Beta Glucan - The Natural Healer

By Man Found Standing, Native American Practitioner

The immune system is used as the body's natural defense against disease. One of the most important functions is its self/non-self recognition. The immune system will attack and defend against viruses, pathogens (germs) or anything else that might be considered a "foreign invader". Every cell in the body has a display marker, a genetic locus or alternative DNA for identification. Any cell that does not display this marker is treated as an invader and is attacked. Sometimes, if the immune system is not working properly or weakened, it may start to attack the body. This may lead to such diseases as allergies, asthma, arthritis, chronic fatigue, diabetes, tumors, cancer, and so forth. A wide range of factors may restrict the immune

system response: old age, poor diet, mental or physical stress, radiation, toxins in the environment, and lack of sleep to name a few.

Science has done extensive research for the fight against diseases when the immune system does not work properly and over the years has focused on beta glucan research. Beta glucan, found in high concentrations in **Shiaqga**, has been determined to be an acceptable immune system modulator that binds and stimulates the macrophages (white blood cells) that attack foreign invaders (disease) and signals to other immune cells to move to the site of the infection or disease to speed up the healing process.

Macrophages are involved with the everyday process of detoxifying the body, performing intestinal flora maintenance, and preventing infection. When taking beta glucan orally (which is acid resistant), it passes through

the stomach unchanged. Macrophages in the intestine absorb the beta glucan that is circulated through the blood and lymph systems and release cytokines that stimulate immune activation. Beta glucan is a diverse group of sugar molecules that are found naturally in oats, barley, mushrooms, fungi, yeast, and bacteria. Some well-known benefits of beta glucan include:

- Production of healthy white blood cells.Stimulates and communicates to the immune system receptors: pattern recognition receptors (PPRs), Toll-like receptors (TLRs), killer activated /inhibitor receptors (KARs & KIRs), complement receptors, Fc receptors, B cell receptors, and T cell receptors.
- Encourages a higher number of macrophages in early inflammatory stages of repair (speeds the healing of wounds and infections).Enhances the

resistance from microbes, bacteria, and viruses.Lowers cholesterol .
- Regulates blood sugar and digestion
- Slows or reverses the aging process
- Prevents infections

A human research review on beta glucan, by Przomysl Spozysczy v. 56, 2002,pp 20-1, states:

“Dietary beta glucan enhances immunity by activation of macrophage cells, doubling their counts in 24 hours. Dietary beta glucan also acts as an antioxant protecting the body against free radical damage and lowers blood cholesterol levels. Dietary beta glucan can be helpful in treatment of many immunity-related diseases.”

Research and applications:

Radiation: Patchen M.L., McVittie T.J.; Temporal Response of Murine Pluripotent Stem Cells and Myeloid and Erythroid Progenitor Cells to Low-dose Glucan Treatment. Acta Hemat; 70:281-288. Experimental Hematology Dept, Armed Forces Radiobiology Research Institute, Bethesda, MD. 1983.

"Clearly, there are numerous possible uses for an agent such as glucan, which is a potent stimulator of Hemopoietic activity. Currently, we [U.S. Armed Services] are using glucan to enhance Hemopoietic proliferation in conjunction with Hemopoietic injury induced by radiation."

Wound Healing: Williams D.L., Browder I. and DiLuzio N.R., "Soluble phosphorylated glucan: methods and compositions for wound healing," U.S. Patent 4975421, Issued Dec 4, 1990.

"The soluble phosphorylated glucan are useful for promoting the wound healing process. The soluble phosphorylated glucan are also useful for prophylactic and therapeutic applications against neoplastic, bacteria, viral, fungal and parasitic diseases."

Viral Diseases: Browder IW., Williams D., Pretus H., et al; Beneficial Effect of Enhanced Macrophage Function in the Trauma Patients. Ann. Surg.; Vol 211: 605-613. Dept of Surg and Physiol, Tulane U Sch of Med, LA and Institute Di Chirurgia D'Urgenza, U of Torino, Torino, Italy.* 1990.

