



VeriPrime Bulletin: Beta Glucans

Key Points:

- Beta Glucan molecule is a proven, natural immune stimulant fed to cattle.[1,2,3]
- It is not a yeast
- Purity is critical and required for bioactivity. [4]
- Beta Glucan molecules differ, from each source's extraction, in homogeneity, structural characterization, and molecular mechanism, as well as their clinical application vary significantly. [5]
- Proprietary Formulation – Testing multi-source formulations by measuring cellular, humoral, and mucosal immunity is required to produce an effective Beta Glucan product.

Five years ago, when we started looking at beta glucans on behalf of our members, we had two questions in mind.

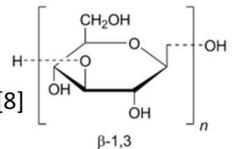
1. How do we avoid using antibiotics in the bunk?
2. How do we get more from current vaccines and antibiotics?

Beta Glucans had widespread use in poultry, swine, and aquaculture. Specifically designed glucans fed dairy cows reduced mastitis (udder infection) by >40%. [6]

We started searching for a product that might reduce pneumonia in feedyard cattle.

Beta Glucan Molecule

- In the past 50 years, over 6,000 peer reviewed publications have proven natural Beta Glucan's role as a biologically active immune modulator. [8]
- Highly pure Beta Glucan molecules must be enzymatically extracted from the cell wall of yeast, fungi, seaweed, or grain seeds. [5-7]
- Most pure Beta Glucans strongly differ in biological effects [9,10]
- Currently, Highly Bioactive Beta Glucan molecules can only be identified by testing immune responses in the target species.[8]



In all, VeriPrime feedyard members and research veterinarians evaluated over 20 different beta glucan formulations. Plant based, mushroom based, and several yeast derived beta glucans were tested. Some were completely ineffective while others showed promising results.

Final formulations were tested looking for the best improvement of acquired immunity, stimulation of mucosal immunity, and increased effectiveness of macrolide antibiotics.

This paper is meant to provide a review of beta-glucans, their chemical and biological properties, their role in immunological reactions and a summary of VeriPrime's investigations.

Thumbnail Results:

- 10% increase in Total White Blood Cells (P<0.01%)
- 6% increase in Lymphocytes (p<0.05%)
- 41% increase in Monocytes (p<0.001%).
- 3X improvement in titers [IBR] (p<.05%)
- Reduced Pulls, Retreats, Dead (> 30% reduction)
- >40% Less CTC/OTC use

Introduction

Beta Glucans belong to a group of biologically active natural compounds called biological response modifiers. These substances represent highly conserved structural components of cell walls in yeast, fungi, grain and seaweed. As they are not found in animals, these carbohydrates are considered to be classic pathogen-associated molecular patterns (PAMPs), and are recognized by the innate immune system. [11]

The effects of highly purified, highly active B-glucan molecules on immune reactions are well established. [1,2,6,10]

Molecular Structure

Glucan derived from baker's yeast (*Saccharomyces cerevisiae*) is a 6-branched 1,3- β -glucan which is the best characterized and has produced the highest biological effects. .

These polysaccharides are a heterogeneous group of glucose polymers, consisting of a backbone of β (1 \rightarrow 3)-linked β -D- glucopyranosyl units with β (1 \rightarrow 6)-linked side chains of varying distribution and length.

We recommend that readers interested in the introduction of a significant number of biologically active glucans read an excellent review written by Harada and Ohno (2008).

The general structure of the glucan molecule is summarized in Figure 1 a. and a three-dimensional picture of the same molecule in Figure 1 b.

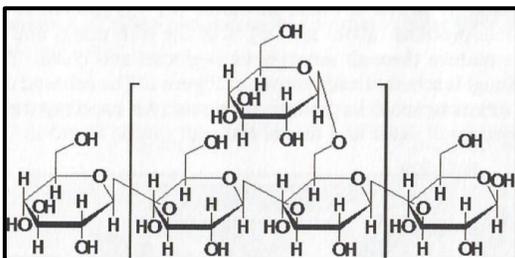


Fig. 1a

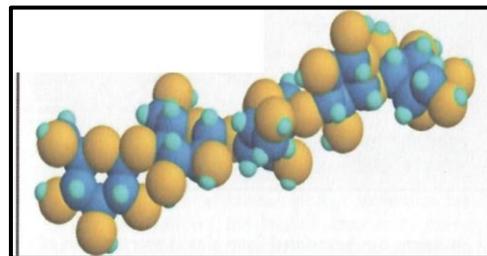


Fig. 1b



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History

Beta glucan's role as an immune-modulator has been well documented for over 50 years. Initial interest in the immunomodulatory properties of polysaccharides was raised after experiments revealed that a crude yeast cell preparation stimulated macrophages via activation of complement [13]. Further work identified the immunomodulatory active component as beta glucan [14]. Beta glucans show notable physiological effects; this is their most important quality and the reason why so much attention has been focused on them. Numerous studies (currently more than 6,000 publications) have subsequently shown that beta glucans, either particulate or soluble, exhibit immunostimulating properties, including antibacterial and anti-tumor activities (for review see [2,8]).

Natural products, useful in preventing and/or treating various diseases, have been sought after throughout the history of mankind. One main problem in characterizing natural products also occurred with glucans: in nature, they represent a complex mixture of ingredients, each of which might contribute to biological activity. Therefore, the evaluation of glucan properties had to focus not only on biochemical characteristics and biological activities but, first of all, on adequate isolation techniques which, at the end, gave us the purified material consisting of pure glucan molecules. *As a result, the only meaningful data has come from experiments based on sufficiently purified glucans* (Vetvicka 2001).

