Beta Glucan: A Dietary supplement with multiple therapeutic uses

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Abstract **- Beta-Glucan is a natural polysaccharide with variety of applications due to its unique properties. β-glucan, a major component of cell walls and classified in to microbial or plant-based glucans depending on the source such as bacteria, fungus, yeast and cereal. It is generally used as a dietary fiber. Natural β glucans possess many health promoting effects on human health, such as antitumor, antidiabetic, antilipidemic, lowering blood cholesterol, wound healing and immune modulating properties. This review describes application of beta-glucan in drug delivery and clinical applications of β-glucans.**

Index Terms **- β-glucan, dietary fiber, clinical applications, immunomodulatory agent, wound healing.**

INTRODUCTION

Interest in the food formulation having complex polysaccharides is continuously rising, attributable to the bioactivities and wellbeing of advancing capacities of these polysaccharides. One of such widely known bioactive polysaccharide is Beta-Glucan.1 Beta-glucan is a natural polysaccharide with variety of applications due to its unique properties. Beta-glucan is a generic term for Beta-D-glucose polysaccharide which is a major component of cell walls.2 Beta-Glucan is a non-bland polysaccharide made out of β-D-glucose monomer units held together at β-(1, 3), β-(1, 4) and β-(1, 6) by glycosidic linkage.1 In general Beta-glucan having D-glucose units with β-(1, 3) link which has many therapeutic uses such as immunomodulatory and stimulatory activity wound healing, anti-diabetes, lowering blood cholesterol, anti-tumor, anti-oxidant etc.

Beta-glucan is widely found in cell mass of microorganisms (bacteria, fungi, yeast) and endospermic and aleuronic dividers of the cereal grains (Oats, Barley, ryes, millets).1

Microbial and fungal sourced 1, 3 beta-glucan have natural immunological properties. These 1, 3 Beta-glucans which are components of foreign pathogens, when enter inside the body act as recognition sites for macrophages with the aim of the elimination and removal of pathogens.

SOURCES AND STRUCTURE OF BETA-GLUCAN

Beta-glucan is found at a lower concentration (5% w/v) in cereals whereas in microorganisms, the concentration of these polymers widely varies. Beta-glucan extricated from Baker's Yeast (Saccharomyces cerevisiae) discovered to be 5-7%, Holdfasts and stipes of Durvillaea antarctica have 5% and 33% of Beta-glucan respectively. In Mushrooms the content of Beta-glucan widely vary from about 3.1 to 46.5%. Table 1 elaborates the concentration of Beta-glucan from diverse sources

Sources of Beta-glucan

Cereals	Oats, Barley, Millets
Mushrooms	*Pleurotus ostreatus*, *Pleurotus pulmunarius*, *Pleurotus eryngii*, *Lentinula edodes*
Microorganisms	Yeast, Fungi, Bacteria
Lichens	*Cetraria islandica*
Algae	Euglena Gracilis

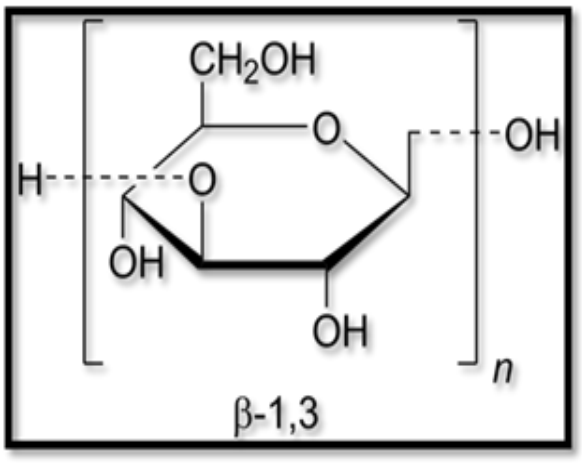
Table 1. Concentration of Beta-glucan from different sources

Food Source	Content	References
Oats	4.5-5.5%	4
Barley	4.5%	4

Whole rye flour	1.0-2.5%	5
Saccharomyces cerevisiae	5%-7%	6
Euglena	90%	6
Stipes of *Durvillaea Antarctica*	33%	7
Holdfast of *Durvillaea Antarctica*	<5%	7
Sparassis crispa	43.6%	9
Inonotus abliquus	3.1%	8
Gyrophora esculenta	22.7%	8
Coriolus versicolor	46.5%	8