"Previous studies have demonstrated that glucan, a beta-1,3-linked glucopyranose polymer, isolated from the inner cell wall of Saccharomyces cerevisiae, is a potent macrophage stimulant and is beneficial in the therapy of experimental bacterial, viral, and

fungal diseases."

From the University of Toronto (European Journal of Clinical Nutrition. 56, 2002, pp. 622-8) beta glucan was given to humans.

“Addition of beta glucan predictable reduces the glycemic index while maintaining palatability.....making it a useful functional food component for reducing postprandial (after meals) Glycemia”. (In other words beta glucan helps normalize blood sugar levels and keeps them from rising.)

These excerpts are just a few that prove the wonders of beta glucan as a natural healer. The science and medical world have known about the benefits of beta glucan for over 30 years! **Shiaqga** with its therapeutic levels of beta glucan is a natural defense against disease that everyone should take,

whether it be to heal the body or as a preventative measure for good health.

Below is a more extensive description of beta glucan research.

Extant Research on Beta 1-3 glucans

Introduction
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(...) Beta-1,3-D-Glucan: An Adjuvant Concept
by Leonid Ber, MD

According to the Webster Medical Dictionary, adjuvant (from Latin ad-juvo, to give aid to) is a substance added to a drug product formulation which affects the action of the active ingredient in a predictable way. This term has been widely utilized in immunology, where it means a vehicle used to enhance antigenicity of vaccines (for example, Freund's adjuvant). Much broader utilization of this term can be applied today to some naturally derived substances. This adjuvant concept closely relates to what is today referred to as a complementary/alternative modality.

Poly-branched beta-1,3-D-glucan is a naturally occurring polysaccharide that can be found in a variety

of fungal cells including cell walls of yeast, such as Saccharomyces cerevisiae, basidiomycetes, such as Lentinulis edodes and Fometopsis pinicola, and to a very small degree from the hull of many grass seeds . As any other glucan (or polyglucose), it consists of glucose units linked together. For example, most starches are alpha-glucans. Out of different glucans, the beta-1,3-D-glucan configuration has been shown to act as a non-specific immune-activator.

Goldman, and later Czop, identified a specific receptor on the cells of macrophage origin that binds to the beta-1,3-D-glucan molecule. This receptor is a protein complex that appears to be present throughout the whole differentiation cycle of macrophages, starting in the bone marrow. Mature macrophages are found in virtually all the tissues including the central nervous system. When a macrophage encounters beta-1,3-D-glucan, it becomes activated. All the functions, including phagocytosis (ability to engulf foreign cells and particles), release of certain cytokines (intercellular hormones), and the processing of antigens are improved and brought up-to-date. Macrophages are extensively involved in everyday detoxifying processes, intestinal flora maintenance, anti-infective and anti-tumor protection and maintenance of overall health integrity. Although most of the research with this substance has been done in vitro and parenterally, later research at Baylor College of Medicine, sponsored by ImmuDyne, indicates the oral effectiveness of purified

beta-1,3-D-glucan (Wyde, 1989).

The integrity of beta-1,3-D-glucan taken orally differs from other food substances. This type of glucan is acid resistant so it passes the stomach virtually unchanged. Further, in the intestine there is a lack of a specific enzyme (beta-1,3-glucanase) that would break it down to glucose or di-glucose so as to be absorbed through the intestinal wall. On the other hand, there are macrophages that inhabit the intestinal wall and are able to pick up beta-1,3-D-glucan particles through beta-glucan receptors. Immediate activation of these cells follows and later, they are able to travel back to the local lymph nodes (Payers Patches) as a part of their natural antigen-presenting function, to release cytokines (IL-1, IL-6, GM-CSF, Interferons) and induce systemic immune activation.

The mechanism described above is called phagocytic transport and it is common for certain microorganisms. Studies conducted with oral application of C13 labeled glucan also support existence of phagocytic transport for beta-1,3-D-glucan.

An adjuvant concept of pharmacological application for beta-1,3-D-glucan was suggested by DiLuzio in the 70s. This article is an attempt to overview this concept from today's perspectives utilizing modern knowledge of oral effectiveness, and a specific transport mechanism of beta-1,3-D-glucan.

