THE EFFICACY AND SAFETY OF BETA GLUCAN

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ABSTRACT

B-Glucans are glucose polymers obtained from various sources, for instance, fungus, grain, and yeast. Several receptors mediate the process of β-glucan actions or activities in the organism; these receptors include the lactosylceramide, scavenger receptor, CR3 (Complement Receptor 3), TLR-2, 4, 6 (Toll-Like Receptors), and Dectine-1 Receptor. The fine structural features and molecular size of β-glucan play a critical role on its chain shape or conformation and solubility and hence, on its rheological features in solutions. Recent data indicate that β-glucans are effective immunomodulators which influence the adaptive and innate immunity. Dermatology is one promising field of β-glucan application; this field incorporates aspects such as wound healing and care. There is a significant increase in the topical or contemporary application of β-glucan; this is mainly due to its pluripotent activity (rejuvenation, moisturization, radioprotection, immunomodulation, regenerative effects, anti-inflammatory, and antioxidant effects) which act as a potential alternative therapy in the management of different skin conditions and diseases. Gamma irradiation is the most effective sterilization procedure for beta glucan.

KEYWORDS: B-glucan, Efficacy, therapy, immune dulators.

The Efficacy and Safety of Beta Glucan on Different Diseases

B-Glucans are glucose polymers derived from various sources, for instance, fungus, grain, and yeast and they belong to a drug category referred to as biological response modifiers.¹⁶,¹⁷,²³ Multiple researches demonstrate the efficacy of β-D- glucans (soluble or particulate) in enhancing the immune functions or roles such as immunomodulatory, antitumor, and anti-infective activity. B-glucans also have an extensive range of treatment applications in the field of healthcare; it is effective in various treatment procedures involving humans, domestic farm animals, fish, rodents, and invertebrates due to its capacity to modulate the immune system.¹¹,¹⁴,¹⁷ All beta glucans are glucose polymers joined by β-glycosidic bonds (1–3; 1–6 or 1–4) and they vary from each other significantly through features such as branching structure and length.²⁹,⁶⁷ The biological activities of various β-glucans differ accordingly with regards to their solubility, molecular structure, and polymer conformation.¹⁹

Several receptors mediate the process of β-glucan actions or activities in the organism; these receptors include the lactosylceramide, scavenger receptor, CR3 (Complement Receptor 3), TLR-2, 4, 6 (Toll-Like Receptors), and Dectine-1 Receptor.³,⁵ Dectine-1 is the most significant receptor that is manifested in various immunocompetent cells.⁴⁵ Examples of these cells include the cutaneous cells (this includes the fibroblasts and keratinocytes), T lymphocytes, monocytes, macrophages, eosinophils, neutrophils, and dentritic cells.⁴⁰,⁵⁶,⁶⁷,⁶⁹ When beta glucans cohere to Dectin-1, they stimulate the synthesis of numerous cytokines or activate various non-immune and immune reaction procedures.⁸

Chemical and Physical Properties of β-Glucan

The fine structural features and molecular size of β-glucan play a critical role on its chain shape or conformation and solubility and hence, on its rheological features in solutions.⁶,¹²,³⁰ The chemical properties of β-glucan may be demonstrated in its water solubility features and its augmented adaptable chain conformation.¹⁴,³² The cellulose-like parts of β-glucan may enhance the stiff ness of molecules in solutions.¹³ All beta glucans are joined by a β-glycosidic chain core (1→3 linear) and they vary according to their branching structures and length.²⁰,²² B-glucans’ branches are significantly variable and constitute two primary branching groups: 1→6 or 1→4 glycosidic chains.²² The branching mechanisms are usually species’ specific.²⁰ For instance, fungi’s β-glucans are made up of 1→6 side branches.²⁵ Bacteria, on the other hand, are made up of 1→4 side branch.²⁵ The branching arrangements follow a specific sequence and a branch may emerge from another branch (secondary branches). B-glucans usually undergo conformational changes to form random, single-helix, and triple-helix coils.⁶⁴ B-
glucans’ immune functions ostensibly depend or rely upon their conformational complexities. Moreover, the high level of structural complexity relates to significantly potent anti-cancer and immunomodulatory effects.

