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Yeast-derived β-1,3/1,6 glucan, upper respiratory tract infection and innate immunity in older adults

Richard Fuller B.M.B.S. [a], Michael V. Moore B.M.B.S. [a], George Lewith D.M. [a], Beth L. Stuart Ph.D. [a], Rory V. Ormiston [b], Helena L. Fisk B.Sc. [b], Paul S. Noakes Ph.D. [b], Philip C. Calder Ph.D. [b,c,*]

[a] Primary Care and Population Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[b] Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[c] NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

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ABSTRACT

Objective: The aims of this study were to test whether yeast-derived β-1,3/1,6 glucan can prevent the occurrence or reduce the severity of upper respiratory tract infection (URTI) and modulate innate immune responses during winter months in community-dwelling older adults.
Methods: This was a double-blind placebo-controlled trial of community-dwelling adults ages 50 to 70 y randomized to once-daily β-1,3/1,6 glucan (Wellmune 250 mg/d; n = 50) or identical placebo capsule (n = 50) over 90 d during winter. URTI episodes were medically confirmed. Symptom severity was recorded via self-reported daily Wisconsin Upper Respiratory Tract Infection Score 21. Blood and saliva samples were collected at days 0, 45, and 90 for measurements of innate immune parameters.
Results: Forty-nine participants completed the trial in each group. Supplementation was well tolerated. Forty-five URTIs were confirmed: 28 in the placebo group and 17 in the Wellmune group (odds ratio, 0.55; 95% confidence interval, 0.24–1.26; $P = 0.149$). There was a strong trend for Wellmune to decrease the number of symptom days ($P = 0.067$). Symptom severity did not differ significantly between groups. Compared with the placebo group, lipopolysaccharide-stimulated blood from participants in the Wellmune group showed an increase in interferon-γ concentration from baseline at day 45 ($P = 0.016$) and smaller decreases in monokine induced by interferon-γ concentration from baseline at days 45 and 90 ($P = 0.032$ and 0.046, respectively). No difference was seen in serum or nonstimulated blood cytokines and chemokines or in salivary immunoglobulin A.
Conclusion: Daily oral β-1,3/1,6 glucan may protect against URTIs and reduce the duration of URTI symptoms in older individuals once infected. This may be linked to effects on innate immune function. Larger studies are needed to confirm the benefits of β-1,3/1,6 glucan on URTIs in this older population.

Introduction

Upper respiratory tract infection (URTI) is the most frequent infectious illness in humans, with an estimated prevalence of two to four episodes per person per year in adults [1]. Although usually self-limiting, URTIs have marked social and economic consequences due to sickness-related absence, need for caregiving, and primary care attendance [2,3]. Effective antiviral treatment strategies remain elusive and the wide variety of causal pathogens and associated antigenic shift provide

This study was funded by a grant to RF and PCC from Biothera (Eagan, MN, USA), the manufacturer of Wellmune; Biothera is now part of Kerry. RF and PCC designed the study. RF recruited the participants, carried out the intervention, and collected saliva and blood samples under the supervision of MVM and GL. RVO, HLF, and PSN conducted the laboratory analysis under the supervision of PCC. RF and BLS conducted the statistical analysis. RF and PCC drafted the manuscript. All authors had input into the manuscript and approved the final version.

* Corresponding author. Tel.: +44 2381 205 250; fax: +44 2381 205 252.
E-mail address: pcc@soton.ac.uk (P. C. Calder).

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significant challenges to the development of vaccines [4]. Within primary care in the United Kingdom, the proportion of antibiotic prescriptions for cough and cold presentations increased from 39 to 51% between 1999 and 2011 [5], despite considerable attention to appropriate prescribing, with respiratory tract infection reported as the leading indication for antibiotic prescription [6]. Novel strategies to prevent URTIs are urgently required to reduce the burden of infection, associated antibiotic use, and the subsequent development of antimicrobial resistance [7].

