The clinical application of immunomodulating beta-glucans

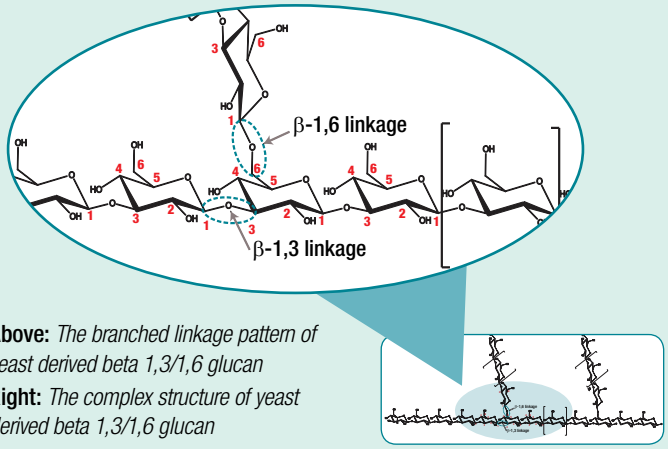
Beta-glucans are a class of long chain polysaccharides that naturally occur in the cell wall of plants such as oats, barley and seaweed, fungi such as baker's yeast, or *Saccharomyces cerevisiae* and mushrooms.[1] A large body of evidence suggests that certain polysaccharides are capable of significant immunomodulation, and possess diverse clinical applications.[2]

Beta-glucan source, structure and classification

Beta-glucans are composed of glucose polymers with many different linkage patterns depending on their source, which accounts for their significant variability in clinical effects. Whilst grain based beta-glucans have a linear structure with a 1,3/1,4 glycosidic linkage pattern and possess little immunomodulating ability, fungal derived beta-glucans have a branched 1,3/1,6 linkage pattern. The more complex structure seen in yeast derived beta-glucans specifically, is thought to explain the significantly increased immunological activity.[3]

Fungal derived beta 1,3/1,6 glucans belong to a group of physiologically active compounds known as biological response modifiers. Biological response modifiers incorporate a subset of compounds which possess immunomodulatory activity, i.e. compounds which are able to positively (immunopotentiate) or negatively (immunosuppress) manipulate immune function.[4]

Figure 1: The unique and complex structure of yeast beta 1,3/1,6 glucan is associated with its increased immune activity.[5]



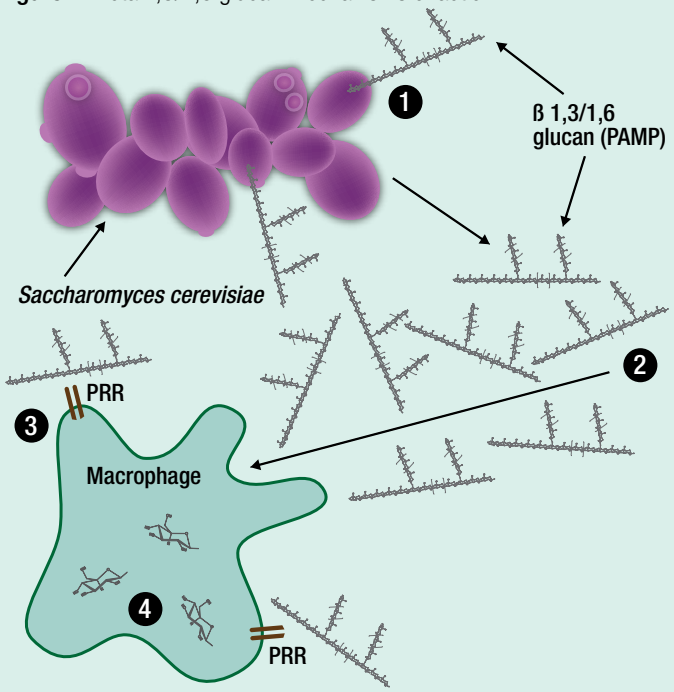
Above: *The branched linkage pattern of yeast derived beta 1,3/1,6 glucan*
Right: *The complex structure of yeast derived beta 1,3/1,6 glucan*