Fig 1: β-glucan of fungi

B-glucans that contain adjacent β-(1→4) branches are likely to portray an inclination for inter-chain aggregation due to the strong bonds of hydrogen along or between the cellulose like portions and, therefore, lower solubility. B-glucans with 1→3 branches break down the β-(1→4) branch sequence’s regularity, thus, enhancing its flexibility and solubility. Various studies denote that the irregular spacing that exists amid the (1→3)-branched residues of β-glucosyl located in the β-glucan sequence accounts for the irregularities in the general polysaccharide conformation, and, therefore, the chains became incapable of aligning closely over extended areas; this keeps the polysaccharide in the solution.

Moreover, β-glucan has limited or intrinsic viscosity which varies amid 0.29 and 9.5dl/g; the variation depends entirely on the isolated polymers’ molecular weights. Rheologically, β-glucans’ solutions fall into the visco-elastic fluids’ group; this is mainly because they have characteristics similar to well-characterized or classified random coil-type polysaccharide.

Effects of β-Glucan in the Immune System

Recent data indicate that beta-glucan is effective immunomodulators which influence the adaptive and innate immunity. The innate system’s capacity to rapidly identify and counter an attacking pathogen is necessary for managing infections. Dectin-1, a transmembrane protein receptor (type II) which coheres to β-1,6 and β-1,3 glucans, regulates and initiates the response of the innate system. Dectin-1 distinguishes β-glucans located in the fungal and bacterial cell wall. Human cells lack β-glucans; this acts as a significant advantage in the process mentioned above. Dectin-1 then triggers appropriate immune responses such as pro-inflammatory and phagocytosis and this consequently facilitates the elimination or eradication of agents that are infectious. Dectin-1 is mainly expressed on cells that take part in innate immune responses; it is located in dendritic cells, neutrophils, and macrophages. Dectin-1’s cytoplasmic tail constitutes an ITAM (Immune-receptor Tyrosine-based Activation Motif) whose primary role is to send signals via the tyrosine kinase together with TLR-2/6 (Toll-Like Receptors 2 and 6). Various signaling molecules take part in the
signaling pathway process; they include CARD9, a signaling protein adaptor, NAFT, activated T-cells nuclear factor, and NF-kB (via the Syk-mediated path or pathway). The signaling process ultimately leads to cytokines release; this includes IL-12 (interleukin), IL-6, IL-10, and TNF-α (Tumor Necrosis Factor). Studies underscore the efficacy of the cytokines mentioned above in cancer therapies.

Dendritic cells located on the macrophages (ICAM-3-Grabbing Non-Integrin Homolog, SIGNR1 (SIGN-Related 1) - Dendritic Cell-Specific) are among the primary mannose receptors that interact with Dectin-1 in β-glucans’ non-opsonic recognition for phagocytosis. According to various studies, TLR-4 blocking inhibits or prevents the synthesis of IL-10, p40, and IL-12 stimulated by PS-G (Purified Ganoderma Glucans); this, therefore, indicates the vital role played by TLR-4 signaling in the maturation of dendritic cells (glucan-induced). The augmentation of MAPK phosphorylation, NF-kB function, and IκB kinase can also create or produce the effect mentioned above. Lentinan, a type of mushroom-extracted β-glucan has the capacity to cohere to the scavenger receptors located on the myeloid cell surfaces and trigger various signaling pathways which include MAPK (Mitogen-Activated Protein Kinase), p38 and Akt kinase, PI3K (Phosphatidylinositol-3 kinase). B-glucans derived from Candida albicans are the only pathogenic fungal beta glucans with the capacity to bind and activate the LacCer receptors and PI-3K pathways respectively to control neutrophil migration effectively. However, these activation pathways may contain other molecules located in β-glucans extracted from Candida.

