

Wellmune® Research Summary

Wellmune is a Product of Kerry, the Global Taste and Nutrition Company



For more information, please contact us at wellmune@kerry.com or visit www.wellmune.com

Wellmune®: Nature's Immune Enhancer

An Innovative Functional Food and Beverage Ingredient That is Clinically Proven to Enhance Immune Function

Introduction

Global consumer demand remains strong for functinal foods and beverages that deliver real immune health benefits. A 2015 Datamonitor survey of nearly 28,000 consumers in 31 markets found that immune health was the number two most desired functional benefit consumers want in a food or beverage. Immunity was second only to general health and wellness, and ranked above heart health (third) and digestive health (fourth). The survey also reports that while an astounding 87% of consumers are interested in purchasing food/beverages with immune health benefits, only 48% are actively buying these products, which is likely due to a lack of availability or recognition of some products' benefits.

The gap between immunity product interest and purchase translates into tremendous opportunity for manufacturers of foods and beverages that can deliver meaningful immune support.

Wellmune[®] is the ideal immune health ingredient for foods, beverages and supplements. It is 100% natural and clinically proven to help safely strengthen the immune system, making it easier for consumers to be well and stay well. Wellmune is a beta 1,3/1,6 glucan from proprietary baker's yeast that boosts key innate immune cells that are part of the body's natural defenses.

Wellmune's unmatched clinical research — more than 10 studies — can support a variety of compelling and regulatory-compliant health claims associated with a strong immune system. These include:

- Everyday Immune Support
- Health & Wellness
- Energy & Vitality
- Stress Protection

- Sports Nutrition
- Children's Immunity
- Healthy Aging



In addition, Wellmune is GRAS-approved under U.S. FDA regulations and has regulatory approval in Europe, China, Australia and other countries around the world. Wellmune is also patented, Kosher, Halal, non-allergenic, gluten-free, GMO-free and Informed Sport® certified. The compelling safety and efficacy research supporting Wellmune make it an ideal ingredient for delivering real health benefits to consumers.

Wellmune Mechanism of Action

Wellmune is a natural yeast beta glucan derived from the cell walls of a highly purified, proprietary baker's yeast (*Saccharomyces cerevisiae*). This unique ingredient triggers human immune defenses that have evolved over thousands of years to protect the body.

The scientific understanding of Wellmune's mechanism of action in the body is well documented in published, peer-reviewed research. Mechanism of action studies, as well as measurement of significant changes in immune responses, are changing the way researchers and physicians think about innate immune function.

Once swallowed, immune cells in the gastrointestinal tract take up Wellmune and transport it to immune organs throughout the body. While in the immune organs, immune cells called macrophages digest Wellmune into smaller fragments and slowly release them over a number of days. The fragments bind to neutrophils, via complement receptor 3 (CR3), which are the most abundant immune cells in the body. In fact, neutrophils account for approximately 65% of all immune cells.

Activated by Wellmune, the neutrophils are now primed for activity. Unlike other immune health ingredients, Wellmune supports immune function without overstimulating the immune system, which may be harmful.





Day 1: Wellmune ingested by macrophages.



Figure 1

Day 2: Macrophages degrade Wellmune and release tiny fragments.



Day 3: Wellmune fragments bind to neutrophils, priming them for activity.





Researchers discovered the mechanism of action through a series of experiments, including those with CR3-deficient mice that confirmed the critical role this receptor plays in triggering an immune response. Other studies tracked fluorescently dyed Wellmune as immune cells transported it throughout the body (figure 1). Within days Wellmune is carried to the spleen, bone marrow and other immune organs.

In a separate study, significant improvement was observed in the killing activity of immune cells. Phagocytic cells, which literally engulf and destroy foreign challengers, showed greater microbial killing in subjects who had taken Wellmune.

Most recently, researchers have focused on specific immune biomarkers that may link health benefits to changes in immune function. While more research is needed, the studies confirm immunological activity consistent with the presence of Wellmune.

Applications

Wellmune is designed for the majority of food, beverage and supplement applications. It is available in two powder forms dispersible for food and select beverage applications and water soluble for certain beverage applications with clarity or other manufacturing requirements. In water at 1 mg per milliliter, soluble Wellmune is odorless, clear and with mild to no taste. Wellmune is stable under the vast majority of manufacturing processes.