Beta-glucan extracted from various sources changes in numerous qualities, for example, glycosidic linkages, level of branching, mol. Weights and dissolvability. Beta-glucan got from Cereals are mostly mixtures of β-(1, 3) and β-(1, 4) glycosidic linkages with no β-(1, 6) linkage. Beta-glucan derived from Yeast (Saccharomyces cerevisiae) is a mixture of linear β-(1, 3) backbone with 30 residue straight chains and to these long branches are connected via β-(1, 6) linkage. Beta-glucan derived from Fungi are straight β-(1, 3) glucans with short, branched chains connected through (1, 6). Bacterial Beta-glucans have straight and unbranched β-(1, 3) D-glucan backbone, while Seaweeds derived β-glucans are species-dependent and may contain straight chain β-(1, 3) residues or the straight chain backbone together with high level β-(1, 6) backbone.1 The chemical structures of β-glucan got from various sources are appeared in figure 1

(A)



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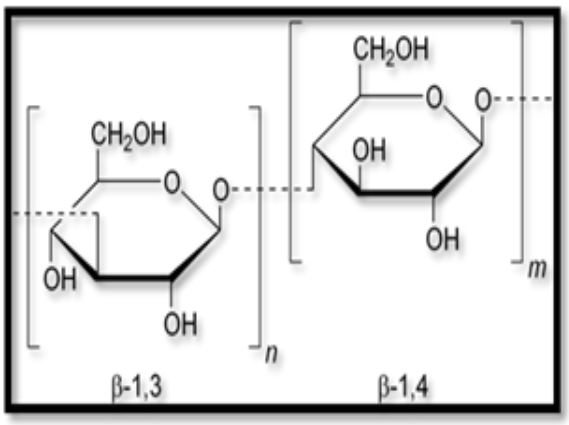

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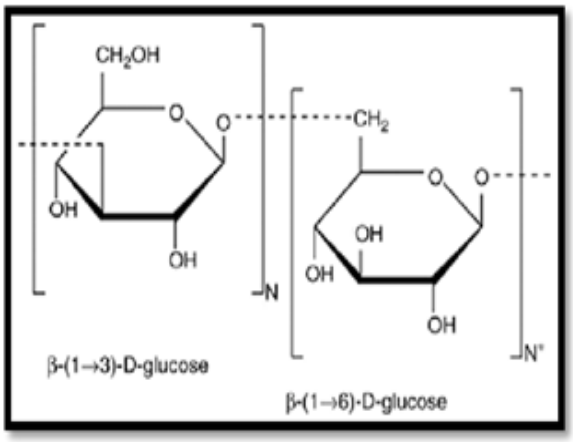

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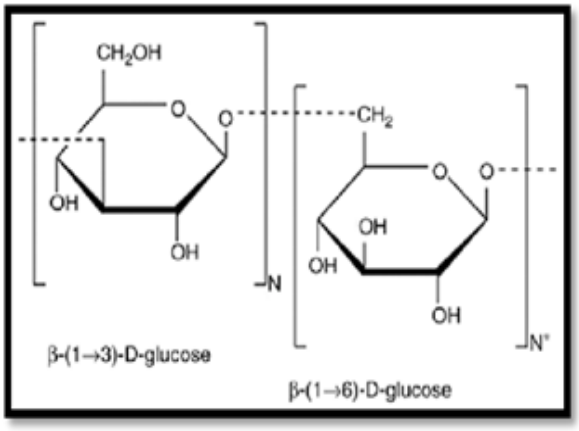

Figure 1. The chemical structure of Beta-glucan from different sources. (A)Beta-glucan from bacteria; linear β-1,3 backbone with no branches; (B) Beta-glucan from cereals, or linches; linear β-1,3 or β-1,4, backbone with no branches; (C) Beta-glucan from seaweeds; β-1,3backbone with β-1,6 branches; (D) β-glucan from fungus or yeast β-1,3 backbone with β-1,6branches that are short (fungus) or long (Yeast).1

Beta-glucans are Semi-crystalline polysaccharides, based on origin and processing method used in their extraction and modification they can exist in a range of conformations like a single, double, triple helices and random coils (figure 2).1 Crystallinity of these polysaccharides can be studied using X-ray Diffraction (XRD).2Bacterial, fungal and yeast-based Beat-glucans are insoluble in water whereas cereal sourced Beta-glucans are soluble in water.

