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Effect of β-Glucan (Angel Yeast) Compared to a Placebo on Cold and Flu Incidence and Symptoms in an Adult Population—A Double Blind, Randomised Controlled Trial

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Abstract

Background: 1-3, 1-6 β-glucan derived from Baker's yeast (*Saccharomyces cerevisiae*) has been widely studied for its immune stimulatory capabilities and safety. Previous studies found β-glucan to have efficacy at reducing incidence of URTIs as well as being a low risk for negative side effects. The current study aimed to examine the effects of yeast β-glucan (Angel Yeast) on cold and flu incidences and symptoms in healthy adults. **Methods:** Two hundred and thirty-one males and females aged 18 to 65 years old supplemented with either β-glucan or a placebo for 3-months. Participants completed a general health questionnaire every 4 weeks and in addition, if participants experienced any cold or flu symptoms, these were recorded daily (along with severity) until resolved or up to 2 weeks. **Results:** Supplementation with β-glucan reduced the self-reported severity of sore throats and improved sleep quality compared to the placebo group. **Conclusions:** Yeast β-glucan supplementation appears to be able to help reduce certain symptoms experienced during a cold or flu episode and is safe and well tolerated.

Keywords

Beta-Glucan, Cold, Flu, Baker's Yeast

1. Introduction

The common cold is one of the most widespread infectious diseases in humans,

presenting as a mild, self-limiting illness, often accompanied by a low-grade fever. The aetiology of the common cold presents as a clinical syndrome brought about by a myriad of distinct viruses [1]. On average, adults experience 2 to 4 colds per year, while children may endure up to 10, with frequency influenced by age and exposure [2]. As there is currently no known vaccine or treatment, the focus lies on seeking ways to reduce symptom severity and/or duration.

Treatment options typically include keeping hydrated, resting, decongestants, antihistamines, pain relievers, vitamin C, Echinacea and zinc to name a few. However, to date, treatments aimed at alleviating symptoms and/or the duration of cold episodes have shown mixed results [3]. One supplement studied for its effectiveness is β-glucans. β-glucans comprise a heterogeneous group of natural polysaccharides present in cereal grains, algae, bacteria, plants, and fungi [4] [5]. Among the most characterized and effective sources of β-glucans are those extracted from the cell wall of Baker's yeast (Saccharomyces cerevisiae) [6] [7]. Baker's yeast, referred to as 1-3, 1-6 β-glucan [8], exhibits high biological activity and, consequently, a potent immunostimulatory effect [9]. This effect is attributed to its insolubility [5], structural complexity [10], and a significant degree of side-chain branching [8] [11].

Potential therapeutic mechanisms of β-glucansinclude: increasing host resistance against bacterial, viral, fungal, and parasitic infections, and suppressing the progression of carcinogenesis [8]. β-glucans are thought to exert therapeutic effects through the ability to enhance the innate immune response [9] [12] and promote adaptive immunity, thereby preparing the body to counter foreign pathogens [5] [13]. Importantly, β-glucans are purported to regulate the immune system without inducing damaging inflammatory reactions, by up regulating both infection-fighting and immunoregulatory molecules [14].

β-glucan supplementation has been shown to reduce URTI occurrence, symptom severity, and stress levels and increased quality of life compared to a placebo in healthy participants with recurring infections [15]. Feldman and colleagues investigated the effects of 500 mg/day of β-glucans compared to a placebo in 40 healthy adults over 12 weeks. Following supplementation, β-glucans supplementation reduced fever scores and the number of sick days taken off work and improved reported quality of life [16].