Mechanism of Action

Binding of beta glucan to specific receptors (either CR3 or Dectin-1) activates the macrophage. The activation of macrophages consists of several interconnected processes including increased chemokinesis, chemotaxis, migration of macrophages, degranulation leading to increased expression of adhesive molecules, and adhesion to the endothelium. [15,16]

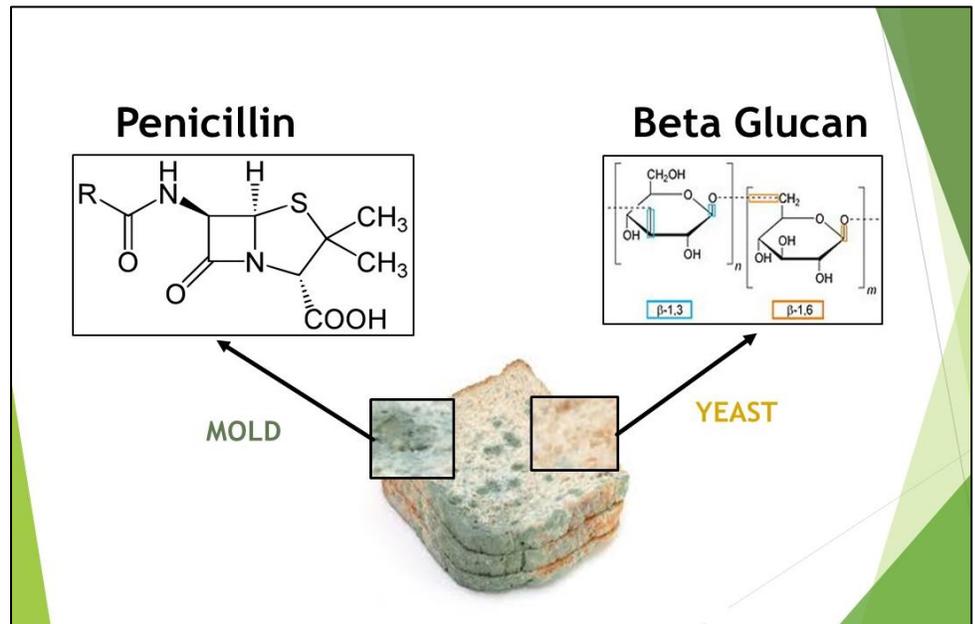
In addition, beta glucan binding triggers intracellular processes, characterized by the respiratory burst after phagocytosis of invading cells (formation of reactive oxygen species and free radicals), the increase of content and activity of hydrolytic enzymes, and signaling processes leading to activation of other cells and secretion of cytokines such as: interleukin 1 (IL-1) and 2 (IL-2), tumor necrosis factor α (TNF- α) and interferon α (IFN- α) [17-19].

For an excellent review regarding interaction of glucans with macrophages, see Schepetkin and Quinn. [20]

Extraction and Purity

Beta Glucan ability to stimulate immune response depends upon purity, homogeneity, and structural characterizations (1,6 branching).

Whole yeasts (ground whole yeast) are not the optimal source of active beta glucan. This is primarily due to their content of available glucan not being high enough, which may result in impurities acting against the biological effects of glucan molecules. [19]



Beta glucan is not located on the surface of the wall but is more or less immersed in the wall material. It is difficult to get the beta glucan molecule out from the yeast wall structure in a highly active form.

The major challenge of extraction is to remove the impurities, such as manno-proteins and lipids (attached to the end points of the side branches in the intact cell wall), without the loss of any biological activity.

Recent advances in enzymatic extraction techniques produce consistent, highly pure beta glucans. This is in contrast to earlier methods using only ground up yeast cells or extractions that use high temperatures, high PH, or solvents that reduce or destroy bioactivity.

Extraction advances were critical producing consistent, predictable beta glucans formulations.



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Differences Among Highly Pure Beta Glucans - Bioactivity

Clinical studies have clearly demonstrated significant differences in bioactivity among highly pure beta glucans. Poorly extracted glucans have minimal (if any) biological effect. Most importantly, some highly purified beta glucans have very low biological activities.

In these cases you need up to 100x more of glucan to illicit high activity. This means that the low activity is not caused by a lower percentage of glucan but, rather, that the glucans with limited biological activities will not be comparable to the “better” glucans regardless of the dosage. [8]

Finally, pure beta glucans can be highly active in one particular part of immune reaction (e.g. stimulation of alveolar macrophages) and mediocre in other parts of immune reaction. [11]

Formulation

Due to significant differences in bioactivity among highly pure beta glucans the best way, perhaps the only way, to select a beta glucan was to test many beta glucans for each desired immune response in cattle.

Over the past 5 years VeriPrime feedyard members and research veterinarians evaluated over 20 different beta glucan formulations. Plant based, mushroom based, and several yeast derived beta glucans were tested. As expected, some were completely ineffective while others showed promising results.

Beta glucans are generally considered to be potent stimulators of cellular immunity, with macrophages and neutrophils being the most important target. Not surprisingly, we started our evaluation measuring the white blood cell counts of cattle on arrival and after being fed beta glucan.

In the beginning we tested each beta glucan individually on small groups of cattle. In the end, as you would expect, we started to create formulations of various beta glucans. Each beta glucan was selected for specific immunity attributes discovered in our investigations.

Final formulations were tested looking for the best improvement of acquired immunity, stimulation of mucosal immunity, and increased effectiveness of macrolide antibiotics.

Depending on the applied dose the effects of individual glucans were long-lasting and in some cases lasted up to two weeks.



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