

Introducing Wellmune[®], an immune health ingredient

Donald J. Cox, PhD, Senior Vice President, Research & Development, Kerry

What is Wellmune[®]?

Wellmune is a bakers yeast beta-glucan. Bakers yeast beta-glucan is a naturally occurring polysaccharide derived from cell wall of bakers yeast (*Saccharomyces cerevisiae*). It is often included in a large and diverse class of polysaccharides commonly referred to as beta-glucans. Beta-glucans are derived from many sources including; oats, barley, seaweed, as well as many types microorganisms (bacteria, yeast and fungi). While they all share a “common” β form of chemical bond between the individual glucose units, there are many subtle, but important differences in structure within the beta-glucan family that lead to large differences in function and potential health benefits.

We define the specific and proprietary form of yeast beta-glucan used in Kerry’s product by the trade name Wellmune. It differs from other forms of beta-glucan in both chemical structure and biological activity. Wellmune has a backbone of glucose molecules linked together via a beta-(1 \rightarrow 3) linkage. In addition there are branch points along the backbone where side chains of are attached via a beta-(1 \rightarrow 6) linkage. Each side chain is typically 4-6 glucose units long. A graphic representation of the chemical structure is provided in Figure 1.

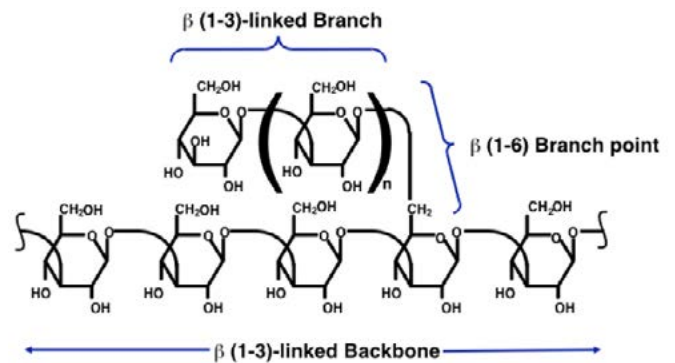


Figure 1. Graphic representation of the structure of bakers yeast beta-glucan

Wellmune is a 100% natural food, beverage and supplement ingredient clinically proven to help strengthen the immune system, making it easier for consumers to be well and stay well. Numerous published, peer-reviewed clinical studies have shown the ingredient’s ability to help safely and naturally support the immune system. Studies amongst a broad range of consumers (marathon runners, women, aging population and stressed individuals) have demonstrated that Wellmune can:

- Enhance key immune functions
- Improve overall physical health
- Maintain healthy energy levels
- Provide immune support as we age
- Help keep us healthy during times of stress.

What does Wellmune do? The mechanism of action of Wellmune.

The innate immune system is the primary line of defense against common health challenges.

Wellmune improves the functioning of the innate immune system by making key white blood cells (specifically called leukocytes) better able to find and kill potential pathogens. The mechanism of action of Wellmune is complex, but can be delineated into a few simple steps.

1. The human gastrointestinal tract contains immune tissue (Peyer's patches) with specific cells that actively collect and transport certain "food" materials into the immune system; Wellmune is one of the materials that is actively collected by these gut immune cells.
2. Processing of Wellmune by specific immune cells (macrophages) produces a biologically active fragment of Wellmune. The Wellmune fragment binds to and enhances key white blood cells called neutrophils.
3. The active fragment of Wellmune has specific effects on neutrophils:
 - When a Wellmune fragment binds to neutrophils, it increases the ability of these cells to navigate towards (chemotaxis) non-self cells (non-self cells are any cells that don't belong in the body, including dead or defective human cells, bacteria, fungi, etc.)
 - The non-self cells are marked and labeled by soluble blood proteins called a complement system, in a process called complement activation
 - When Wellmune carrying neutrophils encounter complement-activated cells, they trigger a specific biological mechanism that kills the non-self cell

How does Wellmune affect innate immunity?