Talbott and Talbott investigated the efficacy of β-glucanson cold and flu symptoms compared to a placebo in three separate studies. Seventy-five marathon runners were supplemented with 250 mg or 500 mg of β-glucan or a placebo daily for 4 weeks following the completion of a marathon. Participants in the β-glucans groups reported significantly fewer URTI symptoms, better overall health, decreased confusion, fatigue, tension, and anger, and increased vigour compared to the placebo [12]. A following study supplemented 150 moderate to highly stressed subjects with 250 mg or 500 mg of β-glucans or a placebo for 4 weeks. The β-glucans supplemented groups reported fewer upper respiratory tract infection symptoms, better overall health, increased vigour, and decreased tension, fatigue, and confusion compared to the placebo group [16]. A third

study supplemented 77 females with moderate levels of psychological stress with 250 mg of *β*-glucans or a placebo for 12 weeks. The *β*-glucans group reported fewer upper respiratory symptoms, better overall well-being, and superior mental/physical energy levels [17].

Fuller and colleagues supplemented 100 healthy participants with either 250 mg of *β*-glucans or a placebo for 90 days. A significant improvement in the ability to "breathe easily" and lower monocyte chemotactic protein-1 were reported for the *β*-glucans group compared to the placebo group, with a reduction in the total number of days with URTI symptoms trending towards significance in the *β*-glucans group [18]. Similarly, Graubaum and colleagues supplemented 100 healthy participants with either 450 mg of *β*-glucans or a placebo for 26 weeks. Fewer subjects in the *β*-glucans group reported experiencing cold and flu symptoms and those who did, reported reduced symptoms ("sore throat and/or difficulty swallowing", "hoarseness and/or cough" and "runny nose") compared to the placebo group [13].

Auinger, Riede *et al*. (2013), supplemented 162 healthy participants with recurring infections with 900 mg of *β*-glucans or a placebo for 16 weeks. The *β*-glucans group reported fewer symptomatic infections, a reduction in the mean symptom score and improved reported sleep difficulties caused by a cold episode compared to the placebo group [19]. Similarly, Dharsono, Rudnicka *et al*. 2019 supplemented 299 healthy participants with 900 mg *β*-glucans or a placebo for 16 weeks. The *β*-glucans group reported a reduction in initial severity of URTIs, severity of physical symptoms over the first 7 days and systolic blood pressure compared to the placebo group [20].

The aim of the current study was to assess the effectiveness of a new *β*-glucan formulation for reducing incidence and severity of cold and flu symptoms compared to a placebo in otherwise healthy adults.

2. Methods

A double-blind, randomised controlled trial with a three-month intervention. This study was conducted as a remote study (using telehealth consultations), with participants recruited from across Australia. Eligible participants were provided with a copy of the participant information sheet, underwent full screening against the inclusion and exclusion criteria, and given a full explanation of the trial and their requirements. Eligible participants gave their written consent and were randomly allocated to either the active *β*-glucan group or placebo group. The active *β*-glucan product was administered as a single 200 mg dose of Angel Yeast *β*-glucan containing a minimum of 85% 1-3, 1-6 *β*-glucan (Angel Yeast Co., Ltd.) taken daily in the morning. The placebo was administered as a single 200 mg dose of maltodextrin taken daily in the morning. Both the active and placebo products appeared identical and were contained in identical product containers to ensure blinding. Group allocation was conducted using Random Allocation Software (sealedenvelope.com) by an individual who was not involved in the trial. Both the participant and investigator were blinded to the

treatment allocation. Of the 352 people screened, 240 participants were enrolled in the study (Figure 1). Participants were included in the study if they met the criteria detailed in Table 1.

Once enrolled, participants completed a Short Form 8 (SF-8) health survey questionnaire at baseline and every 4 weeks during the three-month study period. Upon the onset of any cold or flu symptoms (i.e., coughing, sneezing, stuffy or runny nose, fever, scratchy or sore throat, or nasal breathing), participants recorded their daily symptoms and severity using the Wisconsin Upper Respiratory Symptom Survey 24 (WURSS-24) questionnaire until symptoms subsided. Once symptoms subsided, participants continued taking their trial product and recorded any subsequent episode as a new event, provided they were symptom free for at least 2 weeks.

The primary outcome for this study was the number of cold and flu incidences reported by participants. Secondary outcomes included changes in cold or flu duration and severity (WURSS-24), change in general health (SF-8), days off work, rescue medication use, product tolerance and adverse events.