There is now enough data to support the use of beta-1,3-D-glucan as an adjuvant in several important medicinal applications.

1. Combination "glucan + anti-infective agent"
Beta-1,3-D-glucan itself can elicit broad anti-infective effects. The nature of macrophage activation induced by this compound is non-specific. Staphylococcus aureus, Eschericia coli, Candida albicans, Pneumocytis carinii, Listeria monococytogenesis, Leishmania donovani, Herpes simplex, Ascaris suum - this is an incomplete list of microorganisms, against which a protective effect of glucan has been established. This list, as you can see, includes bacteria, fungi, viruses and parasites. None of the anti-infective agents possess such a broad spectrum of activity. Unlike an antibiotic compound interfering with metabolism of a pathogen, beta-1,3-D-glucan is a substance that modifies host response to cells genetically different from the host.

Numerous studies support the theory that an antibiotic and a macrophage activator work synergistically.

Experimental peritonitis in rats was used to show synergy between widely used antibiotic ampicillin and glucan. A 100% survival was the result of the combination treatment, while glucan alone gave 30% survival, and ampicillin in the given dose elicited 65% survival (20% survival in the control group). All the

results were statistically significant (Lahnborg 1982).

A 56% survival was achieved when subtherapeutic doses of gentamycin was combined with intraperitoneally delivered glucan at just 0.1 mg/mice challenged with Escherichia coli. This was a very significant increase of survival rate, considering that either no treatment or this low dose of antibiotic alone, gave no protection from peritonitis (0% survival), while glucan alone gave 9% increase in survival. The difference between controls and the combination treatment was highly statistically significant (Browder, 1987).

Anti-fungal effect of beta-1,3-D-glucan from yeast cell wall is particularly interesting. It is known that glucan configuration in Saccharomyces cerevisiae resembles the one in Candida albicans. Glucan administered orally in mice with chronic generalized Candida infection, resulted in significant increase in the candidacidal activity of alveolar and spleen macrophages. The resistance not only to systemic infection with Candida albicans, but also Staphylococcus aureus increased, significantly reducing the growth of microorganisms in the kidneys of infected animals. Glucan also worked synergistically with the anti-fungal drug Amphotericin B (Nicoletti, 1992).

Although there is not enough data collected with regard to the anti-viral effect of glucan, there is now work in

progress regarding its adjuvant anti-HIV effect.

Mortality, associated with Herpes simplex in mice was shown to be profoundly modified in early works and later, it was supported by oral studies (Wyde, 1990).

Mice treated with glucan both before and after the lethal viral hepatitis challenge, exhibited only limited liver pathology, minimal plasma enzyme alterations, and greatly enhanced survival versus a group receiving no treatment (DiLuzio, 1980). Macrophage phagocyting function, significantly impaired by hepatitis, was maintained by glucan application.

Another study shows that virally challenged mice have a limited wound-healing capacity that was corrected by systemic glucan application (Kenyon, 1983).

2. Combination "glucan + anti-neoplastic agent"
Glucan anti-tumor effect can be local or systemic. A local injection of beta-1,3-D-glucan suspension into melanoma lesions has been shown to successfully resolve the tumor locally (Mansell, 1978). In these human experiments, the site of injection revealed no previously established tumor, but plenty of macrophages filled with pigments. Obviously, macrophages were drawn to the site where they phagocytized and destroyed pigment-bearing tumor cells. These intralesional injections in some cases were able to control further growth of remote metastasis of

the same tumor which resumed growth after glucan treatment withdrawal.

Unfortunately, no clinical applications were developed out of these results until recently (Carrow, 1996). The latest data contains very promising information, not only in regard to human melanoma, but also to basal cell carcinoma.

Experimental animal data on systemic applications of beta-1,3-D-glucan anti-tumor effects is abundant. Significant reduction in tumor growth and prolonged survival was observed in mice with transplanted melanoma. In mice with adenocarcinoma, there was an 85% reduction of tumor mass accompanied by prolonged survival. An anaplastic mammary carcinoma study showed results of 70% tumor regression and 80% survival versus 100% in the group with no glucan treatment. Chronic administration of glucan to aging mice with lymphocytic leukemia significantly improved their survival (DiLuzio, 1980).

