (IL-6), IL-10, IL-1 receptor agonist (IL-1ra), and IL-8, and blood leukocyte IL-10, IL-8, and IL-1ra mRNA expression. This study is different from our current study in several aspects. The study reported here included both male and female healthy community dwelling adults, while Nieman et al [56] studied male endurance athletes. The chemical

composition of the beta-glucan and its dosage differed between the two studies, thus making direct comparisons difficult. Soluble and insoluble beta-glucans may stimulate the immune system differently [53]. Higher doses of oat-derived beta-glucan may also be required to see any effects on SRI incidence such as those reported in rodent studies [44,45].

The current pilot study reported results from 27 participants who reported 11 colds. The small sample size may be insufficient to detect possible therapeutic or prophylactic effects of beta-glucan from *Saccharomyces cerevisiae*. Given the economic burden of the common cold, alternative approaches that can lessen the financial impact on society and health burden on individuals should be investigated. Further research in larger groups is needed to determine if this type of beta-glucan, 1-3,1-6 linked from *Saccharomyces cerevisiae* can modulate the immune system to reduce the risk of developing seasonal cold and flu illness in healthy people across the age spectrum

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LITERATURE CITED

1. Bramley TJ, Lerner D, Sames M. Productivity losses related to the common cold. *J Occup Environ Med* 2002;44(9):822-9.
2. Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, Bridges CB. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;25(27):5086-96.
3. Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, D'Alessio D. Treatment of the common cold with unrefined echinacea. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137(12):939-46.
4. Goel V, Lovlin R, Barton R, Lyon MR, Bauer R, Lee TD, Basu TK. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther* 2004;29(1):75-83.
5. Henneicke-von Zepelin H, Hentschel C, Schnitker J, Kohnen R, Kohler G, Wustenberg P. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomised, double blind, placebo controlled, multicentre study. *Curr Med Res Opin* 1999;15(3):214-27.
6. Linde K, Barrett B, Wolkart K, Bauer R, Melchart D. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev* 2006;(1):CD000530.
7. Melchart D, Linde K, Fischer P, Kaesmayr J. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev* 2000;(2):CD000530.
8. Naser B, Lund B, Henneicke-von Zepelin HH, Kohler G, Lehmacher W, Scaglione F. A randomized, double-blind, placebo-controlled, clinical dose-response trial of an extract of Baptisia, Echinacea and Thuja for the treatment of patients with common cold. *Phytomedicine* 2005;12(10):715-22.
9. Schoop R, Klein P, Suter A, Johnston SL. Echinacea in the prevention of induced rhinovirus colds: a meta-analysis. *Clin Ther* 2006;28(2):174-83.
10. Schulten B, Bulitta M, Ballering-Bruhl B, Koster U, Schafer M. Efficacy of Echinacea purpurea in patients with a common cold. A placebo-controlled, randomised, double-blind clinical trial. *Arzneimittelforschung* 2001;51(7):563-8.
11. Sperber SJ, Shah LP, Gilbert RD, Ritchey TW, Monto AS. Echinacea purpurea for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2004;38(10):1367-71.
12. Turner RB, Bauer R, Woelkart K, Hulsey TC, Gangemi JD. An evaluation of Echinacea angustifolia in experimental rhinovirus infections. *N Engl J Med* 2005;353(4):341-8.
13. Yale SH, Liu K. Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* 2004;164(11):1237-41.
14. Peters EM, Goetzsche JM, Grobbelaar B, Noakes TD. Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners. *Am J Clin Nutr* 1993;57(2):170-4.

15. Elwood PC, Lee HP, St Leger AS, Baird M, Howard AN. A randomized controlled trial of vitamin C in the prevention and amelioration of the common cold. *Br J Prev Soc Med* 1976;30(3):193-6.

16. Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S. Effect of vitamin C on common cold: randomized controlled trial. *Eur J Clin Nutr* 2006;60(1):9-17.

17. Van SM, Josling P. Preventing the common cold with a vitamin C supplement: a double-blind, placebo-controlled survey. *Adv Ther* 2002;19(3):151-9.