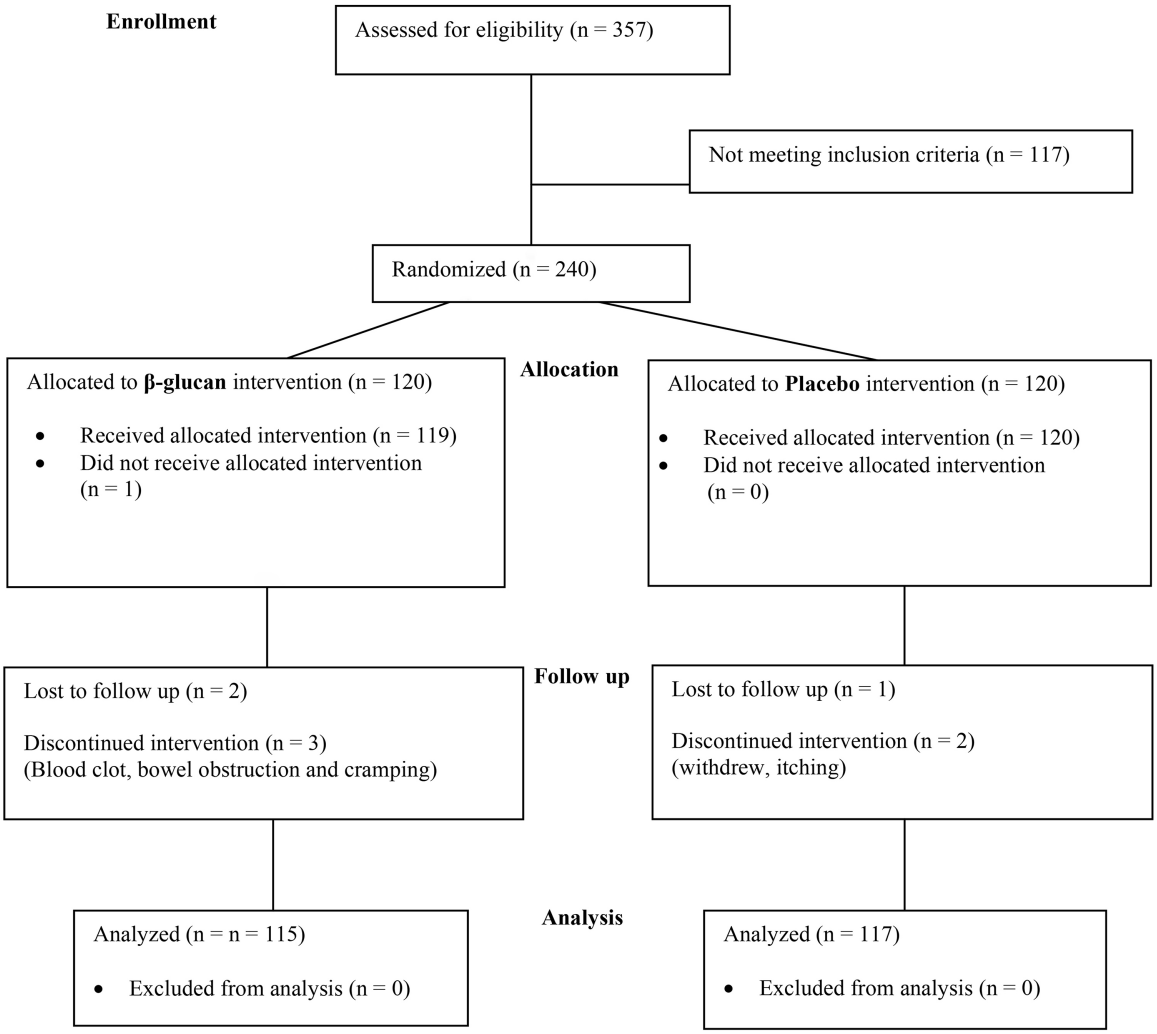

Figure 1. Participant flow diagram.

Table 1. Inclusion and exclusion criteria used for participant screening.