Innate immune cells, including neutrophils and macrophages, form the front line of host defense to pathogenic viral and bacterial challenges [8]. Modification at the initial, nonspecific, level of innate immunity may confer benefit in the prevention or amelioration of URTI. Wellmune is a β-1,3/1,6 glucan derived from the cell wall of *Saccharomyces cerevisiae* ("baker's yeast"). Wellmune has European Food Safety Authority approval for use as a novel food ingredient [9] and is available to the general public as a supplement. Wellmune upregulates phagocytosis and chemotaxis of innate immune cells via priming of lectin-sites on complement-receptor 3 and results in enhanced resistance to infection in animal models [10–15]. A previous trial with 100 healthy young adults (mean age ~21 y) conducted during the winter months demonstrated reduction in the concentration of the chemokine monocyte chemoattractant protein (MCP)-1 during symptomatic URTI, a reduction in the total number of days with cold and flu symptoms, and a tendency toward reduced symptom severity in those treated with 250 mg/d Wellmune compared with placebo [16]. Furthermore, a significant reduction in reported URTI symptoms was seen postevent in marathon runners taking Wellmune [17] and in individuals with moderate lifestyle stress [18]. To our knowledge, effects in older people have not been investigated. Therefore, this study investigated the effect of daily Wellmune supplementation on URTIs and selected innate immune markers in older community-dwelling individuals.

Materials and methods

Study design, participants, and sample collection

This study was a randomized double-blind, placebo-controlled trial of 250 mg Wellmune (Biothera, Eagan, MN, USA; n = 50) once daily for 90 d versus an identical-in-appearance rice-flour placebo capsule (n = 50). The study was approved by the South Central Hampshire B Research Ethics Committee, received Clinical Trial Authorization from the Medicines and Healthcare Products Regulatory Agency, and is listed on the European Clinical Trials Database.

Recruitment and study commencement were completed over a 3-wk period during January 2012, at a single National Health Service Primary Medical Care site in Hampshire, UK. Written invitations and participant information sheets were posted to ~600 registered patients who met the principal inclusion criterion (ages 50–70 y). Invitations to an assessment appointment and to undertake completion of written informed consent were sent in time order of initial patient response.

Inclusion criteria were age 50 to 70 y, general good health, body mass index (BMI) 18 to 40 kg/m^2, agreement to attend all study visits and undergo all procedures, community-dwelling, and at least one self-reported URTI in the previous 12 mo. Exclusion criteria were current symptomatic respiratory illness; current use of oral steroids, antibiotics, or immunosuppressant medication; known immune or autoimmune disorders (including HIV infection, ankylosing spondylitis, Crohn's disease, ulcerative colitis); having low BMI or an eating disorder; severe renal or liver disease; or symptomatic heart failure. Medical records and patient history were used to assess recruitment criteria. Symptomatic respiratory and cardiac conditions were excluded to prevent difficulty assessing URTI symptoms. The lower age limit of 50 y was selected as a generally accepted threshold for the development of age-related immune decline ("immunosenescence") [19], and the upper limit was 70 y to prevent wide heterogeneity in general health and frailty. Smoking status and influenza vaccine uptake over the previous 12 mo were recorded to control for potential confounding.

Randomization to Wellmune or placebo was blinded and a random block allocation sequence generated by the University of Southampton Research Design Service was used. The packaging and capsules used for Wellmune and placebo were identical in appearance and were labeled with a study identifier code 001 to 100. Participants were allocated to the lowest available study identifier on completion of the consent process. Participants were asked to self-administer the intervention once daily before food.

Saliva and blood samples were collected at study entry (day 0), day 45, and day 90. Heparin was used as an anticoagulant. Whole blood was used for culture (see later) and for preparation of plasma, which was stored at −80°C before analysis.

Health diary and Wisconsin Upper Respiratory Tract Severity Score 21

The presence or absence of URTI symptoms was recorded in a daily health diary using the following numerical categories: 1 *no health problems today*; 2 *cold symptoms* (listed as runny nose, blocked nose, sore throat, coughing, sneezing, colored discharge); and 3 *flu-like symptoms* (fever, headache, general aches and pains, fatigue and weakness, chest discomfort). The presence of any two or more URTI symptoms for 2 d consecutively triggered telephone or face-to-face review to medically confirm URTI. Participants were instructed to complete the validated Wisconsin Upper Respiratory Tract Severity Score 21 (WURSS-21) for each symptomatic day. WURSS-21 contains an 8-point Likert scale for specific URTI symptoms and the effects of symptoms on activities of daily living.