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Research - Proof of Efficacy

Kerry is committed to a robust research and development program to evaluate the efficacy of Wellmune in humans experiencing various real-life situations. Years of research has resulted in a product with a well-defined mechanism of action, a compelling body of credible, peer-reviewed science and increasing clinical support of its efficacy.

Numerous clinical studies consistently demonstrate the positive health benefits of Wellmune on the physical and psychological health of individuals experiencing lifestyle and physical stress that often directly lead to illness. The studies featured several different populations, including firefighters, marathoners, medical students and individuals with high lifestyle stress. Each of the following pages highlights select results from these studies. Beginning on page 17 is a bibliography of Kerry's clinical and preclinical research.

The complete body of research supporting Wellmune includes additional clinical research, numerous preclinical studies and human biomarker research. Kerry remains committed to ongoing research that advances the science of its ingredients and understanding of immune health.

For additional information, please visit www.wellmune.com.

Study Name	Study Type	Published		
1. Texas Marathon	Physical Stress Health Effects	Journal of Dietary Supplements, 2013		
2. Exercise Stress	Biomarkers	British Journal of Nutrition, 2012		
3. Medical Students	Physical / Lifestyle Stress	Nutrition, 2012		
4. Lifestyle Stress 90-day	Lifestyle Stress Health Effects	Journal of American College of Nutrition, 2013		
5. Lifestyle Stress 28-day	Lifestyle Stress Health Effects	Agro Foods Industry Hi Tech, 2010		
6. Allergy	Allergic Rhinitis Health Effects	Food Science & Nutrition, 2012		
7. California Marathon	Physical Stress Health Effects	Journal of Sports Science & Medicine, 2009		
8. Cold/Flu	Cold/Flu	Journal of Applied Research, 2009		
9. Firefighters §	Physical Stress Health Effects	Presented at Am. Soc. of Sports Medicine, 2008		
10. Aging Population §	Cold/Flu Biomarkers	Presented at Southampton Translational Clinical Research Conference, 2014		
11. Childrens Study	Lifestyle Stress Health Effects	Journal of Nutrition & Food Sciences, 2016		

Study #1: Texas Marathon



Marathoners taking Wellmune for four weeks experienced a 40% reduction in upper respiratory tract infection symptoms in comparison to the control group.

Wellmune Reduced by 34% Upper Respiratory Tract Infection Symptoms among Marathoners

A study of 182 runners who completed the 2011 LiveStrong Marathon in Austin, Texas, confirmed previous clinical research showing that Wellmune®'s support of the immune system has health benefits for individuals under real-life conditions. The study was conducted by the Health and Human Performance Lab at the University of Houston.

Study Protocol

It is common for runners to develop upper respiratory tract infections (URTI) in the days and weeks following completion of a marathon. The double-blinded study included 96 men and 86 women with an average age of 34 and an average finish time of 4:00 hours. These participants were given either 250 mg of Wellmune soluble or Wellmune dispersible daily or a placebo of rice flour to take for four weeks following the LiveStrong marathon.

Results

Wellmune supplementation significantly reduced the number of days that subjects reported both general health problems as well as cold/ flu symptoms. Based on previous studies conducted by the University of Houston, it is reasonable to speculate that the improvements associated with Wellmune were likely due to alterations in monocytes, plasma cytokines, and improved mucosal immunity.





"Baker's Yeast Beta Glucan Supplementation Increases Salivary IgA and Decreases Cold/Flu Symptomatic Days After Intense Exercise." *Journal of Dietary Supplements*, Early Online:1–13, 2013. Available online at www.informahealthcare.com/jds DOI: 10.3109/19390211.2013.820248.

Study #2: Exercise Stress



Study Protocol: The randomized, double-blinded, placebo-controlled study involved 60 recreational athletes taking either a placebo or 250 mg of Wellmune daily for 10 days.

The athletes then rode an exercise bicycle for one hour in the heat stress chamber. Blood samples were drawn at day 0 and immediately before and after the exercise session and again two hours post exercise.