Inclusion
● Male or female aged between 18 and 65 years old who were able to provide informed consent, ● Agreeing not to take any β-glucan supplement or other supplements or medications aimed at preventing URTI's for the duration of the study period.
Exclusion
● Unstable or serious illness (kidney, liver, GIT, heart conditions, diabetes, thyroid gland function, malignancy, lung conditions, or chronic asthma), ● Anyone regularly (>3 times per week) consuming unprocessed food high in β-glucan or with added β-glucan, ● Acute sickness experienced in the past 2 months, ● Serious mood disorders or neurological disorders, ● People with cognitive damage, ● People who have or have had treatment for cancer, HIV, or chronic use of steroids in the past year, ● Active smokers and/or nicotine or drug abuse, ● Chronic alcohol use (>14 alcoholic drinks per week), ● Allergic to any of the ingredients in the active or placebo formula, ● Pregnant or lactating women, ● Participants medically prescribed medication that would affect the immune and/or inflammatory response, ● Participants who had participated in any other related clinical study during the past month, ● Any condition that the investigator deemed made the participant unsuitable for inclusion.

Power analysis indicated that to achieve statistical power, 33 cold and flu incidents were required per group to detect a change of 25% in cold and flu incidencebetween groups (α error probability of 0.05 and powered to 0.95, effect size$d$ = 0.82). Therefore, 240 participants were recruited with the aim of achieving a minimum of 70 cold and flu event between the two groups.

Statistical analyses were performed using IBM SPSS Statistics (version 25.0) for Windows (IBM, Chicago, IL, USA). Differences between number of cold episodes per group was assessed using Chi Squared tests and changes in cold severity and impact was analysed using Kruskal-Wallis tests adjusted for pair-wise multiple comparisons with Bonferroni corrections. Statistical significance was set at $p \leq 0.05$. Subgroup analysis was conducted on symptom outcome measures from the WURSS-24 where that specific symptom was reported during a cold or flu event (i.e., any score of zero was excluded from analysis).

This study was conducted in Australia, with participants starting the study between November (Summer) 2020 and May (Autumn/Fall) 2021 and completed by September (Spring) 2021. The study was performed in accordance with the current version of the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice. The study protocol was approved by Bellberry Ltd Human Research and Ethics Committee (2020-06-603).

3. Results

There were no statistical differences between the β-glucan and placebo groups for baseline demographics (Table 2). Both groups consisted of approximately twice as many females as males, typically aged in their 30 s - 40 s with average height, weight, and a healthy BMI (Table 2).

There was no statistical difference between groups for the number of participants that completed the study (Table 3). Of the 240 participants that were randomised for this trial, 231 completed the full intervention period (Figure 1). Of the 9 participants who failed to complete the entire study duration, one person in the β-glucan group recorded an event prior to withdrawal and was therefore included in the analysis. Within the β-glucan treatment group, 6 participants withdrew; one before starting, two were lost to follow up, two suffered serious adverse events (blood clot and bowel obstruction) deemed unrelated to the trial product, and one due to an adverse event (pain and cramping) considered possibly related to the trial product. In the placebo group, 3 participants withdrew; one was lost to follow up, one withdrew due to personal reasons, and one withdrew due to reported adverse event (itching), considered possibly related to the product (placebo).

Table 2. Summary of participant baseline demographics.

Parameters	β-glucan (n = 119)	Placebo (n = 120)
Male (n)	39	36
Female (n)	80	84
Age (years)	38.5 ± 11.4	40.4 ± 10.5
Height (m)	1.68 ± 0.10	1.68 ± 0.97
Weight (kg)	76.29 ± 23.73	76.00 ± 20.49
Body Mass Index (kg/m^2)	26.80 ± 8.10	26.87 ± 5.94

One person in the β-glucan group was removed due to withdrawing prior to starting. Values represented as mean ± SD.

Table 3. Trial event outcome measures.