Beta 1,3/1,6 glucan mechanism of action

The most pronounced effect from beta-glucan administration is thought to be related to augmentation of the process of phagocytosis, and the proliferation of professional phagocytes (granulocytes, monocytes, macrophages and dendritic cells). Macrophages are considered to play the most important role in the host's defence against bacteria, viruses and multicellular parasites. As part of the innate immune system, macrophages express pattern recognition receptors (PRRs), whose expression occurs mainly on cells of the immune system and host epithelial cells. Pattern recognition receptors recognise certain molecules on the surface of invading microorganisms. These molecules are collectively referred to as pathogen associated molecular pattern (PAMPs). From an evolutionary standpoint, PAMPs are highly conserved and therefore not subject to variability within the same species. Macrophages detect PAMPs such as beta-glucans through various PRRs such as toll-like receptor-2, dectin-1, complement receptor-3, lactosylceramide and others.[4]

When PRRs recognise beta-glucans the result is twofold: firstly, a cascade of intracellular signalling pathways are activated resulting in secretion of 'level 1' cytokines, and in some cases activation of cellular effector functions, see table 1.[6] Secondly, beta-glucans are themselves phagocytosed and internalised by macrophages and broken down into smaller fragments, which are released over several days. These fragments interact with and modulate the functional capacity of innate immune cells, the complement system and antibody mediated immunity.[3] In short, identification of beta-glucans as non-self molecules by mammalian cells induces beneficial innate and adaptive immune responses.[7]

Figure 2: Beta 1,3/1,6 glucan mechanisms of action.[3,4,6,7]



Key: **PAMP:** Pathogen Associated Molecular Pattern
PRR: Pattern Recognition Receptor

1. Beta 1,3/1,6 glucans are PAMP's located in the cell wall of *Saccharomyces cerevisiae*
2. Purification/isolation of beta 1,3/1,6 glucans (Wellmune®)
3. PRR activation leads to a cascade of intracellular responses which results in:
   - Release of cytokines, chemokines and interferons
   - Complement activation
   - Increased phagocytosis and effector function
4. PRR activation leads to internalisation and fragmentation of beta-glucan compounds resulting in modulation of the complement system and antibody mediated immunity

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Table 1: Physiological response to beta-glucan induced pattern recognition receptor activation.[4,8]

Receptor	Expression	Response
Toll-like receptor-2	Macrophages, dendritic cells, B-cells, T-cells, endothelial cells	Facilitates activation of the adaptive immune system
Dectin-1	Macrophages, neutrophils, dendritic cells, B-cells, T-cells	Increased detection and phagocytosis of fungal pathogens, production of cytokines and chemokines
Complement receptor-3	Neutrophils, monocytes, NK cells, lymphocytes	Triggers phagocytosis and degranulation
Lactosylceramide	Dendritic cells, airway epithelial cells	Production of cytokines and initiation of respiratory burst

Beta-glucans in clinical practice

Wellmune® is a clinically researched beta 1,3/1,6 glucan derived from the cell wall of *Saccharomyces cerevisiae*. As previously discussed, yeast derived beta 1,3/1,6 glucan, is an immunomodulating polysaccharide that is distinct from the well-known oat beta-glucans, and is regarded as a biological response modifier. Clinical research to date has largely focussed on its ability to modulate immune responses during seasonal challenges or in stress induced immunosuppression.

Wellmune® clinical research

Indications based on research from human clinical trials

- Preventing and reducing the duration of seasonal URTIs in healthy adults and children
- Symptomatic management of seasonal allergies
- Improving immunity in physically and psychologically stressed individuals
- Improving overall sense of physical and psychological wellbeing in physically and psychologically stressed individuals

Additional potential indications[9]

- Improving the efficacy of standard antibiotics
- Improving immunity in immunosuppressed individuals
- Conditions with suspected infectious aetiology or other infective illnesses

Upper respiratory tract infection

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.[10] Innate immune cells including neutrophils and macrophages form the front line of host defence to pathogenic viral and bacterial challenges. Modification of this initial, non-specific level of innate immunity may confer benefit in the prevention or amelioration of URTIs.[10]