Studies indicate that β-glucans are capable of inducing cell proliferation in the peripheral cells of the blood mononuclear. Additionally, β-glucans can facilitate functional and phenotypic maturation of dendritic cells derived from the monocytes with the significant production of IL-10 and IL-12. Another study also recorded similar findings using PS-G. In a particular study, dendritic cell treatment using PS-G led to the significant increases in stimulatory capacity of T cells and significant increases in the secretion of IL-10 and interferon-γ by the T cells.
The functioning of the adaptive system occurs via the T cells and antigen-presenting cells’ (accessory cells) integrated action. The antigen presentation of MHC-I (Major Histocompatibility Complex –Class I) to cytotoxic T cells (CD 8{+}) is constrained particularly to proteosome-secreted peptides produced by intracellular infectious agents. The endocytic pathway of MHC-II, on the other hand, only presents proteolytic peptides to T helper cells (CD 4{+}); these peptides are usually derived from extracellular pathogens. Studies indicate that carbohydrates can trigger immune reactions solitarily without T cells. Nonetheless, zwitterionic polysaccharides (those which bear negative and positive charges), for example, β-glucans have the ability to activate CD4{+} T cells via the endocytic pathway (MHC-II). Nitric oxide –mediated mechanisms facilitate the processing of β-glucans to carbohydrates of low molecular weight which subsequently bind to Class II MHC-II within cells like dentritic cells (antigen-presenting cells) for presentation. The mediation of β-glucan through the activated CR3 (Complement Receptor) located on lymphocytes, neutrophils, and NK cells (Natural Killer) is another β-glucan action mechanism. The pathway mentioned above accounts for β-glucans’ opsonic recognition which enhances the lysis of reactor cells and phagocytosis. B-glucana usually nind to the CR3’s lectin domain and prime it following its binding process to iC3B (Inactivated Complement 3b) on the reactor cells’ surface. The activated circulating cells of β-glucan, for example CR3 that contains neutrophils, then triggers cell lysis on tumor cells coated with iC3b. Multiple NK cells in humans express CR3. Studies indicate that the opsonization process of iC3b-coated NK cells causes an increase in target lysis. CR3 molecule’s beta chain (CD18) plays a critical role in the binding of β-glucan.

Additionally lactosylceramide and scavenger receptors can bind to β-glucans and have the capacity to elicit various responses. B-glucans are capable of enhancing the clearance of endotoxin through scavenger receptors by minimizing or reducing the secretion of TNF; this subsequently enhances a significant increase in rat survival following the exposure of rats to Escherichia coli sepsis. Moreover, the cohering of β-glucans to lactosylceramide receptors can facilitate the proliferation of myeloid progenitor and the oxidative outburst response of neutrophils; this, in turn, leads to the significant increases in anti-microbial activities of leukocytes. The binding process mentioned above also enhances the NF-kB activation in human neutrophils. Studies reveal that β-glucans exhibit modulatory activities with reference to immunoglobulin production and T-cell response bias shift. In a specific in vitro study, β-glucans (1,3) extracted from Saccharomyces cerevisiae inhibited the immune reaction of Th1 and improved the immune reaction of Th2; this, in turn, enhanced the anti-inflammatory cytokines’ release, for example, TGF-b and IL-10. Another in vivo experiment, on the other hand, demonstrated the effectiveness of β-1,3-glucan (mushroom) in reducing the immune response of Th2 (OVA-induced) and increasing the immune response of Th1. B-glucans are utilized widely in the food and aquaculture sector due to their immunostimulatory activity. One particular study revealed that β-glucans enhanced the rates of survival of experimental animal (rats) significantly following their pathogenic parasite or microbe infection. Additionally, β-glucans demonstrate their prospective use in therapy. For example, studies indicate that HBV mediated immune suppression in the microenvironment of the liver triggers ineffective immune system responses (an obstruction for virus elimination).