	β-glucan	Placebo	p-value (Chi squared)
Completed study (n)	115	117	
Cold episodes reported (n)	24	23	
Total days in study (n)	10,530	10,530	
Total days sick (n)	141	148	
Sick (%)	20.86	19.65	0.853
Days sick (%)	1.34	1.43	0.798
Average days sick	5.88 ± 3.04	6.43 ± 3.47	0.559
Days off work	0.29 ± 0.55	0.70 ± 1.06	0.053

There was no statistical difference between the β-glucan and placebo groups for the number or duration of illness reported (Table 3). There was no statistical difference between the β-glucan and placebo groups for the average days sick or the number of days taken off work due to sickness (Table 3).

The β-glucan group had a significant improvement for sleeping well from the WURSS-24 (Table 4) compared to the placebo group. No other significant difference between groups was found from the WURSS-24 or SF-8questionnaires. When data was analysed to include only those participants who reported experiencing the symptom during an event, the symptom outcome measure showed the β-glucan group had a significant reduction for sore throats compared to the placebo group (Table 5). No other significant difference between groups was found from the WURSS-24 questionnaire for those who reported the symptom.

The placebo group reported a significantly higher score on the SF-8 general health questionnaire for question 7 (been bothered by emotional problems) at baseline compared to the β-glucan group. This difference was not seen at month 3 (Table 6). Overall, compliance for capsule consumption this study was high and equal for both groups, with 96.1% and 95.2% for the β-glucan and placebo groups, respectively.

Table 4. Symptom outcome measures for all trial participants reporting an event.

Parameter	β-glucan (n = 24) Median (interquartile range)	Placebo (n = 23) Median (interquartile range)	p-value
Runny nose	5.5 (12)	6 (9)	0.748
Plugged nose	5 (12)	8 (18)	0.839
Sneezing	2 (4)	2 (5)	0.966
Sore throat	6.5 (15)	12 (10)	0.088
Scratchy throat	4.5 (10)	7 (12)	0.276
Cough	6 (10)	6 (11)	0.579
Hoarseness	3.5 (9)	2 (11)	1.000
Head congestion	3 (16)	6 (14)	0.423
Chest congestion	0 (3)	1 (11)	0.239
Feeling tired	8 (23)	10 (16)	0.424
Headache	4 (12)	6 (12)	0.248
Body aches	2 (14)	4 (12)	0.686
Fever	0 (1)	0 (2)	0.58
Total symptoms	56 (126)	77 (120)	0.183
Think clearly	4 (13)	6 (10)	0.398
Sleep well	4 (17)	13 (15)	0.039*
Breathe easily	5 (13)	4 (14)	0.643
Walk, climb stairs, exercise	1 (13)	5 (13)	0.559

Continued

Accomplish daily activities	1 (12)	6 (13)	0.193
Work outside the home	0.5 (11)	4 (13)	0.343
Work inside the home	1 (11)	2 (11)	0.513
Interact with others	3.5 (12)	4 (14)	0.730
Live your personal life	2.5 (14)	6 (13)	0.337
Total impact	26.5 (119)	47 (111)	0.142

Values represented as severity, *significantly different from placebo ($p < 0.05$).

Table 5. Symptom outcome measures for trial participant data reporting that symptom during a reported event.

Parameter	*n*	*β*-glucan Median (interquartile range)	*n*	Placebo Median (interquartile range)	*p*-value
Runny nose	19	8 (9)	19	6 (14)	0.644
Plugged nose	20	5 (12)	17	13 (19)	0.117
Sneezing	21	2 (4)	18	3.5 (8)	0.335
Sore throat	22	5.5 (9)	20	12 (15)	0.037*
Scratchy throat	19	4 (10)	21	7 (11)	0.258
Cough	19	7 (10)	20	5.5 (11)	0.857
Hoarseness	14	7.5 (11)	15	3 (14)	0.234
Head congestion	20	3 (15)	19	11 (14)	0.258
Chest congestion	9	3 (12)	14	6 (13)	0.688
Feeling tired	21	8 (21)	23	9 (18)	0.991
Headache	18	5.5 (11)	20	7 (12)	0.478
Body aches	16	6.5 (16)	14	4 (18)	0.294
Fever	6	4 (8)	7	5 (7)	0.445
Total symptoms	24	46.5 (126)	23	48 (69)	0.709
Think clearly	18	5 19)	20	6 (9)	0.988
Sleep well	19	5 (19)	22	12 (15)	0.313
Breathe easily	19	6 (12)	15	9 (11)	0.891
Walk, climb stairs, exercise	14	7.5 (18)	14	7.5 (13)	0.603
Accomplish daily activities	17	4 (16)	18	6.5 (13)	0.195
Work outside the home	12	9 (15)	14	9 (14)	0.527
Work inside the home	14	4 (13)	16	4 (10)	0.854
Interact with others	17	6 (9)	16	9.5 (15)	0.26
Live your personal life	16	3.5 (12)	17	7 (12)	0.326
Total impact	23	24 (62)	23	47 (111)	0.079