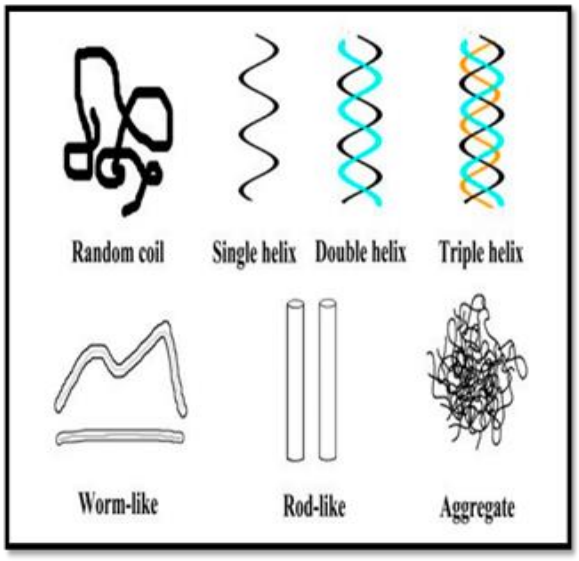

Figure 2. Conformation of Beta-glucan:1

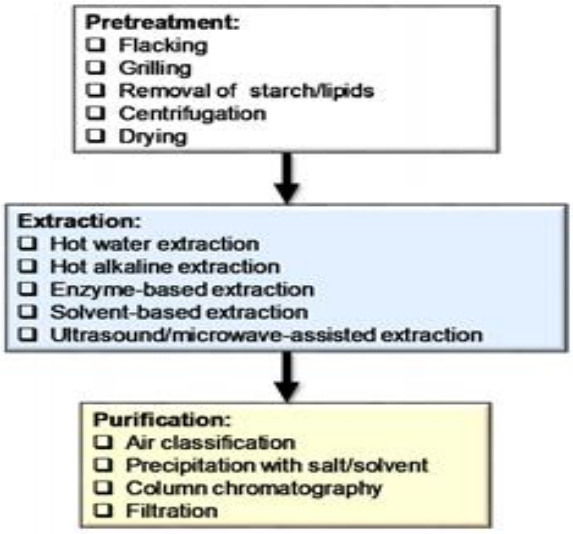

Figure 3. Extraction and purification of Beta-glucan:1

PHAGOCYTIC ACTION OF BETA-GLUCAN

Beta-glucan when taken orally, it passes through the stomach virtually unchanged. Macrophages present in mucosal lining of the intestinal wall pick up beta-glucan through beta-glucan receptors, which result in release of cytokines and induced systematic immune activation. When taken orally beta-glucan prevent the absorption of cholesterol from stomach and intestines. When taken as injectables, they stimulate immune system by increasing concentration of infection preventing chemicals.3

ABSORPTION OF BETA-GLUCAN

Beta-1,3-glucan showed best results when taken on an empty stomach. Radio-labelled studies have shown that both small and large fragments of beta glucan were found in serum which indicates that they are absorbed from the intestinal tract. Insoluble whole glucan particles were physically transported to gut-associated lymphoid tissue (GALT) by M cells within the payer's patches.3

APPLICATIONS OF B-GLUCAN IN DRUG DELIVERY

The structure controlling ability of 1,3-β-glucan based carriers has encouraged the application of these glucans in drug delivery. The glucans can be used as gels, nanoparticles, microparticles or complexes.2

ENCAPSULATION WITHIN GELS

Curdlan a neutral, essentially linear, (1→3)-β-glucan is commonly used for formation of gels. For the encapsulation of curdlan gels drugs such as indomethacin, salbutamol sulphate, theophylline and prednisolone have been used.2 Invitro Drug release from the tablets prepared from spray-dried particles of curdlan/theophylline was observed to have sustained action with a cumulative release of 58% at 8hr.10

MICROPARTICLES AND NANOPARTICLES

Nanoparticles are typically used in drug delivery applications because of high drug encapsulation efficiency, controlled drug release and incorporation of diagnostic agents. Glucan microspheres can be used for delivering various payloads such as proteins, DNA, SiRNA and small molecules. These small molecules are not easily entrapped within in these glucan microspheres and thus the nanoparticles usage is

necessary. These nanoparticles can then be loaded in Glucan microspheres for enhanced uptake.2

Curdlan was used to synthesize nanoparticle formulation for encapsulating curcumin, a water insoluble compound with its promising anticancer activity. This delivery of curcumin has shown enhanced activity by encapsulating it within the curdlan to form 50nm nanoparticles.2

These results demonstrate that curdlan complexed nanoparticles can be one of the promising system for the loading and intracellular release of hydrophobic drugs for various therapeutic applications.