B-glucan and its subsequent derivatives are widely being developed into vaccine delivery systems or vaccine adjuvants because they PRR-recognizable and easily accessible. In multiple vaccine creation, beta glucans obtained from various sources show outstanding supplemental actions to vaccines in administration routes and animal models. For instance, a particular study discovered that β-glucan diet enhanced the potency of the immune response to vaccine by facilitating a significant increase in adaptive and innate immune responses through cytokine gene (IL-12 and INF-c) transcriptions.

How β-glucan works in Wound Healing

Dermatology is one promising field of β-glucan application; this field incorporates aspects such as wound healing and care. There is a significant increase in the topical or contemporary application of β-glucan; this is primarily due to its pluripotent activity (rejuvenation, moisturization, radioprotection, immunomodulation, regenerative effects, anti-inflammatory, and antioxidant effects) which act as a prospectively compatible therapy in the management of different skin conditions and diseases. Additionally, specific β-glucans constitute various anti-infective features and demonstrate prospective anti-bacterial activities against an extensive spectrum of Gram-negative and Gram-positive bacteria. B-glucans, therefore, present an effective wound healing element with an extensive biological activity range and great stability. Wound healing refers to a complex procedure that involves various extracellular and cellular matrix cells (for instance, leukocyte subtypes, nerve cells, mast cells, endothelial cells, fibroblasts, and keratinocytes), and components which play different roles in the three overlapping stages of healing (tissue remodeling, cell proliferation, and inflammation). Cell-surface receptors such as cutaneous cells and immunocytes mediate the response and recognition of β-glucans. There are two possible modes of action associated with the immunostimulatory activities of β-glucans in wound healing: Direct influence or effect on fibroblasts and keratinocytes and the indirect activation via different macrophage cytokines. B-glucan’s release stimulates various growth elements from activated macrophages which consequently support activities such as the increase in the strength of wound tensile, etc.
reepithelialization, angiogenesis, and cellular proliferation. Below is a schematic demonstration of the pluripotent mechanisms of β-glucan.

![Schematic demonstration of the pluripotent mechanisms of β-glucan in wound healing.](image)

**Fig 3: Schematic demonstration of the pluripotent mechanisms of β-glucan in wound healing.**

**In Vitro Experiments**

B-glucans have important biological properties that are critical to the process of wound healing; these properties include immunomodulatory and anti-inflammatory properties. B-glucans accelerate the process of healing in both acute and chronic wounds. A prolonged or extended inflammatory phase typifies chronic wounds. During this phase, macrophages located in the granulation tissue act as an effective source of inflammatory cytokines and growth factors (TNFα, IL-1β, and IL-6) after stimulation with beta glucan. Dectin-1 receptor mediates the pro-inflammatory process mentioned above. Macrophages have the capacity to stimulate various cells, for instance, fibroblasts and keratinocytes which enhance the reepithelialization process of the wound and creates the granulation tissue. B-glucan also exhibits direct antimicrobial activity in in-vitro studies against various bacterial species; they include *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* and indirectly by facilitating macrophage phagocytic activities and bacterial challenge resistance. Studies reveal that β-glucan derived from oats show antimicrobial effects against *Bacillus subtilis* and *Escherichia coli*. In the study, native β-glucans exhibited a thirty-five percent inhibition rate towards bacterial growth. Cationic β-glucans, on the other hand, demonstrated an eighty percent inhibition capacity in both bacterial types. The above outcomes indicate that β-glucan has enhanced antibacterial effects.