Adherence, side effects (self-classified by symptom and severity as mild, moderate, or severe), and concomitant medication use were self-recorded in the health diary that was reviewed along with an unused capsule count during face-to-face interviews at days 45 and 90. Nonadherence was classified as nine or more missed capsules in either 45-d period.

Salivary immunoglobulin A and plasma cytokine concentrations

Secretory immunoglobulin A (SIgA) concentration in saliva was measured using a commercially available enzyme-linked immunosorbent assay kit (Immundiagnostik AG, Bensheim, Germany). Saliva was centrifuged at 3000*g* for 10 min before assay. The manufacturer's instructions were followed. The detection limit of the assay was 13.4 ng/mL.

Plasma was collected from fresh blood collected into heparin and then stored at −80°C until analysis. Cytokines (interleukin [IL]-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 p70, IL-13, IL-17 a, IL-22, interferon [IFN]-γ, tumor necrosis factor [TNF]-α) and chemokines (IL-8, macrophage inflammatory protein [MIP]-1α, MIP-1β, MCP-1, granulocyte colony-stimulating factor [GCSF], monocyte induced by interferon-γ [MIG]) were measured in plasma using flow-cytomix 6- and 13-plex kits (eBiosciences, Hatfield, UK). The manufacturer's instructions were followed. The detection limits of the assays are 0.9 to 20.8 pg/mL; any value lower than the limit of detection was assigned half of the value of the lowest detectable standard.

Whole blood cultures and supernatant cytokine concentrations

Whole blood was diluted 1 in 10 with RPMI culture medium containing 2 mmol/L glutamine and antibiotics. Cultures were stimulated with the toll-like receptor 4 ligand lipopolysaccharide (LPS; ultrapure *Escherichia coli* K12 lipopolysaccaride; InvivoGen, San Diego, CA, USA; final concentration 1 ng/mL). Medium was collected after 24 h and stored at −80°C until analysis. Cytokines and chemokines (as previously listed for plasma) were measured in plasma using flow-cytomix 6- and 13-plex kits (eBiosciences). The manufacturer's instructions were followed.

Sample size and statistical analysis

Given the lack of data regarding Wellmune use in older adults, the pragmatic sample size of 100 participants was selected for this trial, with the aim of further informing effect size, mechanisms of action, and potential benefit of a larger trial; therefore, this trial should be regarded as a pilot study. Data were collated in Excel (Microsoft, Redmond, WA, USA) and transferred to Stata (Stata, College Station, TX, USA) for analysis on an intention-to-treat basis. The χ^2 test was used to determine the odds ratio for between-group difference in the number of URTI episodes and an Anderson-Gill model was used to analyze difference in the number of symptom days due to heterogeneity in the distribution of data between groups. The Mann–Whitney U test was used to analyze between-group difference in mean daily WURSS-21 symptom severity score and between-group difference in the change from baseline at days 45 and 90 in plasma cytokines, LPS-stimulated whole blood cytokines and salivary IgA. In all cases, statistical significance was set at $P < 0.05$.

Results

Participant characteristics

Table 1 lists the characteristics of the 100 participants who entered the study. The groups did not differ according to age or

age distribution, sex distribution, weight or BMI, cigarette smoking or recent seasonal influenza vaccination. Figure 1 shows the flow of participants through the study.

Forty-nine participants completed the study in each group and supplementation was well tolerated. One participant in the placebo group left the trial due to constipation as a reported side effect within days 0 to 45. One participant in the Wellmune group failed to take the supplement on more than 9 d during days 0 to 45 and so was excluded from the study; this participant did not report any adverse events (AEs) from supplementation. Table 2 provides a summary of reported AEs. AEs were more common in the placebo group.

Upper respiratory tract infections

Forty-five URTI episodes were confirmed. Smokers were more likely to experience a URTI than nonsmokers (odds ratio [OR], 2.81; 95% confidence interval [CI], 0.67–11.67), but this difference was not statistically significant, likely due to small sample size (n = 10 smokers). Twenty-eight URTI episodes were reported in the placebo group, whereas 17 were in the Wellmune group (OR, 0.55; 95% CI, 0.24–1.26); this difference was not statistically significant ($P = 0.149$; Table 3). After controlling for both seasonal influenza vaccine uptake within the previous 12 mo and smoking status, the OR for URTI in the Wellmune group was 0.66 (95% CI, 0.28–1.57; $P = 0.346$). Six participants in the placebo group (12%) reported two URTI episodes over the 90 d of the study compared with two participants (4%) in the Wellmune group (Table 3). There was a trend toward fewer symptom days in the Wellmune group (median 3; IQR 2–9) than in the control group (median 3.5; IQR 1–9; $P = 0.067$). No difference was seen in symptom severity between groups in either global or mean daily WURSS-21 scores (data not shown).