GLUCAN COMPLEXES WITH POLYNUCLEOTIDES

Polynucleotides have various applications in drug delivery such as it is used as active therapeutic agent, but one of its disadvantages is its rapid degradation in vivo. Thus, polynucleotide encapsulation has become a necessity in order to maintain their function. Due to the helix forming capabilities 1, 3 beta glucans are preferred for the formation of complexes.2

Curdlan gels are also used for developing protein delivery devices. As the temperature required to form curdlan gels should be lowered, this property is taken as advantage for encapsulation of protein.11

CLINICAL APPLICATIONS OF BETA-GLUCAN

BETA-GLUCAN AS IMMUNOMODULATING AGENTS

Beta-glucans are strong immunomodulators showing both innate as well as adaptive immunity. The main function of innate immunity is to recognise and respond against the pathogens invading our body and controlling infection. 1,3 and 1,5 Beta-glucans bind to its receptor Dectin-1, which initiates and regulates the innate immunity response. 12-14

Diabetes

By performing animal studies and clinical trials, it was found that both oat and fungal beta-glucans showed reduced blood glucose concentration after oral administration. Studies show that beta-glucan isolated from oats lowers the postprandial glycemia. Studies also showed that oat bran flour is more effective that compared to oat crisp, as it has trice higher beta-glucan content.3

Hypertension

Beta-glucan has the ability to reduce hypertension. In genetically modelled rats with spontaneous hypertension (SHR), 5% Shitake (Lentinus edodes) or maitake (Grifola frondosa) diet was given. The results showed decrease in the mean systemic blood pressure. In Zuker fatty rats administration of whole maitake basidiocarps and the water-soluble extract showed decrease in blood pressure.3

Hyperglyceridemia

Oats was first found to have a cholesterol-lowering effect and the active component was found to be Beta-glucan. Oat's beta-glucan reduced both serum total cholesterol and LDL cholesterol.15

Tumor suppression

In Japan since 1986 1,3 Beta-glucans has been used in cancer therapy (in gastric, lung and cervical cancer).16 According to some animal studies Lentinan and pachymaran were found to exhibit high tumour ratio of 99.6%. Besides Lentinan and pachymaran, other 1,3 beta-glucans have also exemplified tumour suppression.17 Some of the prominent examples include scleroglucan with an inhibition ratio of 90%, curdlan with 99-100%,18 inhibition, Grifolan with 97.9%,19 inhibition ratio and 1,3-Beta-glucans from Agaricusblazei with inhibition of 99.3%.20 Animal studies also proved that combination of 1,3-beta-glucan and antibodies in tumor therapy provided effective results than compared to treatment with antibodies alone.21

Infection prevention

Since 1, 3-beta-glucans can induce inflammatory and immune responses, these can be used to prevent most common infections caused by bacteria and fungi and provide infection resistance. It was observed that 1,3-beta-glucans were able to translocate from oral administration to systemic circulation and were able it increases the secretion of interleukins, improved expression of dectin-1 on macrophages. When 1, 3-beta-glucan was administered to mice its resistance towards Staphylococcus aureus was increased from 70% to 97%. 1, 3-beta-glucan improves innate immunity by enhancement in humoral immunity as indicated by changes in the serum IgM and IgA levels.22,23

Wound healing

Beta-glucans were found to show effective wound healing activity. They impact on wound healing by recruiting macrophages at the site of wound and by increasing collagen deposition. In children suffering from partial thickness burns beta glucan collagen matrix wound dressings were used, which reduced the analgesic requirements and repetitive dressing changes. Many composites of beta glucan were produced using poly vinyl alcohol and chitosan, which accelerated the healing process and reduced the healing time by 48% than compared to cotton gauze.3

