



Views on immunology and supplementation

A whitepaper on yeast derived beta-glucans

A well-functioning immune system is crucial to stay healthy. Some nutritional compounds have been proven to support the immune system. A fiber known as beta-glucan, found in bakers yeast and mushrooms, has shown in clinical studies to support the immune system. The typical diet lacks sufficient amounts of beta-glucan and supplementation with beta-glucan will benefit a well working immune system. A new approach to deliver nutraceutical and pharmaceutical supplements is ConCordix which provides a different and novel delivery form than commonly used. Both oil- and water-soluble ingredients can be combined in one supplement. Next to that, absorption of certain oil-based ingredients is significantly higher compared with common delivery form. Because many supplements have disadvantages such as size, taste, and ease to swallow, compliance is often hampered. ConCordix is a patented chewable oral delivery form which is formulated without the addition of sugar and enables that nutraceuticals or pharmaceuticals are easy to take without the necessity of water. Both children and people who have difficulties swallowing pills will benefit from this delivery form.

Immune system

**A well-functioning immune system is crucial to stay healthy.
The overall function of the immune system is to prevent or limit
infection.**

The immune system is generally divided into innate and adaptive immunity. Innate immunity occurs immediately, when circulating innate cells recognize a problem. Adaptive immunity occurs later, as it relies on the coordination and expansion of specific adaptive immune cells [1].

Leukocytes (white blood cells) play a key role in the innate immune response. These cells include: monocytes, macrophages, neutrophils and dendritic cells that phagocytose pathogens. Other leukocytes are mast cells, basophils, eosinophils and natural killer (NK) cells. Innate immune cells express genetically encoded receptors, called Toll-like receptors (TLRs), which recognize pathogen-associated patterns. Collectively, these receptors can

broadly recognize viruses, bacteria, fungi, and even non-infectious problems. However, they cannot distinguish between specific strains of bacteria or viruses, which are recognized by adaptive immune cells [1].

Adaptive immune cells include B and T cells. These immune cells are more specialized, with each adaptive B or T cell bearing unique receptors that recognize specific signals rather than general patterns. Each receptor recognizes an antigen, which is simply any molecule that may bind to the receptor of the B or T cell. Antigens are derived from a variety of sources including pathogens, host cells, and allergens. Antigens are typically presented to adaptive cells in the lymph nodes by innate immune cells [1].

Upon an immune response, a variety of (innate) immune cells are released in order to deactivate pathogens. However, strenuous exercise and ageing both hyper-activate the immune system and lower its protective function [2-3]. In case of an infection or an invading pathogen, monocytes are activated and develop into macrophages. Subsequently, the pathogen is phagocytosed by macrophages and digested by its lysosomal enzymes. Macrophages are also responsible for the secretion of cytokines and inflammatory mediators [4]. NK cells are important for recognizing and killing virus-infected cells or tumor cells. They contain granules, which are filled with proteins that can form holes in the target cell and also cause apoptosis, the process for programmed cell death. Through apoptosis, immune cells can discreetly remove infected cells and limit bystander damage [1].

Nutritional sources have proven to modulate and enhance the immune system. For instance, bioactives derived from foods such as vitamin E, carotenoids and several fibers have the potential to strengthen the immune system and prevent infection [5-7].

Beta-glucan

An immune modulating bioactive that has been well studied is beta-glucan.

Beta-glucan is a type of fiber found in the cell walls of cereals, certain types of mushrooms, (bakers) yeasts, seaweed, and algae. Beta-glucan consists of D-glucose monomers linked by a beta-glycosidic bond [8]. This natural ingredient has proven its effectiveness in reducing chronic diseases, cancer, allergies, gastro-intestinal disorders, and immune related diseases [8]. Beta-glucan derived from fungi and bakers yeast, consists of a (1,3)-beta-linked backbone with small numbers of (1,6)-beta-linked side chains, and is essentially known for its immune modulating effects [8]. In addition, bakers yeast as source for (1,3/1,6) beta-glucan was approved in 2008 as 'Generally Recognized as Safe' (GRAS) by the Federal Drug Administration (FDA).