**Clinical Evidence for the Utilization of β-Glucans in the Management of Non-Healing Burns and Wounds in Humans**

In spite of the plethora of published information on in vivo and in vitro β-glucan impacts on wound healing, researchers have conducted only few clinical studies on humans, using β-glucans in the management of wound care. According to www.clinicaltrials.gov, an online web
source (date: October 1st, 2018) two randomized clinical research involving humans with approximately eighty participants per trial, focusing on the treatment of venous leg ulcers and diabetic foot ulcer using β-glucan products are currently in progress. The first human clinical study whereby authors assessed the efficacy of β-glucan cream (content: pleuran derived from Pleurotus ostreatus) as a contemporary treatment for venous ulcers saw publishing in a scientific meeting proceeding. The study was a non-randomized trial typified by intergroup comparisons through time. The study involved the application of B-1, 3 glucan (water-soluble) isolated or extracted from Saccharomyces cerevisiae (inform of a cream) with an ultimate concentration of three-percent (w/w) onto the ulcer bed of twelve patients directly. The execution of the procedure went on up to the ninetieth day (daily). According to the authors, the average percentage of ulcer reduction was 11.3 percent after a treatment period of thirty days and 55.23 percent after a treatment period of ninety days. Studies indicate that insoluble β-glucan enhances the healing of venous ulcers and increases epithelial hyperplasia. Moreover, β-glucan (insoluble) causes significant increases in fibroblast and plasmocyte proliferation. Four clinical researches (human) involving less than ninety participants revealed that β-glucan has the capacity to accelerate or enhance the wound healing process of chronic wounds. Amid the four studies mentioned above, two utilized water-soluble beta glucans. The other studies (two) employed the use of water-soluble β-glucans. One study was a double-blind controlled trial (placebo).

Various clinical trials indicate the efficacy of β-glucans in healing of burn injuries. In a study involving forty-three patients, a collagen matrix of β-glucan was utilized as the main wound dressing element during the treatment of pediatric burns (partial thickness). In the study, β-glucan was effective in reducing wound pain, improving the healing process of the wound, and it generated excellent cosmetic outcomes in seventy-nine percent of the patients. However, the authors failed to document the adverse impacts of β-glucan during the treatment procedure. The treatment procedure of severe wounds is intensive and protracted and associated with significantly high costs. Numerous approaches or strategies have been created to enhance the treatment of chronic wounds; this also includes topical or modern wound care therapies. The primary reasons behind the use of natural products include low treatment costs and the potential absence of the risk of antimicrobial resistance. A study aimed at analyzing the economic benefits of beta glucan gel in the treatment process of diabetic foot ulcer indicated cost savings of 503.00 £GBP per patient on a yearly budget. The study employed the use of Markov cohort model of simulation. Moreover, β-glucan gel enhanced the healing process of ninety-four percent wounds compared to the seventy-eight percent healing process enhanced by standard care.

B-Glucan sterilization and its Effect on the Bioactivity of β-glucan
β-glucans are currently among the efficient topical agents used in the treatment of severe burns and chronic wounds. Licensed care products for wound dressing which contain β-glucan ought to undergo the process of sterilization. In fact many human clinical testing therapeutic compositions require sterilization which should also meet strict regulations. The sterilization process of products that contain β-glucan is essential due to the availability of potentially harmful contaminants, for example microbial spores and vegetative bacteria. Some conventional sterilization techniques, for instance, heat and ethylene oxide may generate negative impacts on the physical and chemical properties of products and may, subsequently alter the biological properties of β-glucan. Other sterilization procedures, for example, filtration are difficult to execute, particularly on polymeric viscous solution, and are time consuming; this, thus, calls for the adoption of other forms of sterilization.

Gamma Irradiation
The use of gamma irradiation, electron beams, and x rays may cause chemical and physical changes in the structure of β-glucan. However, the techniques mentioned above are effective in reducing β-glucan’s molecular weight to reduce their viscosity, and increase their permeability into various cells, and increase their solubility. Gamma sterilization is a significantly simple procedure which causes significant increases in β-glucans’ functionality. Multiple studies aimed at investigating the impact of irradiation on the pharmacological and biological properties of β-glucan have been conducted. Different doses of gamma irradiation are used during the irradiation process; these doses range from two to seventy-five kGy. Significant decreases in the non-irradiated beta glucans’ molecular weight starts taking place at low irradiation doses of approximately eight kGY. Amid the studied doses of irradiation, fifty kGy proves to be an appropriate dose that allows the maintenance of excellent functional and antioxidant properties. Increasing the dose of gamma irradiation often enhances the physical properties, for instance, compressive strength, and gel fraction of irradiated beta glucans. Gamma irradiation is also used in the preparation of fabricated hydrogels of beta glucan which are effective in wound dressing.