In these and other experimental models, systemic macrophage activation and certain cytokine releases, seem to be critical for clearing tissues from the tumor cells (Proctor, 1980) and inhibiting metastasis (Sakurai, 1991).

A combination of beta-1,3-D-glucan and an antineoplastic agent(s) might have a significant

potential considering its a) direct anti-tumor effect, and b) ability to counteract chemotherapy-induced immunosuppression resulting in higher mortality from opportunistic infections.

The efficacy of glucan in combination with BCNU chemotherapy was measured using the disseminated transplantable leukemia; the combination yielded a high level (56%) of cures compared to no survival for either agent alone (Stewart, 1978).

Glucan application can also protect a patient from leukocytopenia (decrease in the number of peripheral leukocytes) associated with a chemotherapeutic agent, which is one of the major obstacles in the chemotherapy of cancer. A decrease in the number of peripheral leukocytes by 5-fluorouracil was prevented by the oral application of glucan in mice. Proliferative responses of bone marrow cells to granulocyte/macrophage colony stimulating factor (GM-CSF) or granulocyte colony stimulating factor (G-CSF) were suppressed by 5-fluorouracil treatment, and their recoveries were enhanced by glucan and serum level of cytokines such as IL-1 and IL-6 were increased (Miyazaki, 1992).

Interestingly, that use of corticosteroid hormones, also having immunosuppressive effect, and widely used as a part of chemotherapy programs or in autoimmune situations, might be another indication for use of beta-1,3-D-glucan in combination with this class of

drugs. Goldman showed that the amount of beta-1,3-D-glucan binding capacity of macrophages increases when they are exposed to hydrocortisone. She states that this might be a result of enhanced expression of beta-glucan receptor. A logical interpretation of that can be that it's an attempt to compensate the diminished phagocytic ability of macrophages exposed to this class of hormones.

3. Combination " glucan + radiotherapy"
This combination seems to be very logical in the light of the data mentioned above. Radioprotective (bone marrow protective effect) of yeast glucan is well-established and documented with the mechanism of enhancing hemopoietic recovery and hence, by regenerating the host's ability to resist life-threatening opportunistic infections. However, it also has been demonstrated that host resistance to opportunistic infection in glucan-treated irradiated animals is enhanced even prior to the detection of significant hemopoietic regeneration. This early enhanced resistance to microbial invasion could be correlated with enhanced and/or prolonged macrophage (but not granulocyte) function.

These results suggest that early post-irradiation glucan may mediate its radioprotection by enhancing resistance to microbial invasion mechanisms not necessarily predicated on hemopoietic recovery.

Experimental data suggest that glucan can also function as an effective free-radical scavenger (primarily toward hydroxyl radical).

Because macrophages have been shown to selectively phagocytize and sequester glucan, it is possible that these specific cells may be protected by virtue of glucan's free-radical scavenging ability (Patchen, 1987).

Oral application of yeast beta-1,3-D-glucan for 20 consecutive days after a single, near lethal, dose of radiation resulted in 70-90% survival versus 30% in the control group.

4. Combination "glucan + topical agent"
Glucan is an excellent wound healer. In experiments glucan-treated wounds showed a higher number of macrophages in the early, inflammatory stage of repair, with fewer polymorphonuclear neutrophilic leukocytes than did control wounds. Both re-epithelization and the onset of fibroplasia commenced at an earlier stage in glucan-treated wounds than in control wounds. Five days following the incision, glucan-treated wounds were generally completely re-epithelialized, while control wounds were not. The organization of fibroblasts in glucan-treated wounds was more advanced at 5 and 7 days following injury, and the extent of fibroplasia was also greater. By 10 days following injury, glucan-treated wounds were completely re-epithelialized and no formation of granulomas was observed up to one month

following wounding (Leibovich, 1980).

In humans, topical glucan treatment resulted in 73% improvement in chronic decubitus ulcers with complete closure and epitalization in 27% of treated ulcers. All wounds remained clean with no infections occurring during this treatment (DiLuzio, 1984).