Values represented as severity, *significantly different from placebo ($p < 0.05$).

Table 6. SF-8 outcomes for all trial participants.

	Baseline		Month 3		Change from baseline	
	β-glucan	Placebo	*β*-glucan	Placebo	*β*-glucan	Placebo
1) Overall, how would you rate your health during the past 4 weeks.	80.0 ± 16.8	79.3 ± 16.4	77.0 ± 15.1	75.7 ± 16.4	−0.88 ± 17.40	−3.54 ± 18.56
2) During the past 4 weeks, how much did physical health problems limit your physical activities (such as walking or climbing stairs)?	89.5 ± 15.8	85.9 ± 22.8	85.7 ± 20.2	86.4 ± 19.3	−3.76 ± 21.19	0.88 ± 27.94
3) During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?	92.0 ± 12.6	90.8 ± 16.6	90.6 ± 16.8	89.0 ± 16.9	−1.99 ± 18.64	−1.77 ± 17.27
4) How much bodily pain have you had during the past 4 weeks?	82.2 ± 16.0	82.2 ± 19.8	82.3 ± 17.2	81.2 ± 19.3	−0.53 ± 16.14	−0.71 ± 18.11
5) During the past 4 weeks, how much energy did you have?	70.6 ± 15.8	70.1 ± 16.2	68.2 ± 19.2	67.9 ± 16.1	−2.88 ± 19.41	−2.21 ± 16.21
6) During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?	87.6 ± 17.8	88.9 ± 16.9	84.2 ± 21.1	85.7 ± 19.8	−3.98 ± 24.68	−2.65 ± 19.01
7) During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?	78.2 ± 21.0*	83.5 ± 18.0	78.5 ± 20.2	78.7 ± 21.7	−0.22 ± 20.73	−3.98 ± 21.80
8) During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities	88.2 ± 18.1	91.2 ± 15.2	84.9 ± 19.6	89.4 ± 16.2	−3.98 ± 20.48	−1.11 ± 16.16

Values are presented as mean ± SD; *significantly different from placebo group ($p < 0.05$).

4. Discussion

The current study assessed the efficacy of *β*-glucan (Angel Yeast) on cold and flu symptoms in healthy adults. Overall, *β*-glucan was shown to be safe and tolerable amongst participants. Overall, *β*-glucan was able to reduce the severity of a sore throat experienced during a cold or flu episode, in support of existing literature [20]. The proposed mechanism of action for decreasing severity, is the recognition of *β*-glucan by Dectin-1 receptors triggering phagocytosis and the production of proinflammatory factors leading to the elimination of infectious agents, such as those causing sore throats [9].