An irradiated beta glucan has the following properties:
- Significantly higher antimicrobial activities than the native samples.
- Enhanced antiproliferative, antitumor, and antioxidant activity than the native samples
- Enhanced immune system response; this implies that the small molecules of β-glucans (irradiated) have a significantly high chance of binding to receptors.
DISCUSSION
B-glucans are polysaccharides that occur naturally. These glucose polymers are synthesized by various plants, for instance, seaweed, barley, mushrooms, and oats. B-glucans make up the cell wall of various pathogenic bacteria and fungi (Saccharomyces cerevisiae); these bacteria include Cryptococcus neoformans, Pneumocystis carinii, and Candida albicans. B-glucans’ immunomodulatory activity have been researched for years and these evaluations center essentially on the impacts of cytokines secretion, immune cells’ functional changes, and shifts in the response bias of Th2/Th1. Recent data indicate that β-glucans are effective immunomodulators which influence both the adaptive and innate immunity. The innate immune system’s capacity to quickly identify and respond to an attacking pathogen is necessary for controlling infections. β-glucans exhibit both anti-inflammatory and pro-inflammatory activities. For instance, in human macrophages and monocytes, β-glucan derived from mushrooms had a stimulating effect on the secretion of pro-inflammatory cytokines which include TNF-α, IL-1b, IL-6, and IL-8. Contrarily, β-1, 3-glucan and β-1, 6-glucan from a similar source demonstrated substantial anti-inflammatory activity against lipopolysaccharide-induced inflammation. B-glucans also exhibit modulatory activities on the T-cell response bias shift and the forms of immunoglobulin synthesis. For instance, an in vitro study demonstrated that β-1, 3-glucan derived from Saccharomyces cerevisiae enhanced the immune response of Th2 and inhibited the immune response of Th2 by facilitating the anti-inflammatory cytokine release, for example, TGF-b, and IL-10. B-glucans also have various antioxidant and anti-infectious properties as detailed in the paper.

Human clinical trials and in vivo experiments provide compelling evidence concerning the effectiveness of β-glucans in wound treatment. These studies indicate that the β-glucan products including nanofibers and hydrogels with β-glucan molecules enhance the healing and repair of moist wounds mainly because of the activation of the cutaneous and immune cells. Gamma irradiation is the most effective method of sterilizing β-glucan. Nonetheless, more clinical studies on humans should be done to prove the effectiveness of β-glucan in wound dressing and in the treatment of an extensive spectrum of acute burns and wounds.

CONCLUSION
B-Glucans are glucose polymers derived from various sources, for instance, fungus, grain, and yeast and they belong to a drug category referred to as biological response modifiers. Many studies demonstrate the effectiveness of β-D-glucans (soluble or particulate) in enhancing various immune functions or roles such as immunomodulatory, antitumor, and anti-inflammatory activity. Several receptors mediate the process of β-glucan actions or activities in the organism; they include the lactosylceramide, scavenger receptor, CR3 (Complement Receptor 3), TLR-2, 4, 6 (Toll-Like Receptors), and Dectin-1 Receptor. Human clinical trials and in vivo experiments provide compelling evidence concerning the effectiveness of β-glucans in wound treatment. These studies indicate that the β-glucan products including nanofibers and hydrogels with β-glucan molecules enhance the healing and repair of moist wounds mainly because of the activation of the cutaneous and immune cells. Gamma irradiation is the most effective method of sterilizing β-glucan. Nonetheless, more clinical studies on humans should be done to prove the effectiveness of β-glucan in wound dressing and in the treatment of an extensive spectrum of acute burns and wounds.

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