Salivary IgA concentration

No between-group difference was detected in the change from baseline at day 45 or 90 in salivary IgA concentration (data not shown).

Plasma cytokine and chemokine concentrations

No between-group differences were detected in the change from baseline at day 45 or 90 in plasma cytokine and chemokine concentrations (data not shown). However, many of these analytes were present at very low concentrations in many of the samples.

Table 1
Characteristics of participants at study entry according to treatment group

Variables	Wellmune group (n = 50)	Placebo group (n = 50)
Age, y	58.9 ± 5.6* Range: 50–68†	59.16 ± 5.5* Range: 50–68†
Sex, n (%)		
Male	26 (52)	28 (56)
Female	24 (48)	22 (44)
Height, m	1.7 ± 9.4*	1.7 ± 0.9*
Weight, kg	78.5 ± 18.1*	78.8 ± 15.6*
Body mass index, kg/m^2	26.8 ± 4.3*	26.8 ± 4.1*
Current cigarette smoker, n (%)	3 (6)	7 (14)
Seasonal influenza vaccination within past 12 mo (%)	18 (36)	23 (46)

* Values are mean ± standard deviation.
† n = 29 ages 50–60 y and n = 21 aged >60 y in each group.

LPS-stimulated whole blood cytokine and chemokine concentrations

The concentrations of IL-2, IL-4, IL-13, IL-17α, and GCSF were very low in LPS-stimulated whole blood cultures, often being below the limit of detection. In contrast, the other cytokines and chemokines were detected in most samples. The concentrations of IL-1β, IL-6, IL-8, TNF-α, MCP-1, MIP-1α, and MIP-1β were easily detected in all samples. There were some changes with time that occurred in both groups, such that there were few between-group differences in the change from baseline at day 45 or 90. However, LPS-stimulated blood samples from the Wellmune group showed an increase in IFN-γ concentration from baseline at day 45 compared with a small reduction from baseline in the placebo group ($P = 0.016$; Table 4). However, no between-group difference was seen for IFN-γ for the change from baseline at day 90. The concentration of MIG decreased from baseline in both groups at days 45 and 90 (Table 4). However, the decreases were smaller in the Wellmune group at both time points ($P = 0.032$ and 0.046 at days 45 and 90, respectively; Table 4). The concentration of MCP-1 decreased from baseline in the placebo group at days 45 and 90 and in the Wellmune group at day 90. However, the decrease tended to be smaller in the Wellmune group (Table 4).

Discussion

Finding effective prevention and management strategies for URTI remains an area of unmet health care need. Despite the usually self-limiting nature of illness, the high incidence of URTI causes significant health, social, and economic affects, which was estimated by Fredrick et al. to cost the US economy nearly $40 billion per annum due to use of health care resources and lost productivity [2]. Given the scale of the problem, even interventions with a modest ability to reduce URTI incidence, severity, or both may be beneficial if proven safe, effective, and acceptable for widespread use. Here, we examined the ability of Wellmune to reduce incidence, severity, and duration of URTI in elderly individuals living in the community. There was a trend to fewer illness episodes with Wellmune than with placebo (OR, 0.55; $P = 0.149$) and to fewer days of illness ($P = 0.067$) but there was no effect on symptom severity. A previous study observed that in healthy young individuals given the same dose of Wellmune (250 mg/d) for the same duration (90 d) as used here, there was a trend toward fewer days with symptoms of URTI ($P = 0.06$) and no effect on severity of most symptoms as assessed by WURSS-21 [16]. It is clear that larger studies are needed to identify significant effects of Wellmune on URTIs, and that such studies should be performed. Using number of illness episodes as the primary outcome, to detect a difference between groups of about 15% with 90% power a sample size of 217 per group would be needed without any allowance for loss to follow-up. Future studies may benefit from targeting populations at risk for higher incidence or severity of infection, such as the inclusion of adults aged >70 y [20], children [21], or individuals self-reporting high frequency of URTIs.