Using a cross-over study design, the athletes next observed an eightday "wash out" period before repeating the study with the other test variable (Wellmune or placebo).

Wellmune Reduces Immune Suppression Associated with Strenuous Exercise

This clinical study conducted at the Department of Health and Human Performance at the University of Houston indicates that Wellmune[®] may enable both recreational and elite athletes to exercise longer and harder with less risk of immune system suppression that normally follows high-intensity exercise.

The effectiveness of the immune system drops sharply below its normal state two to six hours after strenuous exercise and then gradually recovers within 24 hours. "During this 'open window' period, the athlete is more susceptible to infection, which may result in lost training time as well as missed work or school," said Brian McFarlin, Ph.D., FACSM, Associate Professor of Exercise Physiology, Nutrition, and Immunology.

Study participants also had higher levels of key cytokines (IL-2, IL-4, IL-5 and IFN gamma) following Lipopolysaccharide (LPS) stimulation when taking Wellmune. LPS is derived from gram-negative bacteria and used to mimic a foreign challenge to stimulate an immune response.

"The effect of Wellmune on LPS-stimulated IL-4 and IL-5 production suggests that leukocytes were primed for higher plasma cytokines that directly mediate innate and humoral-dependent immune responses," said Dr. McFarlin. "Our lab has tested numerous compounds but Wellmune is the first to prevent alterations in monocytes and key cytokines following highintensity exercise."





(*) Indicates statistically significant difference (P<0.05) between Wellmune & placebo.

"Baker's Yeast B-glucan Supplementation Increases Monocytes and Cytokines Post-Exercise: Implications for Infection Risk?" (2012) *British Journal of Nutrition*. May 10:1-9.

Study #3: Med Students



In contrast with the placebo group, participants taking Wellmune reported a significant reduction (18%) in the total number of days with selfreportered URTI symptoms (198 days vs 241 days, p+0.039).

Wellmune Reduced Duration of Cold/Flu Symptoms in Study of 100 Medical Students

Wellmune significantly reduced the duration of upper respiratory tract infection (URTI) symptoms in a healthy population of 100 medical students during a 90-day study at the peak of the cold-flu season.

One hundred fourth-year medical students at Southampton University Medical School, United Kingdom, participated in the randomized, double-blind, placebo-controlled study. The students consumed 250 mgs of Wellmune once daily or an identical placebo capsule.

Participants completed a daily health diary recording presence or absence of listed URTI symptoms. Two or more reported URTI symptoms for two consecutive days triggered medical assessment and cytokine analysis within 24 hours. A total of 97 participants completed the trial protocol (Wellmune n=48, Placebo n=49).

Study Results

- There was a significant reduction (18%) in the total number of days with self-reported URTI symptoms in Wellmune group compared to placebo (198 days versus 241 days, p=0.039/per protocol group).
- In total, 24 episodes of URTI were medically confirmed; 12 episodes in each group.
- Wellmune did not induce inflammatory cytokines. No cytokine change was seen during symptomatic URTI between study groups.







Study #4: Lifestyle Stress



In contrast with the placebo group, participants taking Wellmune reported a:

- 58% decrease in upper respiratory tract infection symptoms
- 9.5% increase in overall well-being
- 11% increase in vigor

Wellmune Reduced Upper Respiratory Tract Infection Symptoms during 90-Day Lifestyle Stress Study

In a study of 122 healthy volunteers (32 men, 90 women $38 \pm 12y$), participants taking 250 mgs of Wellmune daily for 12 weeks reported a statistically significant (p<0.05) 58% reduction in upper respiratory tract infection symptoms, compared with individuals taking a placebo. This data was presented at Experimental Biology 2010.

Using a Profile of Mood States (POMS) psychological survey to assess changes in mental and physical energy levels and overall well-being, the study demonstrated statistically significant benefits for the Wellmune group. These participants rated their overall well-being and vigor 9.5% and 11% higher, respectively, compared with the placebo group. Data for both measures had p values of <0.05.

The study results were consistent with data from other clinical studies demonstrating that Wellmune can naturally enhance immune responses during periods of both high physical and psychological stress.