Wellmune increases the ability of white blood cells called leukocytes to react to a non-self cell such as bacteria in two distinct ways:

1. Wellmune helps the innate immune cell find infections more quickly
2. Wellmune activates the innate immune system's defenses in the presence of a non-self cell

Clinical support

Wellmune has been evaluated in a number of clinical studies with study participants selected from the general population, who have various physical and psychological stress situations reflective of real-world situations. This program has resulted in a product with a well-defined mechanism of action, a compelling body of credible, peer-reviewed science and increasing clinical evidence of its efficacy. A summary of human clinical studies on Wellmune is presented in Table 1.



Table 1. Clinical Studies with Wellmune

Study Type	Subjects	Design & Dose	Results	Published/ Presented	Date
Physical Stress & Health Effects	54 wildland fire-fighters	10 day cross over @ 250 mg / day	Lower URTI symptoms (p=0.06), better overall perception of physical health (<0.006)	Am Soc of Sports Med (Presented)	May 2008
Cold/Flu	40 adults	30 day double blind placebo controlled @ 250 mg / day	Reduction in missed days of work or school, reduced fever, better physical health component (SF36 v2 survey)	Feldman et al J. of Applied Research	July 2009
Physical Stress & Health Effects	75 adult marathoners	30 day double blind placebo controlled @ 250 mg / day	Reduced number of URTI symptoms (p<0.05), reduced fatigue, tension and mental confusion, increased vigor	Talbott and Talbott. Journal of Sports Science & Medicine	Dec 2009
Lifestyle Stress & Health Effects	150 stressed adults	30 day double blind placebo controlled @ 250 mg / day	Reduced number of URTI symptoms (p<0.05), reduced fatigue, tension and mental confusion, increased vigor	Talbott and Talbott. Agro Foods Industry Hi Tech	Feb 2010
Lifestyle Stress & Health Effects	122 stressed adults	90 day double blind placebo controlled @ 250 mg / day	Reduced number of URTI symptoms (p<0.05), improved global mood state and increased vigor	Talbott and Talbott. J Am Col. Nutr.	2012
Physical / Lifestyle Stress & Health Effects	100 4th year med students	90 day double blind placebo controlled @ 250 mg / day	Reduced number of URTI symptoms (p<0.06), no changes in immune cell number or profile, no changes in cytokines from baseline	Fuller et al, Nutrition	June 2012
Allergic Rhinitis & Health Effects	48 adults with ragweed allergy	30 day double blind placebo controlled @ 250 mg / day	Reduced frequency and severity of eye and nasal allergy symptoms (p<0.05)	Food Sci & Nutri	May 2012
Physical Stress & Health Effects	182 adult marathoners	30 day double blind placebo controlled @ 250 mg / day	Reduced number of URTI symptoms (p<0.05) for both dispersible and soluble Wellmune	J Dietary Suppl	May 2013

As shown in Table 1, studies assessed the impact of Wellmune on the physical and psychological health of individuals experiencing lifestyle and physical stress that often directly lead to illness. The studies featured members of the general population including firefighters, marathoners, students and individuals with moderate to high lifestyle stress.

A more in depth summary of the clinical data is presented below for review. The complete body of research supporting Wellmune includes additional [clinical research](#), numerous preclinical studies and human biomarker research, which are published in peer-reviewed journals. Wellmune is the subject of ongoing research that advances the science of the ingredients and understanding of immune health.

Human clinical studies on Symptoms of URTI or Allergy

Clinical research demonstrates that Wellmune taken orally improves the health of human subjects. The trials were designed to determine if immune enhancement demonstrated in vitro with Wellmune would result in a reduction in the severity and duration of upper respiratory tract infection (URTI) symptoms in normal as well as stressed populations. Two of the studies also evaluated if Wellmune would improve how “well” subjects felt (documented via Profile of Mood States). The following data summarizes multiple clinical trials conducted with Wellmune. Summary analysis of the studies demonstrates that Wellmune can reduce the duration and severity of upper respiratory tract symptoms in healthy as well as stressed subjects.

In a cold season study published by Feldman et al¹ that involved 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 blind, placebo-controlled study included subjects, aged 18-65, who were



treated daily with either 500mg of Wellmune or a placebo for 90 days. 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). The study results were published in the Journal of Applied Research in 2009.