The intervention was well tolerated in the elderly participants studied here, with no withdrawals due to AEs and with a better (self-reported) AE profile compared with placebo. Informal feedback from participants during the recruitment phase of the study often cited the appeal of nutritional options as a self-care strategy to enhance immune function and prevent the burden of common infections.

Intervention with Wellmune did not modify plasma cytokine or chemokine concentrations in the present study. There also was no

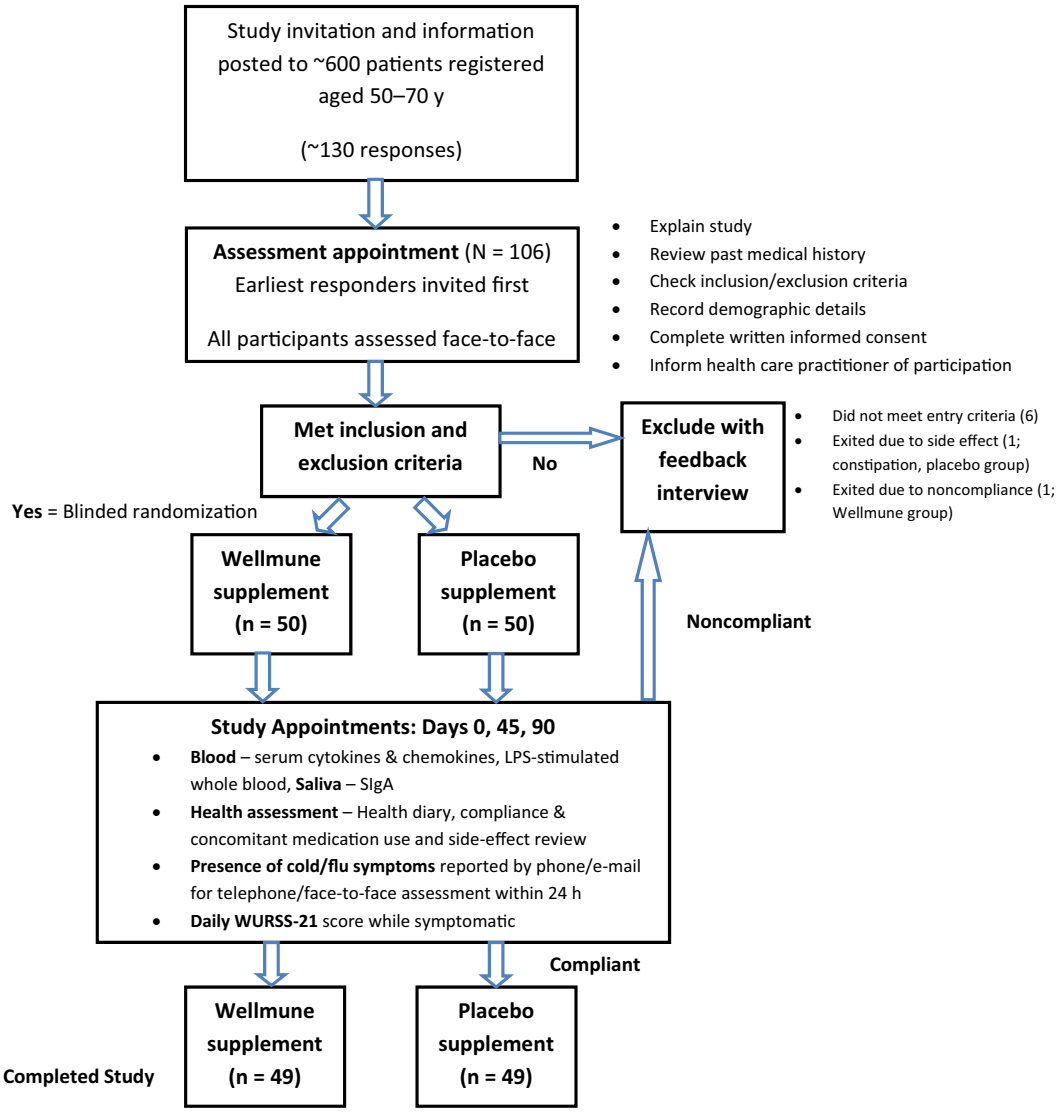

Fig. 1. Consort diagram showing the flow of participants through the study. LPS, lipopolysaccharide; SIgA, secretory immunoglobulin A; WURSS-21, Wisconsin Upper Respiratory Tract Severity Score 21.