"Baker's Yeast Beta-Glucan Supplement Reduces Upper Respiratory Symptoms and Improves Mood State in Stressed Women." *Journal of the American College of Nutrition*, August 2012, vol 31, no. 4, 295-300.

Study #5: Lifestyle Stress



Compared with the placebo group, the Wellmune group reported a:

- 42% increase in vigor
- 38% reduction in fatigue
- 19% reduction in tension
- 15% reduction in stress-induced confusion

Subjects completed the Profile of Mood States (POMS) Survey Instrument. The well-validated POMS employs 65 adjective-based indicators of mood scaled for intensity (0-4); specific combinations of the adjectives define the 6 mood state factors: tension, vigor, fatigue, confusion, anger and depression.

Wellmune Reduced Health Challenges in High Lifestyle Stress Subjects

Individuals with high lifestyle stress taking Wellmune over four weeks reported a significant increase in their general health, compared with the placebo group. Fully 150 subjects with high lifestyle stress were randomized, double blinded and placebo controlled. Subjects were split into three groups: placebo, 250 mgs and 500 mgs/day of Wellmune. There was no statistically significant difference between the 250 and 500 mg/day groups so only the 250 mg/day group vs. placebo is presented below. Subjects maintained a daily health log with entries tracking the occurence and duration of URTI symptoms (cough, sore throat, sneezing, etc.). They also responded to questions regarding physical health the during course of study.









Figure 2. Taking Wellmune significantly increased (p<0.05) self reported health scores.



Figure 3. Analyzed data for specific POMS factors calculated from POMS Score Sheet. Data analysis was by paired t-test. A value of p < 0.05 was considered significant. Each factor was determined using answers to specific adjective-based scales as described in Profile of Mood States manual by McNair et al (28).

"Beta 1,3/1,6 Glucan Decreases Upper Respiratory Tract Infection Symptoms and Improves Psychological Well-being in Moderate to Highly-Stressed Subjects." *Agro Food Industry Hi-Tech* (2010). 21:21-24.



Study #6: **Allergy Study**



Allergy sufferers taking Wellmune experienced a 27% reduction in average allergy symptoms and a 52% reduction in severity of symptoms.

Wellmune Provided Significant Relief to Ragweed Allergy Sufferers

A placebo-controlled, double-blinded study found that Wellmune® reduced alleray symptoms and improved the quality of life of individuals who suffer from ragweed allergy. Ragweed is a leading cause of seasonal allergy symptoms and affects 36 million Americans. Typical symptoms include nasal congestion, sneezing, itchy eyes and difficulty breathing. The cause is an immune system overreaction to raqweed pollen.

Study Design

The study equally divided 48 healthy subjects (31 female, 17 male; 39 ± 13 years of age) into two groups. One group consumed a placebo while the other a 250 mg serving of Wellmune daily for four weeks during September/

October 2010 in an area of southeast Ohio where local pollen counts were high. Allergy surveys, including the validated Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), were used to assess differences in allergy symptoms.

Study Results

Individuals consuming Wellmune experienced statistically significant (p<0.05) relief by several measures:



Symptom severity score

*p<0.05

 A 27% reduction in average allergy symptoms and 52% reduction in severity of symptoms.

8

6

4

2 0

- Reductions in key nasal and eye-related allergy symptoms.
- Overall results demonstrated a 56% improvement on the Quality of Life Index, a scientifically validated tool for measuring how participants rate their overall sense of wellness.

Average symptoms



"B-Glucan supplementation, allergy symptoms, and quality of life in selfdescribed ragweed allergy sufferers." Food Science & Nutrition, 10:1-12. Wellmune

Placebo

Study #7: **CA Marathoners**



In contrast with the placebo group, marathoners taking Wellmune reported a:

- 67% decrease in upper respiratory tract infection symptoms
- 22% increase in vigor
- 48% reduction in fatigue
- 38% reduction in tension

38% reduction in confusion

The well-validated POMS



Wellmune Reduced Fatigue and Improved Health in Marathoners

Wellmune increased vigor and mental clarity while reducing fatigue and upper respiratory tract infection (URTI) symptoms in marathon runners. The double-blind, placebo-controlled study included 75 marathon runners (35 men, 40 women) ages 18-53 (mean age 36 years) who were recruited at the 2007 Carlsbad Marathon in California. Subjects were treated daily with Wellmune, a natural carbohydrate that activates key immune cells to more quickly recognize and kill foreign challenges, or a placebo for four weeks.