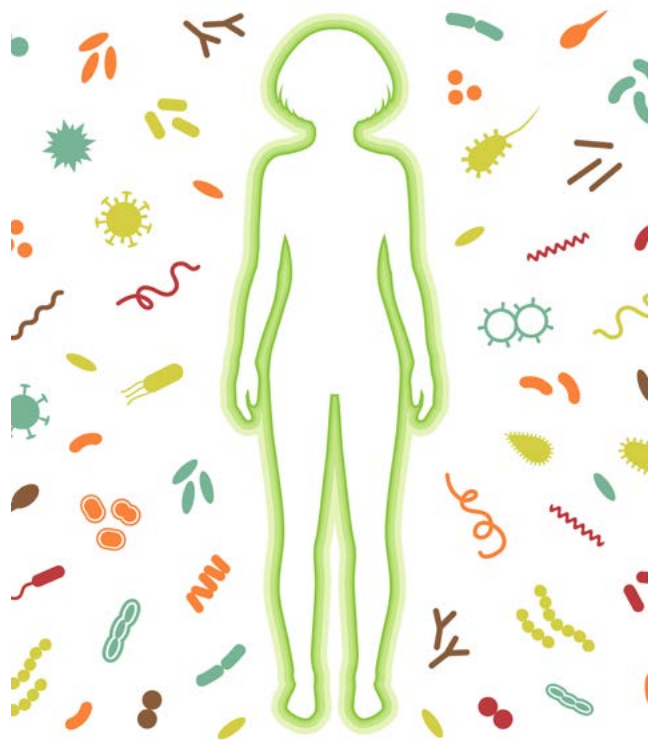
Frequent lifestyle stress can take a toll, even on healthy individuals^{2,3}. A randomized, placebo-controlled, double blind design study was conducted to evaluate the effect of Wellmune on symptoms associated with URTI and psychological well-being during periods of increased lifestyle stress⁴. Moderate to highly stressed subjects (45 men, 105 women) ranging in age from 18-65 (mean age: 39 ± 11 years) consumed placebo, 250 mg, or 500 mg of Wellmune during a 4-week treatment period. Subjects in both treatment groups (250 mg and 500 mg β -1,3/1,6 glucan per day) reported statistically significant improvements for multiple health measures compared to the placebo group. These measures included; fewer upper respiratory tract infection symptoms, better overall health scores as well as increased vigor, and decreased tension, fatigue, and confusion based on the Profile of Mood States assessment.

Extreme physical stress often leads to increased challenges to the immune system; an example of extreme physical stress is running a marathon. A placebo-controlled, double blind study was designed to evaluate the effect of Wellmune on upper-respiratory tract symptoms and mood state in marathon runners⁵. Seventy-five marathon runners (35 men, 40 women) ranging in age from 18-53 years, mean age: 36 ± 9 , consumed placebo, 250 mg or 500 mg of Wellmune daily during the 4-week post-marathon trial period following the 2007 Carlsbad Marathon. Subjects filled out the Profile of Mood States (POMS) assessment and a questionnaire-based health log measuring health status and URTI symptoms after 2- and 4-week treatment administrations. During the course of the 4-week study, subjects in the treatment groups (250 mg and 500 mg Wellmune per day) reported significantly fewer URTI symptoms, better overall health and decreased confusion, fatigue, tension, and anger, and increased vigor based on the POMS survey compared to placebo. The authors concluded that Wellmune may reduce URTI symptoms, and improve overall health and mood following a competitive marathon⁵.

A study conducted by the University of Montana⁶, found that wildland firefighters benefited from Wellmune. The results were presented at the American College of Sports Medicine in May 2008. In a double blind, random crossover design subjects completed two 14-day conditions with a three-day washout between trials. Supplements were consumed once a day and consisted of 250 mg Wellmune and a similar capsule placebo. Subjects completed a daily health questionnaire as used by Nieman et al⁷, with additional questions added that pertained specifically to use of the Wellmune supplement. An individual was classified as having an URTI when they 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 subjects overall health during the 14-day trial. In comparison with the placebo group, Wellmune subjects experienced a 23% reduction in upper respiratory tract infection symptoms ($p=0.071$) and a dramatic improvement in overall physical health ($p=0.006$).