18. Schmiedel V, Klein P. A complex homeopathic preparation for the symptomatic treatment of upper respiratory infections associated with the common cold: An observational study. *Explore (NY)* 2006;2(2):109-14.

19. Winkler P, de Vrese M, Laue Ch, Schrezenmeir J. Effect of a dietary supplement containing probiotic bacteria plus vitamins and minerals on common cold infections and cellular immune parameters. *Int J Clin Pharmacol Ther* 2005;43(7):318-26.

20. Predy GN, Goel V, Lovlin R, Donner A, Stitt L, Basu TK. Efficacy of an extract of North American ginseng containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: a randomized controlled trial. *CMAJ 2005*;173(9):1043-8.

21. Meydani SN, Leka LS, Fine BC, Dallal GE, Keusch GT, Singh MF, Hamer DH. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* 2004;292(7):828-36.

22. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA* 2002;288(6):715-21.

23. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001;111(2):103-8.

24. Eby GA, Halcomb WW. Ineffectiveness of zinc gluconate nasal spray and zinc orotate lozenges in common-cold treatment: a double-blind, placebo-controlled clinical trial. *Altern Ther Health Med* 2006;12(1):34-8.

25. Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000;79(10):778-80, 782.

26. Hulisz D. Efficacy of zinc against common cold viruses: an overview. *J Am Pharm Assoc* (2003) 2004;44(5):594-603.

27. Marshall I. Zinc for the common cold. *Cochrane Database Syst Rev* 2000;(2):CD001364.

28. McElroy BH, Miller SP. An open-label, single-center, phase IV clinical study of the effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) in reducing the duration and symptoms of the common cold in school-aged subjects. *Am J Ther* 2003;10(5):324-9.

29. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *QJM* 2003;96(1):35-43.

30. Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000;133(4):245-52.

31. Silk R, LeFante C. Safety of zinc gluconate glycine (Cold-Eeze) in a geriatric population: a randomized, placebo-controlled, double-blind trial. *Am J Ther* 2005;12(6):612-7.

32. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001;33(11):1865-70.

33. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000;31(5):1202-8.

34. Turner RB, Fowler SL, Berg K. Treatment of the common cold with troxerutin. *APMIS* 2004;112(9):605-11.

35. Gruber C, Riesberg A, Mansmann U, Knipschild P, Wahn U, Buhring M. The effect of hydrotherapy on the incidence of common cold episodes in children: a randomised clinical trial. Eur J Pediatr 2003;162(3):168-76.

36. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. *J Manipulative Physiol Ther* 1999;22(8):530-3.

37. Niederman R, Kelderman H, Socransky S, Ostroff G, Genco C, Kent R, Jr., Stashenko P. Enhanced neutrophil emigration and Porphyromonas gingivalis reduction following PGG-glucan treatment of mice. *Arch Oral Biol* 2002;47(8):613-8.

38. Luhm J, Langenkamp U, Hensel J, Frohn C, Brand JM, Hennig H, Rink L, Koritke P, Wittkopf N, Williams DL, Mueller A. ?-(1?3)-D-glucan modulates DNA binding of nuclear factors ?B, AT and IL-6 leading to an anti-inflammatory shift of the IL-1?/IL-1 receptor antagonist ratio. *BMC Immunol* 2006;7:5.

39. Bedirli A, Kerem M, Pasaoglu H, Akyurek N, Tezcaner T, Elbeg S, Memis L, Sakrak O. Beta-glucan attenuates inflammatory cytokine release and prevents acute lung injury in an experimental model of sepsis. *Shock* 2007;27(4):397-401.

40. Ikewaki N, Fujii N, Onaka T, Ikewaki S, Inoko H. Immunological actions of Sophy beta-glucan (beta-1,3-1,6 glucan), currently available commercially as a health food supplement. *Microbiol Immunol* 2007;51(9):861-73.

41. Liang J, Melican D, Cafro L, Palace G, Fisette L, Armstrong R, Patchen ML. Enhanced clearance of a multiple antibiotic resistant Staphylococcus aureus in rats treated with PGG-glucan is associated with increased leukocyte counts and increased neutrophil oxidative burst activity. *Int J Immunopharmacol* 1998;20(11):595-614.

