Yeast β-Glucan with Immune-Modulatory Properties

Subjects: Immunology

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β-glucans are a large class of complex polysaccharides with bioactive properties, including immune modulation. Natural sources of these compounds include yeast, oats, barley, mushrooms, and algae. Yeast is abundant in various processes, including fermentation, and they are often discarded as waste products. The production of biomolecules from waste resources is a growing trend worldwide with novel waste resources being constantly identified. Yeast-derived β-glucans may assist the host's defence against infections by influencing neutrophil and macrophage inflammatory and antibacterial activities. β-glucans were long regarded as an essential anti-cancer therapy and were licensed in Japan as immune-adjuvant therapy for cancer in 1980 and new mechanisms of action of these molecules are constantly emerging.

Keywords: β-glucans ; yeast ; bioactive properties ; anti-cancer ; immune-modulation

1. Introduction

Bioactives such as β-glucans have anti-cancer, anti-inflammatory, and immunomodulatory properties [1][2][3][4]. Sources of β-glucans are diverse but can be initially divided into cereal sources, including oat and barley, and non-cereal sources, such as mushrooms, yeast, algae, and bacteria [5]. Classification of β-glucans is essential, as origin dictates structure, which greatly influences biological activity. Firstly, all β-glucans are homo-polysaccharides composed of glucose units [6][7]. Secondly, they all possess a 1,3 linked backbone fundamental to their activity [8].

Structural contrasts occur in the branching off the 1,3 backbone; the molecule can be branched at various locations and can also be non-branched [9]. Cereal-derived β-glucans have a very different branching structure than non-cereal-derived. There are also inter-source variations. Branching at the 1,4 position is characteristic of cereal derived β-glucans, whereas branching at the 1,6 position is characteristic of non-cereal derived β-glucans [10][11]. β-glucans, usually from non-cereal sources, can also contain no branching, such as Curdlan, isolated from *Agrobacterium* [12].

Cereal derived β-glucans have a primarily metabolic effect, including the modulation of the gut microbiome and cholesterol reduction, reducing cardiovascular issues. Non-cereal-derived β-glucans elicit their effects usually through interaction with the immune system. Therapeutic effects include anti-inflammatory, anti-cancer, and anti-infective properties [5]. Recognition by immune cells is not exclusively linked to branching but to the length of the polysaccharide polymer and its tertiary structure as well [8][13].

Other influences on final conformational structure aside from the originating source include extraction procedure and growth or culture conditions [14]. Herein lies the hurdle of the clinical translation of β-glucans. There are substantial structural variances between β- glucans, including those originating from the same source. These variances include the chain length of the backbone and branching, type of branching, and 3D conformational structure, which can display a random, single helix, or triple helical structure [15]. Thus, research groups are reporting differences in activity which can be seen in an abundance of in-vitro and in-vivo tests and clinical trials registered for the use of β-glucans. β-glucans have been extensively studied in infectious illnesses and tumour immunology.

Yeast cells are an abundant source of β-glucans and are well documented for their biological activity in both humans and animals [5][16]. *Saccharomyces cerevisiae* (*S. cerevisiae*), or baker's yeasts, are the most often utilised in winemaking and brewing [17][18][19]. Usually, β-glucans are found in residues and byproducts from these applications. One-third to one-half of the yeast's cell wall is made up of β 1,3-glucan, whereas β 1,6-glucan makes up 10% to 15% of the polysaccharide in the cell wall [20]. This branched structure is a known bioactive that is often discarded as a waste byproduct.

2. Yeast as a Source of β-Glucans

Yeasts are unicellular fungi that reproduce asexually through budding or fission and sexually through spore formation. Currently, 500 yeast species are recognised. The most often used yeasts are *S. cerevisiae*, which are used in winemaking

and brewing [17] and the creation of a variety of nutraceutical goods [18][21]. Most commercially available hormones are produced using recombinant *S. cerevisiae.* Insulin and glucagon are two of these hormones [22].

S. cerevisiae has a thick cell wall made up of polysaccharides and proteins which protects the inner compartments of the cell [23][24]. Up to 55% of the cell wall is composed of β-glucans of 1,3 linkage and 12% of 1,6 β-glucans [23][24]. Yeast-derived β-glucans contain a linear backbone of (1,3)-linked D-glucose molecules with (1–6) side chains of various lengths. In yeast β-glucans, synthesis can occur in various cell regions. The formation initially occurs in the plasma membrane and is then catalysed enzymatically. The enzyme involved in β-glucan synthesis is β-glucan synthase, encoded by the FKS1 and FKS2 genes [25]. The synthase linked to the cell membrane of *S. cerevisiae* employs UDP-glucose as a substrate [26] [27].