Fuller and colleagues showed supplementation with a yeast derived 1-3, 1-6 glucopolysaccharide was able to significantly improve breathing in participants

[18]. However, as with the present study, trending factors were found, including total number of days with URTI symptoms ($p = 0.06$). The current study found the overall symptom severity score trended towards significance ($p = 0.08$) in those reporting symptoms. The current study also found the measure of 'sleep well' significantly improved in the β-glucan group compared to the placebo (**Table 4**). However, when data was analysed for those participants reporting sleep difficulties, the significance was lost. Therefore, specific studies may be required to investigate the effect β-glucan has on improving sleep loss as a cold and flu symptom, or a larger study population may be required to see an effect. It is possible that β-glucan can affect sleep quality by improving other URTI symptoms rather than directly affecting any physiological aspect of the sleep cycle. The main reason people tend to lose sleep from a cold or flu is due to either a pestering cough or sore throat preventing sleep. If other URTI symptoms can be treated, it is plausible that sleep quality will increase also. Other studies have also shown varied results, including reduction in overall URTI symptom score and reduced sleep difficulties, however, these studies were conducted using specific population groups, such as marathon runners and stressed females [16] [17] [21].

A reduction in days taken off work also trended towards significance in the present study. The β-glucan reported having less than half the time off work compared to the placebo group (0.3 days vs 0.7 days, respectively, $p = 0.053$). With the number of events reported, additional factors that may affect people taking time off work was unable to be taken into consideration. Factors to consider include work conditions, environment, location, and leave availability. A factor that needs to be considered in any cold and flu study conducted over this study period is COVID-19. With people largely working from home during COVID-19, people could still work when experiencing cold and flu like symptoms and therefore days taken off due to cold or flu symptoms are likely reduced.

A significant limitation of this study is primarily attributed to the unprecedented circumstances of the COVID-19 pandemic. Conducted during 2020 and 2021, the peak of the pandemic, the research period coincided with numerous lockdowns, prompting a substantial shift to remote work and heightened safety measures, including hand sanitation and face masks. This altered lifestyle likely led to a decrease in cold and flu events as individuals took precautions to prevent transmission and infections.

Furthermore, the reduced community activity during the pandemic provided individuals with more opportunities for rest and expedited recovery. A further limitation of the study was in recording enough cold and flu episodes to meet the initially calculated statistical power. The diminished occurrence of such events was likely influenced by the broader decline in infections during the study period, directly linked to the impact of COVID-19.

Regrettably, due to study constraints, the study had to conclude once it reached the initially approved participant recruitment target, falling short by 23

cold and flu events to achieve the calculated power. The unavailability of these additional events potentially limits the comprehensiveness of the findings. Despite these limitations, the study yielded encouraging results by identifying significant differences, suggesting potential insights into the interaction between pandemic-related factors and respiratory illnesses.

Dose is another factor that may have affected the results of this study. The dose used (200 mg per day) is amongst the lowest reported for studies investigating the effects of β-glucan [22]. Several studies have tested doses at 250 mg per day [23]-[26], with doses as high as 900 mg per day being reported [12] [16]. The difference a higher dose may have had on the results is unknown, as higher dosed studies also have variable results and often focus on different cohorts, for example, marathon runners [24] [26].

Future research on the effects of β-glucan may benefit from using a larger number of participants. Fuller and colleagues recruited 100 people and reported 24 events [18], with the present study recruiting 240 people and reporting 47 events. With both studies reporting a trend towards significance for several outcomes, a larger cohort may be required to reach the power necessary to achieve significance. Future research may also benefit from investigating a higher daily dose or a split dose, where participants consume a capsule in the morning and one in the evening. A split dose may help boost the immune response by maintaining a higher blood concentration for a greater proportion of both the day and night. Alternatively, an evening dose may be worth testing, to see if elevated levels while sleeping help fight any pathogens better. Research focused specifically on sleep may also be worth investigating. With many studies showing a trend towards improved sleep, a better targeted study may be required to see the effects.

Overall, yeast β-glucan was shown to be safe and tolerable, with results indicating it can reduce the severity of a sore throat experienced during a cold or flu episode. However, further research into the optimal dose and setting is required.

Study Approval Statement

This study protocol was reviewed and approved by Bellberry Limited, approval number 2020-06-603.

Consent to Participate Statement

Written informed consent was received from all participants in this study.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: DB and AR; data collection: DB and AR; analysis and interpretation of results: DB and AR; draft manuscript preparation: DB, HZ, ZC and AR. All au-

thors reviewed the results and approved the final version of the manuscript.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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