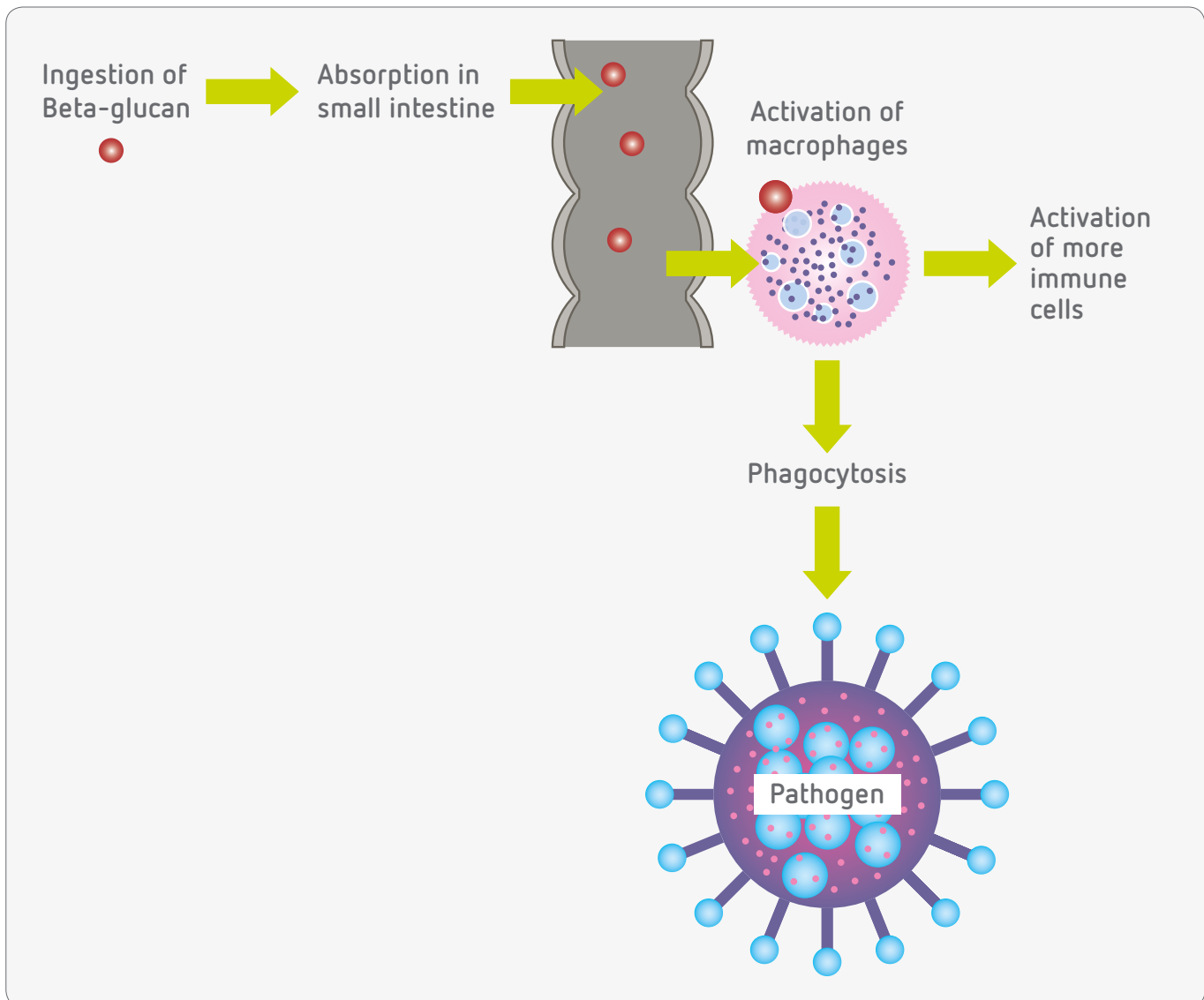
The key role of beta-glucan is to reinforce the ability of the innate immune system so that it quickly recognizes and responds to an invading pathogen which is essential for controlling infection and keeping the body healthy. Importantly, beta-glucan activates the innate immunity with subsequent effects on the adaptive immunity activation, without overstimulating the immune response [8-9]. The beneficial effect of bakers yeast beta-glucan on the immune system has been demonstrated by increasing resistance against

several bacterial, fungal, and viral pathogens [10-12]. The mechanism of action of beta-glucan found in bakers yeast can be delineated into a few simple steps and is depicted in the figure below:

1. After ingestion, beta-glucan reaches the small intestine where absorption takes place.
2. The small intestine contains immune tissue, called Peyer's patches, which comprises large amounts of macrophages. Here beta-glucan binds to the macrophages which will cause activation of the macrophage.
3. Activated macrophages capture beta-glucan followed by the release of biologically active beta-glucan fragments. These fragments bind to leukocytes such as neutrophils, other macrophages and NK cells.
4. The binding of the beta-glucan fragments to these leukocytes increases the ability to navigate towards the pathogens and to kill them by phagocytosis.

As a consequence, the action of beta-glucan enhances the immune response by a more efficient phagocytosis in order to clear the body from pathogens [14-18].

Figure 1: Mechanism of action of beta-glucan



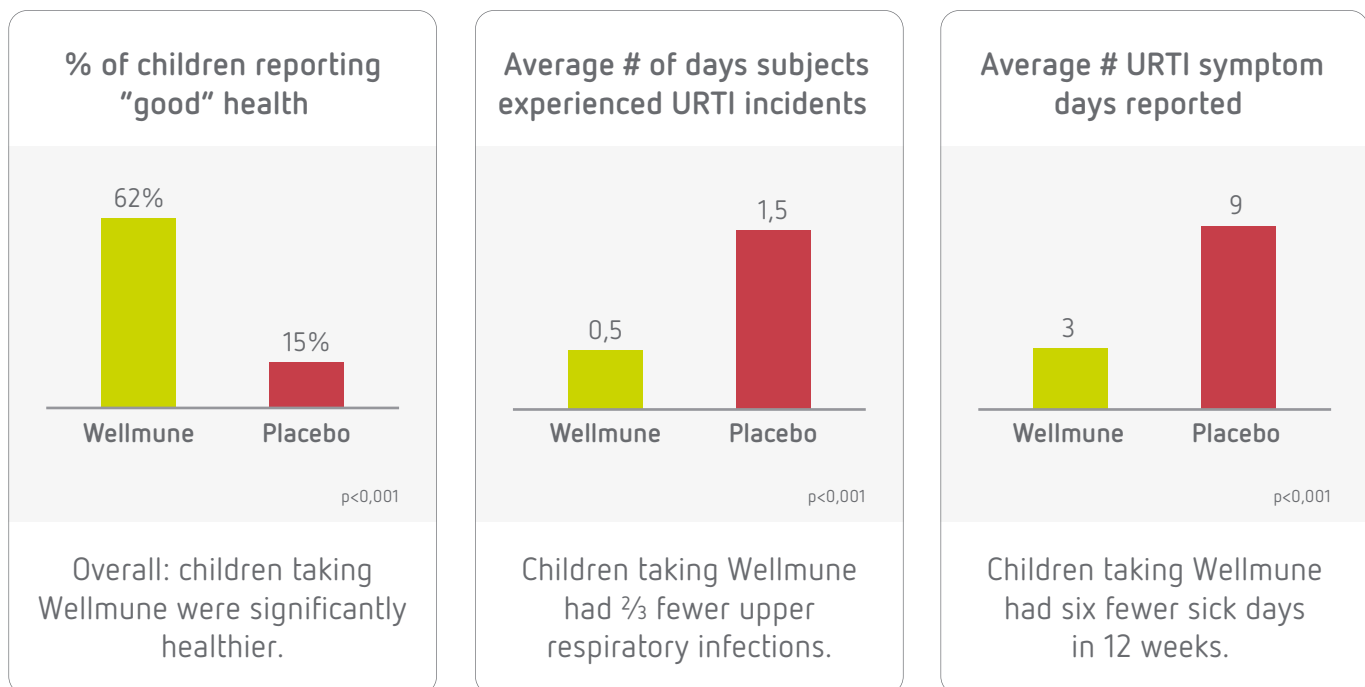
To enable an adequate immune effect from beta-glucan, supplementation has been in favor as many people consume a diet that lacks sufficient amounts of beta-glucan. In addition, children also benefit from supplementation, as they often dislike most of the foods that contain beta-glucan (e.g. mushrooms), which increases the risk of a weak responding immune system.