The protocol of this study was identical to the study completed with high lifestyle stress subjects (page 10).



Figure 1. Total number of subjects reporting any of 11 pre-selected upper respiratory tract infection symptoms. Subjects were orally administered placebo, 250 mg Wellmune or 500 mg Wellmune. Statistical analysis was by paired t-tests.

*A value of $p \le 0.05$ was considered significant.



Figure 2. Subjects responded to two and four week supplement effectiveness question: "During the course of the supplement regimen, my health has been ...: Scores for the question were based on a scale of 0-10 with 0 being worse, 5 being same and 10 being better health. Data analysis was by paired t-test. *A value of $p \le 0.05$ was considered significant.



Figure 3. Analyzed data for specific POMS factors calculated from POMS Score Sheet. Data analysis was by paired t-test. A value of p < 0.05 was considered significant. Each factor was determined using answers to specific adjective-based scales as described in Profile of Mood States manual by McNair et al (28).

"Effect of Beta 1,3/1,6 Glucan on Upper Respiratory Tract Infection Symptoms and Mood State in Marathon Athletes." Journal of Sports Science and Medicine (2009). 8:509-515.

Study #8: Cold & Flu



Wellmune Maintained Physical Health and Reduced 'Down Time' During 90-Day Study

In a cold season study with 40 healthy subjects, Wellmune reduced the incidence of fever and eliminated the need to miss work or school due to cold-like symptoms. The double-blinded, placebo-controlled study included subjects, aged 18-65, who were treated daily with either 500mg of Wellmune or a placebo for 90 days. Cold/flu symptoms were evaluated by medical staff within 24 hours of onset.

In contrast with the placebo group, the Wellmune group reported an increase in general health markers, including physical energy and emotional well-being, as measured by a clinically validated health survey questionnaire (SF-36v-2).

While there were no significant differences in the incidence of symptomatic respiratory infections among the study groups, the duration and severity of symptoms were alleviated in subjects receiving Wellmune.

In the study results, the Wellmune group reported:

- No missed work or school due to colds, compared with 1.38 days of work/school missed for the placebo group. (p = 0.026)
- No incidence of fever, compared with 3.50 incidence in the placebo group. (p = 0.042)
- An increase in quality of life, including physical energy and emotional well-being, as measured by a clinically validated health survey questionnaire (SF-36v-2). (p = 0.042)
- No adverse events were detected and no safety concerns were present.

Medically-verified Symptoms and Study Outcomes

Variable	Wellmune	Placebo	P-value
Incidence of Fever	0.00	3.5 ± 3.42	0.042
Number of missed days of work/school	0.00	1.38 ± 1.25	0.026



"Randomized Phase II Clinical Trials of Wellmune® for Immune Support During Cold and Flu Season." The Journal of Applied Research (2009). 9:20-42.

Study #9: FireFighters



Wildland Firefighters Reported Improved Health with Wellmune

A study conducted by the University of Montana, which included funding from the U.S. Air Force, found that wildland firefighters benefited from Wellmune.

In a single-blind, random cross-over design, subjects completed two 14-day conditions with a three-day washout between trials. Supplements were consumed once a day and consisted of Wellmune and a similar capsule placebo.

In comparison with the control group, Wellmune subjects experienced a:

- 23% reduction in upper respiratory tract infection symptoms (p value = 0.06)
- Dramatic improvement in overall physical health (p value = 0.006)

Subjects completed a daily health questionnaire as used by Nieman et al. (2002), with additional questions added that pertained specifically to the supplement.

An individual was classified as having an URTI when he or she recorded a cold or flu symptom for a minimum of two consecutive days.

At the conclusion of each trial, subjects completed an overall health performance questionnaire, which contained questions regarding the subject's overall health during the 14-day trial.





"Effects of an Immunomodulating Supplement on Upper Respiratory Tract Infection Symptoms in Wildland Firefighters." *Medicine & Science in Sports & Exercise*. 40(5):S353.