Immunity and physical and psychological stress

Decreased immune efficiency may result in increased susceptibility to, or prolonged duration of infections or illness. Upper respiratory tract infections which may be associated with up to 400 different viruses, are noted more often in athletes and stressed individuals.[10]

Psychological stress has been shown to impair immune function with an observed reduction in immune cell populations, antibody production and altered cytokine responses. Individuals under significant stress also report a higher incidence and greater severity of illness.[11]

Additionally, suppression of mucosal immunity is commonly observed in the 24 hours after strenuous exercise, resulting in an increased risk of developing an URTI. Salivary IgA is considered a reliable biomarker of mucosal immunity, and is commonly reduced following strenuous exercise. A reduction in salivary IgA is associated with an increase in the number of URTI symptomatic days post exercise, and Wellmune® supplementation has been found to prevent the post-exercise suppression of salivary IgA.[3]

In both physically and psychologically stressed individuals, Wellmune® supplementation reduced the incidence and duration of URTIs, and improved overall perceived general health and psychological wellbeing – see table 2.

Reducing exercise intensity and/or stressful stimuli may help to address the underlying cause of impaired immunity, however, in many cases such reductions are not always viable, and Wellmune® may be one of several useful countermeasures in the naturopathic management of these patients, whilst the stressor persists.[3]

Figure 3: Proportion of adults reporting symptoms of URTI 2 weeks post marathon.[12]

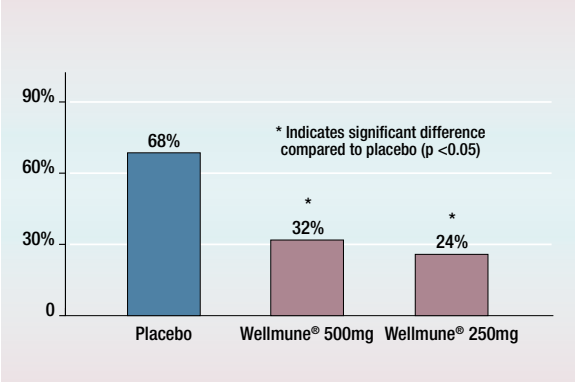
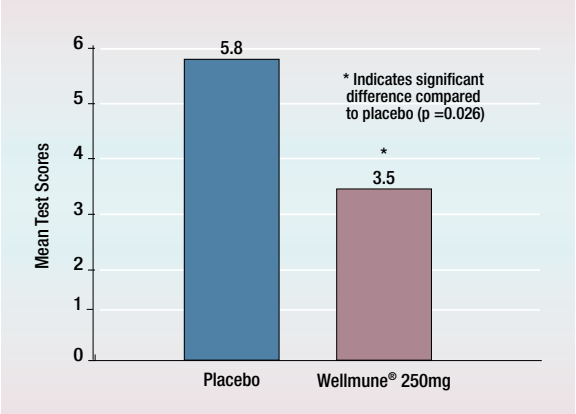


Figure 4: Number of symptomatic days (cold or flu) over a 28 day period post marathon.[3]



Children

Upper respiratory tract infections are the most common acute respiratory infections in children, accounting for nearly 90% of all cases. Infections, especially URTIs are common in early childhood due to their narrower airways and immature lungs and immune system, and occur at double the rate in young children under 4 compared with children aged 4-7 years.[6] Supplementation with 35mg or 75mg of Wellmune® in children aged 1-4 years, was found to significantly reduce the incidence and duration of URTIs and total infectious episodes compared to placebo. See figures 5, 6 and 7.

Figure 5: Average duration of URTI symptoms (days) during 12 week study period.[6]

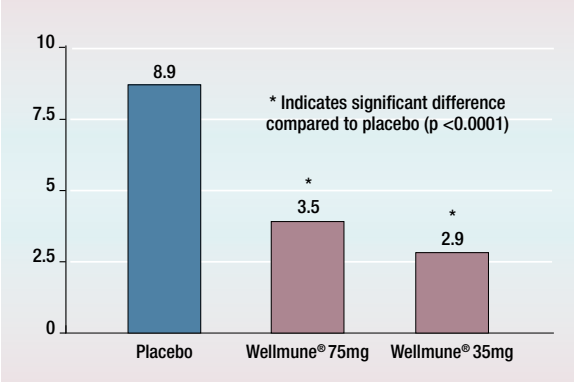


Figure 6: Average number of URTI episodes per child during 12 week study period.[6]