effect on salivary SIgA concentration. Furthermore, there was a limited effect of Wellmune on the inflammatory response of immune cells in cultured blood. In a previous study in young adults [16], there was no effect of Wellmune on plasma cytokine or chemokine concentrations in the absence of any illness symptoms; the current finding of lack of effect of Wellmune on plasma cytokines and chemokines in older individuals is consistent with this. In an earlier study, Wellmune resulted in lower plasma MCP-1 concentration during infection [16], that is, in the presence of an immune or inflammatory stimulus. Therefore, it is interesting that, in the present study, Wellmune did promote an increase in LPS-stimulated IFN-γ production (at day 90) and smaller time-dependent decreases in LPS-stimulated MCP-1 (trend at day 90) and MIG (at both days 45 and 90) than seen in the placebo group. These observations suggest priming of innate immune cells to an inflammatory stimulus by Wellmune; the stimulus was infection in vivo in the study in young adults [16] and ex vivo exposure to LPS in the present study. There is evidence that Wellmune can prime innate immune cells to a subsequent immune stimulus [10–15]. Such an effect may underlie the trends to an effect seen on URTI incidence and duration in the present study. It is likely that the

Table 2
Summary of self-reported side effects according to treatment group

Placebo group	Wellmune group
Indigestion (mild) n = 1	Bloating (mild) n = 1
Generalized itch (moderate) n = 1	Headaches (moderate) n = 1
Constipation (severe) n = 1*	
Constipation (mild) n = 1	
Nausea (mild) n = 1	
Tiredness (mild) n = 1	

* Withdrew from the study.

Table 3
Comparison of the number of participants experiencing URTI episodes by treatment group

	No episodes	1 episode	2 episodes
Placebo group, n (%)	28 (56)	16 (32)	6 (12)
Wellmune group, n (%)	35 (70)	13 (26)	2 (4)

URTI, upper respiratory tract infection

Table 4
Within- and between-group differences in the change from baseline at days 45 and 90 in selected cytokines and chemokines in LPS-stimulated blood samples

	Placebo group: day 0	Wellmune group: day 0	Placebo group difference: day 0–45	Wellmune group difference: day 0–45	Between groups *P* value	Placebo group difference: day 0–90	Wellmune group difference: day 0–90	Between groups *P* value
IFN-γ	139.4 (0.8–859.5)	107.8 (0.8–637.3)	4.8 (−48.5 to 432.8)	−49.1 (−639.7 to 73.8)	0.016	15.5 (−172.1 to 319.5)	0 (15.2–372.8)	0.758
MCP-1	2335 (1277.6–2911.8)	1411.1 (986.5–2744.6)	477.9 (−323.7 to 1997.9)	77.7 (−729 to 919.9)	0.102	1666.6 (507.3–2400.7)	796.7 (347.1–1492)	0.069
MIG	104.6 (37.8–205.7)	58.2 (17.7–144.5)	79.7 (0–187.3)	22.6 (−38.2 to 131.5)	0.032	104 (38.7–202.2)	48.4 (2.3–102.4)	0.046

IFN-γ, interferon-γ; MCP-1, monocyte chemoattractant protein-1; MIG, monocyte induced by IFN-γ
Data are median and 25th and 75th percentiles

main responder cell type in LPS-stimulated whole blood cultures is the monocyte. We did not assess the effects of Wellmune on isolated innate immune cells or on innate immune responses other than peptide mediator production, such as phagocytosis and natural killer cell activity. These immune outcomes should be assessed in future studies.

Conclusion

Daily supplementation with Wellmune is well tolerated in older community-dwelling individuals and may have a role in the prevention and faster resolution of URTI. This effect may be related to differences in innate immune responses in individuals consuming Wellmune. Larger studies seem warranted to explore the role of Wellmune for the prevention and control of common infections.

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