S. cerevisiae is an industrial microorganism used for protein, chemical, and metabolite synthesis. The unicellular eukaryote is one of the most researched and utilised industrial microorganisms. It is used to make numerous industrial compounds and heterologous proteins in addition to alcohol fermentation, baking, and bio-ethanol processes [28]. Beer production can generate important byproducts in the form of spent brewer's yeasts which contains β-glucans [29].

3. Production of Yeast β-Glucans from Waste Streams

Biotechnological and commercial interest in the manufacture of yeast is continuing to grow for applications including food, livestock feed, medicinal, cosmetic, and wastewater treatment applications [30].

Numerous cultivation variables, such as the type and availability of carbon and nitrogen sources, the cultivation temperature, pH, degree of aeration, osmotic pressure, time of incubation and growth phase, and mode of yeast propagation all affect the content and characteristics of structural polymers in the yeast cell wall [31][32][33].

The polymerisation of yeast β-glucans depends on external factors, including the growth phase and carbon source [34]. The chemical structure and concentration of the polysaccharide are also determined by the species' genetic profile [35]. Thus, yeast β-glucans have a variety of lengths, which may be quantified analytically. Conventional chemical characterisation techniques include Fourier transform infrared (FT-IR) and Nuclear magnetic resonance (1_HNMR) which determine the structure of a molecule [36]. The characterisation is vital as the chemical structure and function will all have effects on the immune counterpart interaction.

Yeast may be quickly grown in a variety of different growth conditions. The biomass of food-grade yeasts is chiefly produced using traditional substrates such as molasses, a byproduct of the sugar industry. Additionally, starch, distiller's wash, whey, fruit and vegetable wastes, and unusual materials such as petroleum byproducts can also be used [37].

Although yeast β-glucans are usually produced in laboratories using biotechnological processes, they can also be sourced as byproducts from industrial processes. The environmental impact of industrial wastes derived from food sources is a challenge, reuse and disposal options are continuously being researched and tested. Byproducts of the food sector, potato juice and glycerol are two examples, are rich in nutrients and can be used as a digestate for microorganisms through recycling. Potato juice and glycerol are byproducts of the manufacturing of potato starch and biodiesel, respectively [38][39]. These two byproducts were utilised in research by Bzducha-Wróbel et al. (2015) to develop yeast, alter the cell wall structure, and acquire yeast biomass, eventually increasing the amounts of (1,3)/(1,6)-glucans. Interestingly, the Y.B.D medium, deproteinated potato juice, and 5–10% glycerol as a carbon source enhanced β-glucans synthesis from 31% to 44% [40].

Chotigavin et al. (2021) studied the effects of tannic acid on *Saccharomyces carlsbergensis*, a brewer's yeast. Beer fermentation produces a lot of waste. Tannins are utilised in brewing while mashing the hot wort. Tannins interact with the yeast cell wall to form polysaccharides and cause stress in yeast cells which is counteracted by a buildup of β-glucans in the cell wall. Tannic acid increases the thickness of the β-glucan-chitin layer while decreasing the mannoprotein layer. Thicker cell walls correspond with higher carbohydrate and β-glucan levels. The addition of 0.1% w/v tannic acid boosted β-glucan synthesis and content by 42.23%. The stirred tank culture produced 1.4 times more β-glucans than the shaking flask culture [41][42][43].

A novel source for the commercial synthesis of yeast β-glucans was investigated by Varelas et al. (2016). The group isolated β-glucans for the first time from winery spent yeast biomass. During the winemaking process, a byproduct known as wine lees is produced. Most byproducts include spent yeasts, bacteria, tartaric acid, ethanol, phenolics, and pigments. Thus, β-glucans can be sourced from the yeast waste biomass that accumulates in wine tanks throughout the winemaking process. This study showed that the isolated β-glucans contained some amount of tartaric acid and polyphenols, which

could not be omitted. Considering wine lees, especially red ones, are more complex mixes than brewery wastes, the purity of β-glucans in wine lees samples was lower than the purity reported by other studies from brewery wastes [44]. Nonetheless, this work identifies a valuable waste source of β-glucans that are most often disposed of in landfills.