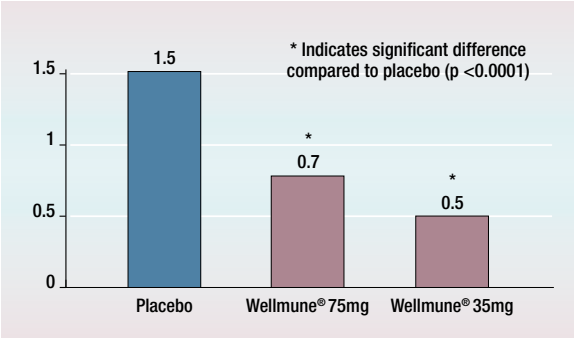
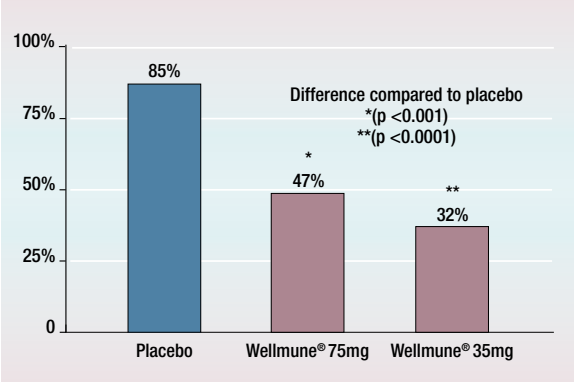


Figure 7: Proportion of children experiencing at least 1 illness episode (URTI, bronchitis, pyrexia or diarrhoea) during 12 week study period.[6]



Allergies

Allergic diseases have various manifestations, and seasonal allergic rhinitis is one of the most common presentations. Inadequate control of allergic rhinoconjunctivitis leads to reduced quality of life (QOL) and productivity. Beta 1,3/1,6 glucans are thought to improve allergic symptomology through stimulation of macrophage induced anti-inflammatory mediators and inhibition of Th2 responses.[7] Early studies using injectable yeast derived beta-glucan in asthmatic children, demonstrated significant symptom improvement.[13] More recently, oral Wellmune® supplementation was found to significantly improve seasonal ragweed allergy symptoms compared to placebo in an otherwise healthy adult cohort, results summarised below.[7]

Wellmune® supplementation:

- Decreased nasal symptoms by 59%
- Decreased sleep abnormalities by 53%
- Increased quality of life scores by 56%
- Decreased eye symptoms by 57%

Overall physical and psychological wellbeing

A consistent improvement in overall perceived physical and psychological wellbeing is reported in trials with Wellmune® supplementation (see table 2). Improvements in mood, tension, fatigue, vigour and overall perceived general health and psychological wellbeing, are an expected and logical result of improvements in immunity and physical well-being. The lack of any improvements on the anger and depression subscales is consistent with this hypothesis, and is not surprising considering Wellmune® is not thought to possess any psychoactive properties.[14] However pre-clinical research demonstrates that Wellmune® inhibits the stress induced increases in cortisol levels, suggesting that yeast derived beta-glucans could exert some direct anti-stress effect.[15]

Table 2: Results of human clinical trials from Wellmune® supplementation.

Study population	Major study findings
Children	• Reduced incidence of total infective illness • Reduced incidence and duration of URTI episodes[6]
Individuals under intense physical stress (marathon runners)	• Reduced incidence and duration of URTI episodes post marathon • Prevented the post-exercise suppression of salivary IgA • Improved overall perceived health and psychological wellbeing[3,12]
Individuals under moderate to severe psychological stress	• Reduced incidence and duration of URTI episodes • Improved mood states, psychological wellbeing and self-reported physical health[11,14]
Sufferers of seasonal ragweed allergy	• Reduced allergy symptom severity • Reduced sleep problems, nasal symptoms, eye symptoms • Improved QOL, global mood state and emotional wellbeing • Improved physical energy[7]
Healthy populations (prevention of URTI)	• Reduced incidence and duration of URTI episodes • Reduction in missed days at work • Reduced incidence of fever • Improvements in perceived general health[10,16]