Clinical studies

A recent study showed that Wellmune® beta-glucan supplements effectively improved the immune function in children.

This randomized, double-blinded, placebo controlled study was conducted in Asia and included 156 initially healthy children of 1-4 years old. The children received a Wellmune® supplement, or a placebo daily. The main ingredient of each Wellmune® supplement was beta-glucan whereas the placebo did not contain beta-glucan. After 12 weeks of supplementation 62% of children taking the Wellmune® supplement reported "good" health status compared with only 15% of children taking a placebo. Moreover, children taking Wellmune® supplements had two-thirds fewer upper respiratory tract infections (URTI) and six fewer sick days over a 12-week period [19].

Figure 2: Improvement of immune function in children (Wellmune® supplements)



Another study reported that children between 8 to 12 years old with chronic respiratory problems showed a significant improvement of mucosal immunity after taking 100 mg/d beta-glucan for 12 weeks [20].

Also adults suffering from ragweed allergy showed a significant reduction of more than 50% in severe allergy symptoms after taking 250 mg/d Wellmune® supplement [21]. Other studies that focused on physical and lifestyle stress and biomarkers of cold and flu demonstrated that a daily dose of 250 mg Wellmune® supplement effectively reduced respiratory tract infections and the duration of colds and flu symptoms [22-27].

Studies still continue to find an optimal daily dose. However, an effective dose to enhance immune responses in adults ranges between 50 and 1,000 mg/d of beta-glucan [28]. For children the effective daily dose is 2.5 mg beta-glucan (Wellmune®) per kg/body weight [19-20, 28].

Supplementation of beta-glucan comes in different delivery forms. Large tablets and capsules are often a problem to swallow and especially children dislike the taste of these kinds of delivery forms. A solution to these issues is a delivery form that is easy to take, and has a pleasant taste.



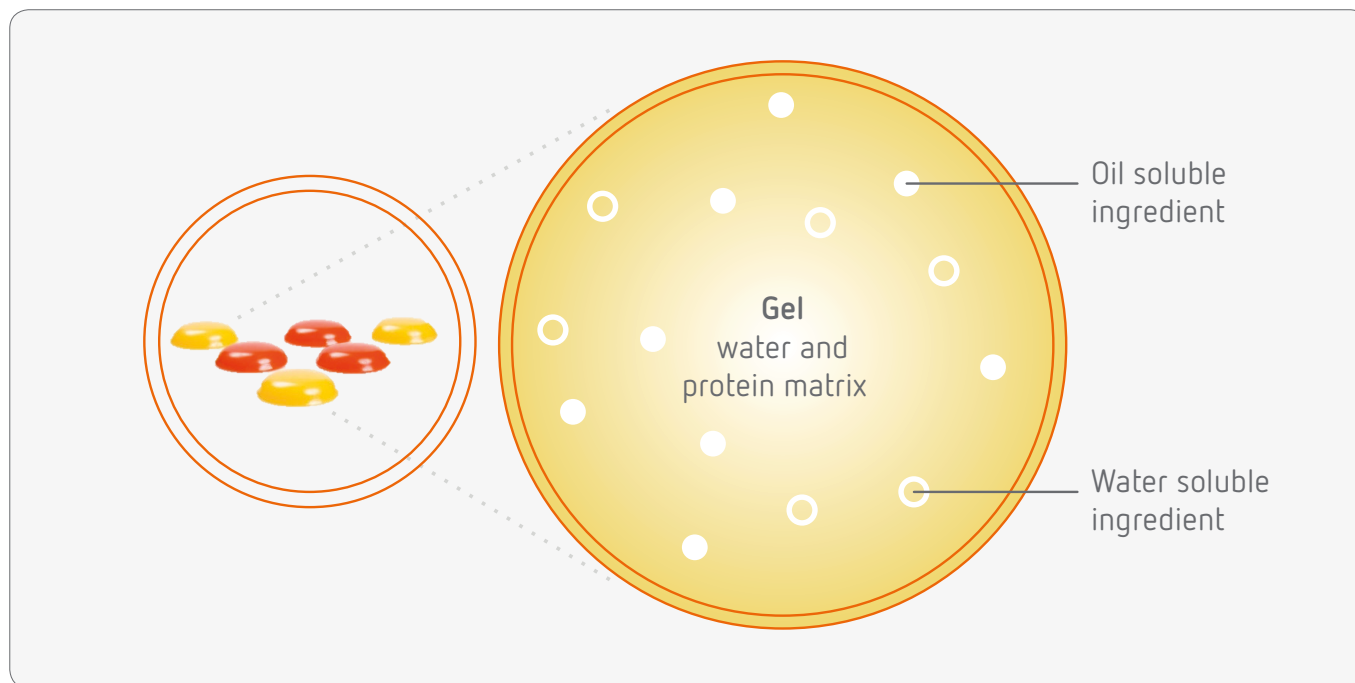
The disruptive delivery form opening new opportunities in the nutraceutical and pharmaceuticals industry.