Antimicrobial Effect

Beta-glucans obtained from oats has been demonstrated to have antimicrobial effect against E. coli and B. subtilis. Comparison of cationic and native beta-glucans were studied. Native beta-glucan was seen to inhibit the growth of these bacteria approximately by 35%, while cationic was seen to cause 80% in both microorganisms, indicating that beta-glucan amination promotes antimicrobial effects. In the same study it was observed that cationic beta-glucan has been seen to be more effective against E. coli (gram negative) than B. subtilis (gram positive) as the interaction of the polycations with the negatively charged bacteria surface, altering membrane permeability and thereby inhibiting growth.24

Radiation Exposure

Beta-glucan isolated from the yeast cell wall polysaccharides which is entirely made of beta (1,3), linked together in linear chains with a variable frequency of beta(1,6) -linked sidechains is popularly known as biological response modifier (BRM). Beta glucan was demonstrated to have a specific hematopoietic activity. Mice receiving lethal dose 900-1200cGy of radiation was able to survive due to enhanced combinational anti-infective activity and hematopoietic stimulating activity.3

Septic shock

Beta glucan has the ability to reduce septic shock by the mechanism of the immune enhancement. Onderdonk et.al investigated on the ability of the yeast beta-glucan to reduce septic shock using in vivo models and they found that mice were protected from the specific infection from E. coli or S. aureus bacteria as they were four to six hours prior injected with PGG-glucan.23

Allergic Rhinitis

Allergic Rhinitis is caused by an IgE-mediated allergic inflammation of the nasal mucosa. When yeast beta-glucan was orally administered, they decreases the levels of IL-4 and IL-5 cytokines responsible for the clinical manifestation of this disease, while increasing Il-12 levels. These studies shows that glucan has role in treatment in patients with allergic diseases.3

Arthritis

Studies showed that yeast-derived glucan causes a decline in oxidative tissue damage during the process of arthritis diseases, which suggests a role in the treatment of arthritis.3

ADDITIONAL APPLICATION

1. Cereals, mushrooms and yeast facilitates bowel motility and can be used in the amelioration of intestinal problems (particularly constipation).3
2. Oats, barley and edible mushrooms beta-glucans decreases the level of serum cholesterol and liver low-density lipoproteins and reduces cardiovascular diseases hazards.3
3. Beta-glucan found in baker's yeast and certain fungi have anti-cancer properties.3
4. Beta-glucan is also promoted as a dietary supplement for weight loss, beta-glucan have some effect on effective glycemic index and insulin response.3

SAFETY CONCERNS WITH BETA-GLUCANS

Beta-glucans are safe in adults when administered or taken orally or injectable used for short period of time.3

Some of the potential side effects of Beta-glucan when administered orally are not known. When used by injection, Beta-glucan can cause chills, fever, headache, joint pains, nausea, vomiting, dizziness, rashes and increased urine. Beta-glucan causes thickening of the skin of the hands and feet in AIDS patients.25,26.

DRUG INTERACTIONS

Beta-glucan was observed to have drug interaction with diclofenac, etodolac, flubiprofen, ibuprofen, indomethacin, meclofenamate, piroxicam, aspirin.3

CONCLUSION

Beta-glucans are sugars that have medicinal use. β-Glucan is a generic term for β-D-glucose polysaccharide, a major components of cell walls of bacteria, fungus, yeast and has the ability to stimulate immune system. β-glucans are used for high cholesterol, diabetes, cancer, and HIV/AIDS. β-glucans are also used as immunity booster in people weak defense mechanism, conditions such as chronic fatigue syndrome, or physical and emotional stress; or by treatments such as radiation or chemotherapy. β-glucans are also used for colds (common cold), flu (influenza), H1N1 (swine) flu, allergies, hepatitis, Lyme disease, asthma, ear infections, aging, ulcerative colitis and Crohn's disease, fibromyalgia, rheumatoid arthritis, and multiple sclerosis. β-glucans can be administered by IV (intravenously) or by injection into the muscle, to treat cancer and to boost the immune system in people with HIV/AIDS and related conditions. β-glucans are also given by IV to prevent infection in people, after surgery.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

ABBREVIATIONS

XRD: X-Ray diffraction; GALT: Gut associated lymphoid tissue; DNA: Deoxyribonucleic acid; Si RNA: Small interfering RNA; LDL Cholesterol: Low density lipoprotein Cholesterol; BRM: Biological responce modifier; Il: Interleukin; HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome; IV: Intravenously.

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