Study #10: Aging Population



Immune-Boosting Wellmune Supports Health of Older Adults

Wellmune supported the health of older adults during cold and flu season, according to a pilot study conducted at the University of Southampton Hospital in the United Kingdom.

The randomized, double-blinded study consisted of 100 healthy adults aged 50-70 years consuming 250 mgs of Wellmune or a placebo for 90 days. Wellmune demonstrated a trend towards reducing the number of upper respiratory tract infections (URTI) and statistically significant changes and trends in cytokine levels that are part of the body's response to viral encounters and inflammation.

Incidence of respiratory tract infection were medically confirmed. Blood biomarker evaluation included plasma cytokines and LPSinduced cytokine response.

<u>Results</u>

- 1. Statistical trend towards reduced symptom days of cold (p=0.0674) were observed.
- 2. Wellmune stimulated a LPS-induced cytokine response:
 - Significantly for increased IFN-gamma (p=0.016) and maintained levels of MIG (CXCL9) (p=0.032).
 - There also was a trend towards increased IL-12p70 (p=0.075) and IL-10 (p=0.084).

Richard Fuller, M.D., who led the study within the Department of Primary Care and Population Science, said: "Respiratory infections are a major source of health burden and a leading cause for antibiotic use. The concept of using Wellmune as a nutritional supplement to support immune defences was very popular with study participants. The results of this pilot are encouraging and further studies certainly seem justified."

Medically-verified Episodes of Upper Respiratory Tract Infections

	0 Episodes	1 Episode	2 Episodes	Total
Placebo	28 (56%)	16 (32%)	6 (12%)	50
Wellmune	35 (70%)	13 (26%)	2(4%)	50





Study #11: Children



The study found that 62% of children taking Wellmune reported "good" health status compared to only 15% of the children taking a placebo. The study also found children taking Wellmune had two-thirds fewer URTI symptoms and six fewer sick days over a 12-week period.

Data Shows Children Taking Wellmune are Significantly Healthier

A randomized, doubled-blinded and placebo-controlled study with 156 healthy children aged 12 to 48 months demonstrated that Wellmune helped keep children healthier by decreasing episodes of common childhood illnesses and symptoms of illness, such as upper respiratory tract infections (URTI).

Children were divided into three groups receiving: 75 mgs of Wellmune, 35 mgs of Wellmune, or a placebo in liquid each day. Investigators observed the health of children after administration of Wellmune or the placebo, recorded the total days and times of upper respiratory tract infections and the total days and times of all kinds of infection symptoms. All records were medically verified and no significant difference between the Wellmune dose groups was found.

Previously, Mead Johnson Nutrition conducted two clinical studies with young children, which demonstrated children consuming a formula with Wellmune had significantly fewer acute respiratory infections or fewer episodes of allergy symptoms than children drinking unfortified cow's milk. One study also found that duration of their illnesses was signficantly shorter and, as a result, the children drinking the formula with Wellmune missed significantly fewer days at daycare.





"Baker's Yeast Beta-Glucan Decreases Episodes of Common Childhood Illness in 1 to 4 Year Old Children during Cold Season in China." *Journal of Nutrition & Food Science*; 2016, 6:518.

"Follow-up Formula Consumption in 3- to 4-Year-Olds and Respiratory Infections: An RCT Pediatrics"; originally published online May 19, 2014 DOI: 10.1542/peds. 2013-3598.

"Formula with docosahexaenoic acid, prebiotics, and beta-glucan supports respiratory and skin health in children." *The FASEB Journal*. vol. 28 no. 1 Supplement 382.6. 2014.



Kerry Research

NUTRITION







Research supporting the safety and efficacy of Kerry beta glucan ingredients is the subject of numerous peer-reviewed science and medical journal articles and presentations at scientific forums. Abstracts of these articles are available at www.wellmune.com/research.

Clinical Research

Meng F. Baker's Yeast Beta-Glucan Decreases Episodes of Common Childhood Illness In 1 to 4 Year Old Children during Cold Season in China. Journal of Nutrition & Food Science 2016; 6:518.

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