ConCordix is a patented delivery form developed by Vitux and offers a new approach to administering nutraceuticals and pharmaceuticals. It overcomes many of the issues consumers and manufactures come across:

- Foul tasting of tablets, powders or capsules;
- Swallowing large tablets or capsules;
- Compliance;
- Absorption of the ingredient;
- Combining oil- and water-soluble ingredients.

An important feature of this delivery form is its ability to combine both oil- and water-soluble ingredients that opens new possibilities for manufacturers and consumers. Moreover, it has been demonstrated that short-term absorption of fish oil delivered by ConCordix was significantly increased compared with normal soft gel capsules [29]. As a consequence, more effective health benefits are accomplished with the same concentration of ingredients.

Figure 3: Oil- and water-soluble fraction ConCordix



To achieve a better compliance to supplement intake, ConCordix is a chewable formulation that can be manufactured in many different flavors without the addition of sugar.

Intake is easy by just chewing the supplement which overcomes the necessity of water for ingestion that most common delivery forms (tablets, capsules or powders) need. This will benefit many people who have difficulties swallowing or dislike the taste of common used pills. For example, many commonly used delivery forms have a foul taste or trigger gastric reflux. Intake of omega-3 supplements often cause gastric reflux that causes people to quit taking more supplements. A recent randomized placebo-controlled double-blind study demonstrated that supplements containing omega-3 fatty acids (fish oil) delivered by ConCordix did not affect the compliance of supplement intake in children. Of the 413 children (aged 8.5 years) 204 children received omega-3 fatty acids delivered in ConCordix, the rest of the subjects received a placebo also delivered in ConCordix. After the intervention period of 3 months it became clear that only 5.4% of children in the intervention group stopped taking omega-3 fatty acid ConCordix supplements before the study was ended. Importantly, also a comparable number of children (4.3%) in the placebo group stopped taking the ConCordix supplements before the end of the study. This indicated that fish oil taste was surprisingly well hidden when delivered in ConCordix which might increase compliance [30].

Conclusion

**A well-functioning immune system is crucial for staying healthy.
Beta-glucan has proven to benefit the immune system at all ages.**

Since the majority of people consume a diet that lacks sufficient sources of beta-glucan their immune system might not be able to adequately respond to pathogens. Therefore supplementation with beta-glucan is an excellent way to increase immune function. The novel delivery form ConCordix enables to combine both oil- and water-soluble ingredients and provides a solution for many nutraceutical and pharmaceutical manufacturers. A larger health effect of certain ingredients is established by the increased absorption due to this delivery form. Next to that, the chewable formulation offers easy ingestion of the supplements and the different flavors without the addition of sugar makes that people are more likely to adhere to their supplement routine.

Vitux uses state-of-the-art manufacturing methods and only the freshest ingredients in producing turnkey products and customized dietary supplements of the highest quality. Feel free to get more information about ConCordix or any of our other delivery forms and visit our website: www.concordix.com or contact one of our experts.

Vitux AS
Brynsveien 11
NO-0667 Oslo
Norway
+47 77 75 99 00
info@concordix.com
www.concordix.com

ConCordix®

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