Considering the data above, a topical combination of an antibiotic and beta-1,3-D-glucan as an adjuvant for wound healing applications, seems to be appropriate.

An interesting effect of topical application of glucan was observed in regard to non-wounded aged skin. Revitalizing, such as reducing the number, depth and length of wrinkles, thickening, reducing roughness and dryness of the skin was shown in a group of female volunteers (Smith, 1991).

Applied topically, glucan activates epidermal macrophages (Langerhans cells). This mechanism plus its free-radical scavenging effect makes it a photoprotective agent. Glucan application resulted in the reduction of after-UV erythema and preservation of the amount of Langerhans cells in the epidermis (Elmets, 1992). A combination of a sunscreen + glucan is suggested.

Anti-irritant effect of beta-1,3-D-glucan was also shown in combination with otherwise severe irritation causing

levels of lactic acid (Smith, 1991). Glucan also has a synergistic effect with another anti-aging topical ingredient: retinoic acid (Retin-A). Similar to corticosteroids, Retin-A significantly increases the number of beta-glucan receptor-sites on phagocytic cells.

5. Combination "glucan + nutrients"
Very recent discoveries have been made on combined use of glucan and vitamin C derivatives.

Intracellular ascorbate content in phagocyting cells reaches 40 times the level of plasma ascorbates. Macrophages activated with beta-1,3-D-glucan exhibit a significant drop in the intracellular ascorbate content. This might lead to the exhaustion of free-radical scavenging capacity of these cells, as well as to impaired motility and certain enzyme production by macrophages.

There are products on the market now that combine beta-1,3-D-glucan and vitamin C derivatives to replenish ascobate levels in the glucan-activated macrophages. This is not only physiological from the standpoint of glucan pharmacological effects, but it also seems to have a great impact on results of Vitamin C treatments.

Commercial application of yeast derived purified beta-1,3-D-glucan, available in a dietary supplement form

and in a pure form for compounding, started in 1995. There is obviously a lack of recent double-blind human studies but plenty of anecdotal clinical data ranging from tumor mass rejection to healing of chronic wounds. Hopefully, we will see more studies with beta-1,3-D-glucan in the near future as this substance gains acceptance within the medical community.

Clinical directions presented in this paper are not by any means a complete list of all possible applications and combinations with this substance. A good physician can find more ways to utilize this material in practice. Now, when we have a better understanding of its mode of action, we can prognose and prove in practice the benefits of using beta-1,3-D-Glucan by itself or by adding it to either conventional or alternative types of therapies that would affect such therapies in a predictable way.

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Overview of the Research Alphabetical Listing

Note: *Beta 1-3 glucan research is on the main focused on yeast-source glucans. Quantitative analysis has determined that the polypore and other basidiomycetes contain significantly more beta glucans than yeast-based products. Notwithstanding the research has to do with yeast-type fungi, the data is viable and transferable to the basidiomycete-based glucans. The importance of this finding cannot be overlooked, because the amount of yeast-based B1-3 glucan that can be naturally absorbed from the ingestion of brewer's or dietary yeast is vastly smaller than from the ingesting of basidiomycete-based glucan. For this reason, yeast-based glucan must be highly processed and concentrated. Basidiomycete-based glucan is rendered bio-available with minimal processing.*

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Administration of glucan particles ...stimulates...proliferation of macrophages and increases in phagocytic and secretory

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References and quotes contained herein should not be construed as express or implied representations, endorsements or warranties of Carmel Research, Inc.

Fungal beta-glucan interacts with vitronectin and stimulates tumornecrosis factor alpha release from macrophagesEJ Olson, JE Standing, N Griego-Harper, OA Hoffman and AH Limper