The structure and content of molasses yeast β-glucans were investigated using High-Performance Liquid Chromatography (HPLC) and NMR [45]. In addition, the effects of β-glucans on the Abelson leukaemia virus-transformed monocyte/macrophage cell line (RAW 264.7) challenged with LPS were investigated. The product yield was reduced due to the yeast cell state. Compared to freshly produced yeast in the laboratory, the yeast waste material was damaged and partially deactivated before extraction. The β-glucan sample demonstrated very effective immune-modulating properties. The extract significantly suppressed TNF-α compared to the positive control and considerably reduced IL-6 production [45].

4. Pathogen Associated Molecular Pattern Recognition

Immune system effectiveness is crucial for eradicating pathogens rapidly and successfully. The immune system is broadly divided into innate or nonspecific immunity and acquired or specific immunity. Innate immunity is the initial line of defence against nonspecific invaders and is instantaneous. Monocytes, macrophages, dendritic cells, and neutrophils are all included in the innate system. Acquired immunity is a more gradual response that occurs after the initial contact and is dependent on B-cells and T-cells. Following the first exposure, the secondary reaction is swift. Both innate and adaptive immune cells are interdependent.

Immune cells recognise β-glucans as foreign material or pathogen-associated molecular patterns (PAMPs) as they are prevalent in microbial cell walls. Microbial-based PAMPs are also known as MAMPs. Pathogen recognition receptors on immune cells and mucosal membranes identify and bind these patterns (P.R.R.s) [46]. To exert their biological effects, immune cells must identify β-glucans via P.R.R.s. C-type lectin receptors (CLRs) detect fungal signals [47].

4.1. β-Glucan Induction of Trained Immunity

Initially, it was believed that innate immune cells behaved randomly and lacked the potential for immunological memory. The trained immunity hypothesis implies that innate immune cells respond more effectively and rapidly to viral and microbial infections before sensitisation with specific microbial components (including yeast-derived β-glucans). It has been claimed that stimulants such as β-glucans can induce it [48][49][50], as a result, when these cells are exposed to β-glucans, they build a “memory” which improves their capacity to fight infection [51][52]. Administration of β-glucans primes the immune response to recognise future microbial insults.

The induction of trained immunity is a potential technique for defending against bacterial and viral illnesses. This is achieved by epigenetic reprogramming in innate immune cells, resulting in increased cytokine production and metabolic alterations that shift the cell’s metabolism away from oxidative phosphorylation and glucose fermentation. When these epigenetically “trained” cells encounter secondary stimuli, they are programmed to respond more robustly to those stimuli [53]. Studies suggest that β-glucans can be used in vaccinations as adjuvants. This is because β-glucans activate and modify all parts of the immune system because they induce long-lasting, effective immunity that is widely protective, thus increasing antigen recognition [54].

5. Recognition Receptors for β-Glucans

Dectin-1 is often referred to as the β-glucan receptor. Dectin-1 is expressed on monocytes, macrophages, neutrophils, dendritic cells, and T lymphocytes, activated by the binding of β-glucans [55][56]. The receptor is also present in mucosal immune cells where pathogens invade. By regulating the inflammasome and transcription factor activation, this binding generates cytokines, chemokines, and reactive oxygen species (ROS) [46][57][58]. This recognition relies on the 1,3 backbone [59]. Several other receptors react to β-glucans, including lactosylceramide, scavenger, and Toll-like receptors [55][60]. Toll-like receptor (TLR2) binding causes ROS, pro-inflammatory indicators, and pathogen clearance phagocytosis [61]. The pathway activated after binding can either stimulate the immune response and initiate a cascade of inflammatory mediators or, in contrast, dampen down inflammation through modulatory processes [16].

When β-glucans bind to Dectin-1, it increases phosphorylation of its intracellular immunoreceptor tyrosine-based activation motif (ITAM) and Syk and activates the PI3K/Akt pathway. This finally results in phagocytosis, the creation of ROS, microbial death, and cytokine release [62][63][64]. A more detailed graphical representation of this process can be found at [65][66].

Neutrophils, monocytes, and natural killer (NK) cells express the CR3 receptor. CR3 is distinctive in that it contains two different binding sites for ligands. A carbohydrate-binding lectin-like domain, which can bind β-glucans, serves as the second ligand-binding site. Binding will enhance cytotoxicity against iC3b-opsonized target cells such as tumour cells, phagocytosis, and degranulation [67]. The CR3 produced by innate cells such as macrophages, dendritic cells, natural killer cells, and neutrophils binds to yeast-derived low molecular weight soluble β-glucans. The CR3 receptor is activated by the binding of soluble β-glucans and iC3b, and this leads to the destruction of tumour cells coated with iC3b through CR3-dependent cellular cytotoxicity (DCC) [68].

