Research - Proof of Efficacy

Biothera is committed to a robust research and development program to evaluate the efficacy of Wellmune WGP 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.

Nine clinical studies consistently demonstrate the positive health benefits of Wellmune WGP 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 15 is a bibliography of Biothera’s clinical and preclinical research.

The complete body of research supporting Wellmune WGP includes additional clinical research, numerous preclinical studies and human biomarker research. Biothera 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.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Type</th>
<th>Published</th>
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<tbody>
<tr>
<td>2. Exercise Stress</td>
<td>Biomarkers</td>
<td>British Journal of Nutrition, 2012</td>
</tr>
<tr>
<td>5. Lifestyle Stress 28-day</td>
<td>Lifestyle Stress Health Effects</td>
<td>Agro Foods Industry Hi Tech, 2010</td>
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§Manuscript in preparation
Wellmune WGP Reduced by 40% 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 WGP®’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 WGP 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.

**Wellmune WGP 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 WGP® 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 WGP. LPS is derived from gram-negative bacteria and used to mimic a foreign challenge to stimulate an immune response.

“The effect of Wellmune WGP 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 high-intensity exercise.”

![LPS-Stimulated Cytokine Production](image)

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

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

Wellmune WGP 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 WGP 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 WGP n=48, Placebo n=49).

Study Results
• There was a significant reduction (18%) in the total number of days with self-reported URTI symptoms (198 days versus 241 days, p=0.039).

• In total, 24 episodes of URTI were medically confirmed; 12 episodes in each group.

• Wellmune WGP did not induce inflammatory cytokines. No cytokine change was seen during symptomatic URTI between study groups.

“Influence of yeast-derived 1,3/1,6 glucopolysaccharide on circulating cytokines and chemokines with respect to upper respiratory tract infections.” *Nutrition 28:665-669.*
In contrast with the placebo group, participants taking Wellmune WGP reported:

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

In a study of 122 healthy volunteers (32 men, 90 women, 38 ± 12y), participants taking 250 mgs of Wellmune WGP 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 WGP 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 WGP can naturally enhance immune responses during periods of both high physical and psychological stress.

Wellmune wgp Reduced Health Challenges in High Lifestyle Stress Subjects

Individuals with high lifestyle stress taking Wellmune wgp 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 two groups: placebo and 250 mgs/day of Wellmune wgp. Subjects maintained a daily health log with entries tracking the occurrence and duration of URTI symptoms (cough, sore throat, sneezing, etc.). They also responded to questions regarding physical health during the course of study.

Compared with the placebo group, the Wellmune wgp 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.

“Beta 1,3/1,6 Glucan Decreases Upper Respiratory Tract Infection Symptoms and Improves Psychological Well-being in Moderate to Highly-Stressed Subjects.”

Wellmune wgp Provided Significant Relief to Ragweed Allergy Sufferers

A placebo-controlled, double-blinded study found that Wellmune WGP® reduced allergy 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 ragweed 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 WGP daily for four weeks during September/October 2010 in an area of south-east 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 WGP experienced statistically significant (p<0.05) relief by several measures:

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

- 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.

Wellmune wgp 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 wgp, 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).

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

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

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 wgp or 500 mg Wellmune wgp. Statistical analysis was by paired t-tests.

* A value of p ≤ 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 ≤ 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].

Wellmune wgp Maintained Physical Health and Reduced ‘Down Time’ During 90-Day Study

In a cold season study with 40 healthy subjects, Wellmune wgp 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 wgp 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 wgp 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 WGP.

In the study results, the Wellmune WGP 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wellmune</th>
<th>Placebo</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Incidence of Fever</td>
<td>0.00</td>
<td>3.5 ± 3.42</td>
<td>0.042</td>
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<tr>
<td>Number of missed days of work/school</td>
<td>0.00</td>
<td>1.38 ± 1.25</td>
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Wildland Firefighters Reported Improved Health with Wellmune wgp

A study conducted by the University of Montana, with funding from Biothera and the U.S. Air Force, found that wildland firefighters benefited from Wellmune wgp.

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 Immune Health Basics® and a similar capsule placebo.

In comparison with the control group, Wellmune wgp 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.