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beta-Glucans are polymers of D-glucose which represent major structural components of fungal cell walls. It was shown previously that fungi interact with macrophages through beta-glucan receptors, thereby inducing release of tumor necrosis factor alpha (TNF-alpha). Additional studies demonstrated that vitronectin, a host adhesive glycoprotein, binds to fungi and enhances macrophage recognition of these organisms. Since vitronectin contains a carbohydrate-binding region, we postulated that vitronectin binds fungal beta-glucans and subsequently augments macrophage TNF-alpha release in response to this fungal component. To study this, we first determined the release of TNF-alpha from alveolar macrophages stimulated with fungal beta-glucan. Maximal TNF-alpha release occurred with moderate concentrations of beta-glucan (100 to 200 micrograms/ml), whereas higher concentrations of beta-glucan (> or = 500 micrograms/ml) caused apparent suppression of the TNF-alpha activity released. This suppression of TNF-alpha activity by high concentrations of beta-glucan was mediated by the particulate beta- glucan binding soluble TNF-alpha, through the lectin-binding domain of the cytokine, rendering the TNF-alpha less available for measurement. Next, we

assessed the interaction of vitronectin with beta-glucan. Binding of 125I-vitronectin to particulate fungal beta-glucan was dose dependent and specifically inhibitable by unlabeled vitronectin. Furthermore, treatment of beta-glucan with vitronectin substantially augmented macrophage TNF-alpha release in response to this fungal component. These findings demonstrate that fungal beta-glucan can directly modulate TNF-alpha release from macrophages. Further, these studies indicate that the host adhesive glycoprotein vitronectin specifically binds beta-glucan and augments macrophage cytokine release in response to this fungal element.

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The influence of glucan polymer structure and solution conformation on binding to (13)-ß-D-glucan receptors in a human monocyte-like cell line Antje Mueller2,6, John Raptis2,6, Peter J. Rice3,6, John H. Kalbfleisch4,6,

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Glucans are (1–3)-ß-D-linked polymers of glucose that are produced as fungal cell wall constituents and are also released into the extracellular milieu. Glucans modulate immune function via macrophage participation. The first step in macrophage activation by (1–3)-ß-D-glucans is thought to be the binding of the polymer to specific macrophage receptors. We examined the binding/uptake of a variety of water soluble (1–3)-ß-D-glucans and control polymers with different physicochemical properties to investigate the relationship between polymer structure and receptor binding in the CR3- human promonocytic cell line, U937. We observed that the U937 receptors were specific for (13)-ß-D-glucan binding, since mannan, dextran, or barley glucan did not bind. Scleroglucan exhibited the highest binding affinity with an IC50 of 23 nM, three orders of magnitude greater than the other (13)-ß-D-glucan polymers examined. The rank order competitive binding affinities for the glucan polymers were scleroglucan>>>schizophyllan > laminarin > glucan phosphate > glucan sulfate. Scleroglucan also exhibited a triple helical solution structure (= 1.82, ß = 0.8). There were two different binding/uptake sites on U937

cells. Glucan phosphate and schizophyllan interacted nonselectively with the two sites. Scleroglucan and glucan sulfate interacted preferentially with one site, while laminarin interacted preferentially with the other site. These data indicate that U937 cells have at least two non-CR3 receptor(s) which specifically interact with (13)-ß-D-glucans and that the triple helical solution conformation, molecular weight and charge of the glucan polymer may be important determinants in receptor ligand interaction.

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'Dectin-1 and its role in the recognition of beta-glucans in macrophages' Gordon D. Brown. Sir William Dunn School of Pathology, University of Oxford. gbrown@molbiol.ox.ac.uk

The innate cellular recognition of pathogens is dependent on germ line encoded receptors which recognise conserved microbial structures. Using a novel method to isolate these receptors, we identified Dectin-1 as the

macrophage b-glucan receptor. Dectin-1 acted as a classical pattern recognition receptor, recognising a variety of b-1,3 and/or b-1,6 linked glucans, as well as intact yeasts, and is the primary receptor for these carbohydrates in macrophages. Dectin-1 also mediates the phagocytosis of particulate glucans, an activity which is dependent of the cytoplasmic tail of this molecule. In addition to these exogenous ligands, the receptor recognised an endogenous ligand on T-cells, but through a binding site which was distinct from that which recognised b-glucans. We found Dectin-1 to be expressed in many tissues and highly expressed on the surface of immune cells, especially those of the monocyte / macrophage and neutrophil lineages. We have also identified the human homologue of Dectin-1 and have shown that it is structurally and functionally similar to the mouse receptor.