Several studies show a suppression of both immune system function and mood state following psychological stress^{2,3}. Previous research has demonstrated that Wellmune is effective in reducing the incidence of URTI symptoms^{1,4,5,6}. In this lifestyle stress study, presented at the 2010 Experimental Biology meeting⁸, the authors evaluated the effect of Wellmune on URTIs and psychological well-being. Ninety healthy female subjects (90 women, 38 ± 12 years) pre-screened for moderate levels of psychological stress, consumed a placebo or 250mg of Wellmune daily for 12-weeks. The POMS psychological survey was used to assess for changes in mental/physical energy levels (Vigor) and overall well-being (Global Mood State). A quantitative health perception log⁷ was used to track URTI symptoms. Subjects in the treatment group



reported fewer URTI symptoms compared to Placebo, better overall well-being and superior mental/physical energy levels. These data show that daily dietary supplementation with Wellmune reduced URTI symptoms and improved mood state in stressed subjects, and thus may be a useful approach for maintaining immune protection against daily stressors.

Another study with Wellmune involved 100 4th year medical students at Southampton University in the UK⁹. This study was a double blind, placebo-controlled trial over 90 days during peak URTI season. One hundred individuals were recruited and randomized to receive Wellmune 250mg once daily (n=50) or a matched placebo capsule (n=50), mean ages 21.94 vs. 21.28, respectively. Routine blood tests, serum cytokine and chemokine samples were measured at Day 0 and Day 90. Participants completed a daily health diary. Two or more URTI symptoms for two consecutive days triggered assessment and cytokine analysis within 24-hours. Symptom severity was monitored using a validated survey (WURSS-21¹⁰). Interestingly, the number of days with reported URTI symptoms was reduced



in the Wellmune group compared to placebo (198 vs. 241, $p=0.06$). The Wellmune group showed a significant improvement ($p=0.049$) in one symptom severity score (ability to breath easily) vs. the placebo group. Side-effect profiles were similar in active and placebo groups with transient symptoms only. Cytokine data showed no significant difference between active and placebo groups, suggesting that daily administration of Wellmune 250mg does not induce inflammatory cytokine changes either at rest or during immune challenge such as URTI. A study published in Food Science and Nutrition 2012 evaluated the effect of a Wellmune on allergy symptoms, ragweed specific IgE, and quality of life (QOL) indices in self-described ragweed sufferers¹¹. Forty-eight healthy subjects consumed a placebo (P, 250 mg, N=24) or 250mg of Wellmune (W, N=24) daily for 4-weeks during September/October (high local pollen count). Allergy surveys, including the validated Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), were used to assess differences in allergy symptoms. There were no differences between groups on IgE markers. Subjects in the Wellmune group reported fewer allergy symptoms (W = 4.2 v. P = 5.8) and reduced severity of allergy symptoms (W = 6.9 v. P = 14.3) compared to placebo ($p<0.05$). Subjects in the Wellmune group reported significant reductions in nasal (W = 0.7 v. P = 1.6) and eye symptoms (W = 0.6 v. P = 0.8) with a 56% improved QOL Index. These data show that daily supplementation with Wellmune reduced allergy symptoms and improved quality of life in individuals that suffer from ragweed allergy. This data clearly demonstrates the immuno-modulation effects of Wellmune and the ability to maintain the homeostatic balance of the immune system.

A second marathon runner study was completed in 2011 and evaluated efficacy of Wellmune during a physical stress period. The study was conducted by the University of Houston¹² and included evaluation of both the dispersible and soluble forms of Wellmune. The study was

similar in methodology to the marathon study published by Talbott and Talbott⁵. Subjects that had completed a marathon began daily supplementation with Wellmune or placebo immediately post race and continued for 28 days. Cold and flu symptoms were tracked via several survey tools daily (WURSS-21 survey¹⁰ and Nieman et al survey⁷). The study was double blinded and placebo-controlled and the investigators did not know the identity of the variables until after all the data analysis was completed. Both forms of Wellmune (dispersible and soluble) significantly reduced the average number of days subjects reported cold or flu symptoms compared to the placebo. There was no significant difference between average number of symptom days between the dispersible and soluble groups. This study confirms that conversion from the dispersible form to the soluble form does not reduce the biological activity of Wellmune. In addition, this study represents the fifth independent research group that has found similar health benefits for Wellmune.