6. Yeast β-Glucan Administration to Humans

Yeast β-glucans' are currently registered for a range of clinical trials on clinicaltrials.gov (accessed on 28 March 2022) as outlined in **Table 1**. In terms of administration, oral glucan has been investigated the most, but intravenous and intraperitoneal glucan injections have also been employed. Oral glucans are phagocytosed by intestinal epithelial cells or pinocytic microfold cells (M-cells), which transfer glucan from the intestinal lumen to immune cells within Peyer's patches [13][69]. Conversely, in humans, researchers found no changes in cytokine production or the microbicidal activity of leukocytes after seven days of oral glucan ingestion, and no glucan itself in volunteers' serum [70]. They are also administered for different interventions. The immune-modulatory properties and anti-cancer properties dominate the majority of studies carried out.

Table 1. Registered clinical trials on yeast β-glucan as a potential therapeutic agent. Information from clinicaltrials.gov (accessed on 28 March 2022). * n/a; information not available.

Clinical Trial Number	Title	Yeast β-Glucan Dose	Disease	Phase
NCT03495362	The Effect of Insoluble yeast Beta-glucan Intake on Pre-diabetic Patients	Oral administration of 500 mg insoluble β-glucan twice a day	Pre-diabetic	n/a *
NCT05074303	Beta-glucan and Immune Response to Influenza Vaccine (M-Unity)	Oral administration of 500 mg/day	Influenza Vaccine	Phase I
NCT00492167	Beta-Glucan and Monoclonal Antibody 3F8 in Treating Patients with Metastatic Neuroblastoma	Oral administration Dose escalation	Neuroblastoma	Phase I
NCT01829373	Lung Cancer Vaccine Plus Oral Dietary Supplement	Oral administration	Lung Cancer	Phase I
NCT01727895	Effects of Orally Administered Beta-glucan on Leukocyte Function in Humans (BG)	Oral administration of 2 capsules of 500 mg/Daily	Immunologic Deficiency Syndromes	n/a
NCT04798677	Efficacy and Tolerability of ABBC1 in Volunteers Receiving the Influenza or COVID-19 Vaccine	Oral administration Powder for dissolution in water	Immunity Vaccine Reaction Influenza COVID-19 Cytokine Storm Immunologic Deficiency Syndromes	n/a

Clinical Trial Number	Title	Yeast β-Glucan Dose	Disease	Phase
NCT03782974	A Follow-up Trial of Proglucamune® in the Treatment of Protective Qi Insufficiency, a T.C.M. Condition	Oral administration of 100 mg/day	Protective Qi Insufficiency (a Condition Term from T.C.M.)	n/a
NCT04710290	A Cohort Study of Beta-Glucan or Beta-Glucan Compound in Metastatic Cancers	Oral administration of beverage powder or capsule	Metastatic Cancer	Phase II Phase III
NCT01910597	Phase I, Dose-Escalation Study of Soluble Beta-Glucan (S.B.G.) in Patients with Advanced Solid Tumours	n/a	Advanced Solid Tumours	Phase 1
NCT04301609	Clinical Trial to Assess the Improvement of Fatigue, Sleep Problems, Anxiety/Depression, Neurovegetatives Alterations, and Quality of Life After the Administration of ImmunoVita® in Chronic Fatigue Syndrome Patients	Oral Administration	Chronic Fatigue SyndromeMyalgic Encephalomyelitis	n/a
NCT04387682	Myeloid-derived Suppressor Cells (MDSCs) in OSCC Patients	Dietary Supplementation	Squamous Cell Carcinoma of the Oral Cavity	n/a
NCT03717714	Polycan in Combination with Glucosamine for Treatment of Knee Osteoarthritis	Oral Administration of 50 mg/day	Osteoarthritis of the Knee	n/a
NCT01402115	A 12-week Human Trial to Compare the Efficacy and Safety of Polycan on Bone Metabolism	Dietary Supplementation	Bone Health in Perimenopausal Women	Phase II Phase III
NCT04810572	Nutraceutical Composition Containing Natural Products Derivatives on the Modulation of the Endocrine Neuroimmune Axis (NCCNPDMENA)	Dietary Supplementation	Insulin Resistance Inflammatory Bowel Diseases Obesity Healthy	n/a
NCT00911560	Bivalent Vaccine with Escalating Doses of the Immunological Adjuvant OPT-821, in Combination With Oral β-glucan for High-Risk Neuroblastoma	Oral Administration of 40 mg/kg/day	Neuroblastoma	Phase II Phase III

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