Beta-glucans in oncology

Immunomodulating polysaccharides are a diverse group of compounds of varying origin. Whilst rice bran arabinoxylan compound (RBAC) is considered to be the 'gold-standard' biological response modifier in oncology support due to its wealth of clinical data, the research into yeast derived beta-glucans is more limited. Preliminary research suggests that beta-glucans derived from *S. cerevisiae* can activate dendritic cells and stimulate Th1 immune responses, leading to anti-tumour activity. In addition, animal models have demonstrated that soluble yeast derived beta-glucans can inhibit lung and liver tumour metastasis.[8]

Furthermore, beta-glucan therapy as an adjuvant to standard oncology treatments is increasingly being explored, with co-administration with antibody based treatments showing significant promise as a potential therapy. Conflicting data in the literature is likely due to the variability in source, structure and purity of beta-glucan extracts, and further controlled experiments with well-defined beta-glucan sources are needed to further elucidate the potential role of beta-glucans as potent anti-metastatic agents.[8]

Synergism

Vitamin C demand is significantly increased in phagocytosing cells, with intracellular ascorbate concentration found to be 40 times the plasma levels. A significant drop in intracellular ascorbate levels is observed in macrophages activated with beta 1,3/1,6 glucan, suggesting exhaustion of ascorbate supply could limit maximal macrophage cytotoxicity.[9] Preliminary animal research suggests a beneficial synergistic immunomodulatory role for these compounds when co-administered.[17]