42. Onderdonk AB, Cisneros RL, Hinkson P, Ostroff G. Anti-infective effect of poly-beta 1-6-glucotriosyl-beta 1-3-glucopyranose glucan in vivo. *Infect Immun* 1992;60(4):1642-7.

43. Kaiser AB, Kernodle DS. Synergism between poly-(1-6)-beta-D-glucopyranosyl-(1-3)-beta-D-glucopyranose glucan and cefazolin in prophylaxis of staphylococcal wound infection in a guinea pig model. *Antimicrob Agents Chemother* 1998;42(9):2449-51.

44. Davis JM, Murphy EA, Brown AS, Carmichael MD, Ghaffar A, Mayer EP. Effects of oat beta-glucan on innate immunity and infection after exercise stress. *Med Sci Sports Exerc* 2004;36(8):1321-7.

45. Murphy EA, Davis JM, Brown AS, Carmichael MD, Carson JA, Van Rooijen N, Ghaffar A, Mayer EP. Benefits of oat ?-glucan on respiratory infection following exercise stress: role of lung macrophages. *Am J Physiol Regul Integr Comp Physiol* 2008;294(5):R1593-R1599.

46. Babineau TJ, Hackford A, Kenler A, Bistrian B, Forse RA, Fairchild PG, Heard S, Keroack M, Caushaj P, Benotti P. A phase II multicenter, double-blind, randomized, placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients. *Arch Surg* 1994;129(11):1204-10.

47. Babineau TJ, Marcello P, Swails W, Kenler A, Bistrian B, Forse RA. Randomized phase I/II trial of a macrophage-specific immunomodulator (PGG-glucan) in high-risk surgical patients. *Ann Surg* 1994;220(5):601-9.

48. Dellinger EP, Babineau TJ, Bleicher P, Kaiser AB, Seibert GB, Postier RG, Vogel SB, Norman J, Kaufman D, Galandiuk S, Condon RE. Effect of PGG-glucan on the rate of serious postoperative infection or death observed after high-risk gastrointestinal operations. Betafectin Gastrointestinal Study Group. *Arch Surg* 1999;134(9):977-83.

49. Sandvik A, Wang YY, Morton HC, Aasen AO, Wang JE, Johansen FE. Oral and systemic administration of beta-glucan protects against lipopolysaccharide-induced shock and organ injury in rats. *Clin Exp Immunol* 2007;148(1):168-77.

50. Kournikakis B, Mandeville R, Brousseau P, Ostroff G. Anthrax-protective effects of yeast beta 1,3 glucans. *MedGenMed* 2003;5(1):1.

51. Brown GD, Gordon S. Immune recognition of fungal beta-glucans. *Cell Microbiol* 2005;7(4):471-9.

52. Castro GR, Panilaitis B, Bora E, Kaplan DL. Controlled release biopolymers for enhancing the immune response. *Mol Pharm* 2007;4(1):33-46.

53. Rice PJ, Adams EL, Ozment-Skelton T, Gonzalez AJ, Goldman MP, Lockhart BE, Barker LA, Breuel KF, Deponti WK, Kalbfleisch JH, Ensley HE, Brown GD, Gordon S, Williams DL. Oral delivery and gastrointestinal absorption of soluble glucans stimulate increased resistance to infectious challenge. *J Pharmacol Exp Ther* 2005;314(3):1079-86.

54. Nerren JR, Kogut MH. The selective Dectin-1 agonist, curdlan, induces an oxidative burst response in chicken heterophils and peripheral blood mononuclear. *Vet Immunol Immunopathol* 2009 Jan 15;127(1-2):162-6. Epub 2008 Sep

55. Shah VB, Huang Y, Keshwara R, Ozment-Skelton T, Williams DL, Keshvara L. Beta-glucan activates microglia without inducing cytokine production in Dectin-1-dependent manner. *J Immunol* 2008 Mar 1;180(5):2777-85

56. Nieman DC, Henson DA, McMahon M, Wrieden JL, Davis JM, Murphy EA, Gross SJ, McAnulty LS, Dumke CL. ?-Glucan, Immune Function, and Upper Respiratory Tract Infections in Athletes. *Med Sci Sports Exerc* 2008;40(8):1463-71.