Consumer Benefits

The market for immune health products has exploded the past decade - both across multiple immune health market segments (sports nutrition, healthy aging and moms and children) and from a reactive and proactive healthcare approach. For example, immune/digestive health products are a large and growing business across the globe. In the U.S. alone, the estimated market value in 2015 was \$14.9 billion + 7% 3-year CAGR.

What's interesting is that the growth of functional foods, beverages and supplements may still be in its early stages. Consumer acceptance of products created to provide specific health benefits is a recent phenomenon. Twenty years ago, consumers were focused on the absence of nutritional negatives (low sodium, refined sugar, artificial sweeteners). They've since come



to accept the presence of nutritional positives (calcium, fiber) but now are seeking targeted functional benefits (heart health, energy, digestion).

Driving this shift are consumers who are taking a long-term approach to their health, moving from reactive, short-term fixes to a more pro-active, preventative approach. With long-term immune health at the forefront of consumers' concerns, an unmet demand for innovative products that can deliver proactive and proven immune health benefits is driving the growing functional food, beverage and supplement markets.

It is also essential when formulating and/or marketing immune health products that manufacturers choose credible functional ingredients with easy to communicate benefits. Ubiquitous functional ingredients fail to differentiate products and make it more difficult to make compelling product claims. Truly innovative ingredients, backed by credible research, can offer simple product claims that resonate with consumers. For example, Wellmune consumer research on immune health

shows that consumers attribute a variety of health benefits to a healthy immune system; health and wellness, productivity, energy, mood, mental clarity, stress management, athletic performance, and quality of life.

Conclusion

Wellmune is a GRAS (generally recognized as safe) food ingredient that can enhance the ability of the immune system to maintain good health. There is an extensive body of published, peer reviewed science that supports the safety, mechanism of action and effectiveness of Wellmune in shortening the duration and severity of upper respiratory tract symptoms in both well and stressed subjects. Kerry is committed to continuing to conduct and publish additional clinical trials with Wellmune.



References:

1. Feldman S, Schwartz HI, Kalman DS, et al. Randomized phase II clinical trials of Wellmune® for immune support during cold and flu season. *J Appl Res Clin Expt Ther.* 2009;9:30-42.
2. Cohen S, Frank E, Doyle WJ, et al. 1998 JM Jr et al. Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol.* 1998; 17:214-23.
3. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA.* 2007; 298:1685-7.
4. Talbott S, Talbott J. 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;21:21-4.
5. Talbott S, Talbott J. Effect of Beta 1, 3/1, 6 Glucan on Upper Respiratory Tract Infection Symptoms and Mood State in Marathon Athletes. *J Sports Sci Med.* 2009;8:509-15.
6. Domitrovich SG, Domitrovich JW, Ruby BC. Effects of an immunomodulating supplement on upper respiratory tract infection symptoms in wildland firefighters. abstract published in *Medicine & Science in Sports & Exercise.* 2008;40(5):S353.
7. Nieman DC, Henson DA, Fagoaga OR, et al. Change in salivary IgA following a competitive marathon race. *Int J Sports Med* 2002;23:69-75.
8. Talbott S and Talbott J. Baker's Yeast Beta-Glucan Supplement Reduces Upper Respiratory Symptoms and Improves Mood State in Stressed Women. *J. Am. Col. Nutr.* 2012; 31:1-6.
9. Fuller R, Yam T, Butt H, et al. Influence of yeast-derived 1,3/1,6 glucopolysaccharide on circulating cytokines and chemokines with respect to upper respiratory tract infections. *Nutrition* 2012; 28:665-669.
10. Barrett, RL Brown, MP, Mundt N et al. The Wisconsin Upper Respiratory Symptom Survey is responsive, reliable, and valid. *Journal of Clinical Epidemiology.* 2005; 58:609-617.
11. Talbott, SM, JA Talbott, TL Talbott and E Dingler. 2012. β -Glucan supplementation, allergy symptoms and quality of life in self-described ragweed allergy sufferers. *Food Science & Nutrition.*2012; 10:1-12.
12. McFarlin BK, Carpenter KC, Davidson T, McFarlin MA. Baker's Yeast Beta Glucan supplementation increase salivary IgA and decreases cold/flu symptomatic days after intense exercise. *J. Dietary Supplements.* 2013;10:171-183.