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WELLMUNE® LITERATURE REVIEW

Objectives/Condition	Methods and Dose	Results	Study Design
Infective Illnesses in Children			
To evaluate the effect of Wellmune® on the incidence of infective illnesses in children	174 healthy children aged 1-4 years were randomised to receive either: **Arm 1: Wellmune®** (75mg) **Arm 2: Wellmune®** (35mg) **Arm 3: Placebo** daily for 12 weeks	During the study period the number of children who experienced at least 1 episode of infectious illness was significantly less in the Wellmune® groups (35% and 47% for the 35mg and 75mg group respectively) compared to placebo (85%). Wellmune® significantly decreased the number and duration of upper respiratory tract infection (URTI) episodes compared to placebo. The average URTI duration was 8.9 days in the placebo group compared to 3.5 and 2.9 days in the 75mg and 35mg group respectively. The average number of URTI episodes was 1.5 in the placebo groups compared to 0.7 and 0.5 in the placebo groups. The difference between the 75mg and 35mg group was not significant across all study parameters suggesting that 35mg is sufficient for children between 12 and 48 months of age. Adverse events were mild in nature and not thought to be related to the treatment.	Randomised, double-blind, placebo-controlled study[6]
Physical Stress and Upper Respiratory Tract Infection (URTI)			
To evaluate the effect of daily Wellmune® supplementation on URTI duration post-marathon	182 marathon runners were randomised to receive either: **Arm 1: Soluble Wellmune®** (250mg) **Arm 2: Insoluble Wellmune®** (250mg) **Arm 3: Placebo** daily for 28 days post-marathon	Self-reported ill-health was greater in the placebo group (5.8 days) compared to both Wellmune® groups (3.5 days). A second experimental group demonstrated that Wellmune® supplementation prevented the post-exercise suppression of salivary IgA. Both the soluble form of beta-glucans used in the manufacture of beverages and the insoluble form used in food products demonstrated similar effects.	Randomised, double-blind, placebo-controlled study[3]
To explore how Wellmune® affects mood, URTI symptoms and overall health status following marathon completion	75 marathon runners were randomised to receive either: **Arm 1: Wellmune®** (250mg) **Arm 2: Wellmune®** (500mg) **Arm 3: Placebo** daily, 30 mins before breakfast for 4 weeks	A significant decrease in URTI symptoms was observed in both treatment groups. After 2 weeks, 68% of subjects in the placebo group reported symptoms associated with URTI, whereas this number was only 32% and 24% in the 250mg and 500mg groups respectively. Subjects in the active groups also reported better overall health currently, and better overall health when compared to their typical health history. Reductions in fatigue, tension and confusion, and in increased rating of vigour, were also seen in the active treatment groups. The 500mg group tended to produce a slightly greater effect than the 250mg group.	Randomised, double-blind, placebo-controlled study[12]
Psychological Stress and URTI			
To explore the effect of 12 weeks Wellmune® supplementation on mood, upper respiratory symptoms and overall health status in moderately stressed women	90 female subjects with moderate levels of perceived stress were randomised to receive either: **Arm 1: Wellmune®** (250mg) **Arm 2: Placebo** daily, 30 mins before breakfast for 12 weeks	The incidence and duration of URTI symptoms was significantly decreased by Wellmune® supplementation compared to placebo. After 12 weeks, 29 percent of subjects in the placebo group reported URTI symptoms, whereas only 11% of subjects in the beta-glucan group reported symptoms. Significantly improved mood states compared to placebo were also observed for the vigour and global mood state subscales.	Randomised, double-blind, placebo-controlled study[11]
To investigate the effects of Wellmune® supplementation on the physical and psychological wellbeing of subjects who self-reported moderate to high levels of perceived stress	150 moderate to highly stressed subjects were randomised to receive either: **Arm 1: Wellmune®** (250mg) **Arm 2: Wellmune®** (500mg) **Arm 3: Placebo** daily, 30 mins before breakfast for 12 weeks	Individuals in both treatment groups reported significant improvements in measurements of physical health compared to the placebo group. Active treatment resulted in a significant decrease in URTI symptoms. After 2 weeks, 32% of subjects in the placebo group reported symptoms associated with URTI, whereas this number was only 10% and 8% in the 250mg and 500mg groups respectively. Overall perception of health was significantly improved by both Wellmune® groups compared to placebo. Improvements were also seen in psychological health after 4 weeks of treatment in both treatment groups, and after 2 weeks of treatment in the 500mg group, with improvements in tension, confusion, fatigue and vigour noted.	Randomised, double-blind, placebo-controlled study[14]
Prevention of Seasonal URTI in Healthy Individuals			
To investigate the effect of daily Wellmune® supplementation on URTI incidence in the elderly	100 individuals (aged 50-70 years) were randomised to receive either: **Arm 1: Wellmune®** (250mg) **Arm 2: Placebo** daily for 90 days	There was a near-statistically significant reduction in illness episodes (p=0.149) and number of days of illness (p=0.067) in the Wellmune® group compared to placebo in this pilot study. It is estimated that a larger sample size of 217 participants per group would be needed to detect a significant difference between groups and further studies are warranted.	Randomised, double-blind, placebo-controlled, pilot study[10]
To determine whether Wellmune® supplementation can reduce the incidence and/or duration/severity of respiratory illness during peak cold/flu season	27 healthy adults were randomised to receive either: **Arm 1: Wellmune®** (500mg) **Arm 2: Placebo** daily for 90 days	Whilst there were no significant differences between groups in terms of incidence or duration of URTI symptoms (probably due to the small study size), subjects receiving Wellmune® reported no missed days at work (compared to an average of 1.38 days in the placebo), and displayed a significantly lower fever score. Subjects in the Wellmune® group also reported a significantly greater "general health" score over the 90-day study period.	Randomised, double-blind, placebo-controlled, parallel-group trial[16]
Allergy			
To investigate whether Wellmune® supplementation would alleviate the physical and psychological effects of allergies and improve QOL in self-described moderate ragweed allergy sufferers during the ragweed allergy season	50 self-described sufferers of moderate ragweed allergy were randomised to receive either: **Arm 1: Wellmune®** (250mg) **Arm 2: Placebo** daily in the morning for 4 weeks	Compared to placebo, allergy symptom severity was reduced by 52% after 4 weeks of Wellmune® supplementation. Reductions in sleep problems by 53%, nasal symptoms by 59% and eye symptoms by 57% and an increase in QOL by 56% were reported according to the Rhinoconjunctivitis QOL questionnaire. Wellmune® supplementation also significantly improved global mood state and emotional well-being as well as physical energy.	Randomised, double-blind, placebo-controlled study[7]

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