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Review

β-Glucans from Yeast—Immunomodulators from Novel Waste Resources

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Abstract: 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. This paper outlines yeast β-glucans' immune-modulatory and anti-cancer effects, production and extraction, and their availability in waste streams.

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

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1. Introduction

Bioactives such as β-glucans have anti-cancer, anti-inflammatory, and immunomodulatory properties [1–4]. 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 homopolysaccharides 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 [17–19]. 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.

This review will focus on yeast β-glucans, their production from waste streams, and their vast effect on the immune system which can reduce infection, as well as target cancerous cells. This review also discusses the benefits of administering β-glucans from yeast to livestock to prevent infection and replace antibiotics and concludes with methods of extraction, which are fundamental to activity.

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 [31–33].

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 [41–43].

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].

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 [48–50], 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 [62–64]. 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
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

Table 1. *Cont.*

Clinical Trial Number	Title	Yeast β-Glucan Dose	Disease	Phase
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

6.1. Immune-Modulatory Effects of Yeast β-Glucan

Clinical trials, including baker's yeast β-glucan, indicated favourable benefits for upper respiratory tract infections [71,72]. Administration of β-glucan from brewer's yeast in two randomised, double-blind, placebo-controlled clinical trials reduced the incidence of common cold episodes in healthy subjects. Some studies have also demonstrated that β-glucan positively enhances the immune system after exercise [73,74]. When yeast β-glucan was provided prophylactically before cycling activity, it affected the production of cytokines in response to heat and exercise [75].

In another study, when Yestimun, a commercial β-glucan from yeast, was administered in winter, upper respiratory tract infection (URTI) was significantly reduced during the first seven days of an episode. In this study, the incidence of URTI, severity, and duration were measured. Results demonstrated that supplementation with β-glucan over 16 weeks reduced the severity of physical URTI symptoms during the first week of an episode [4]. When yeast β-glucans were distributed to the older population to observe their effects on upper respiratory tract infections, fewer illness episodes in treatment groups than in the control were observed [71,76].

After intensive exercise, physiological reactions can inhibit innate immune function, putting people at an increased risk of getting upper respiratory tract infections. Athletes must be able to perform, tolerate, and recover from strenuous physical activity [77,78].

Supplementing indigestible carbohydrates such as β-glucan can help maintain a healthy immune system. This is because they access the large intestine rather than the small intestine. They are then presented to macrophages at this location. When macrophages are exposed to certain β-glucan, they exhibit increased phagocytic activity and a more anti-inflammatory pattern or phenotype [51,79]. Thus, yeast β-glucan may enhance athletes' resistance to infection during training.

In a study by Zabriskie et al. (2020), the effects of yeast β-glucan on exercise-induced immunosuppression, muscle injury, muscular function, and mood after a long treadmill session were measured. Compared to placebo, supplementation significantly lowered the degree of response and shortened the time course rise in cytokine expression and myoglobin concentrations. In this study, yeast β-glucan influenced muscular function, muscle injury, and mood. MCP-1 is a chemokine that affects monocyte and macrophage motility and infiltration. MCP-1 production affects insulin signalling and muscle-adipose tissue cross talk. MCP-1b down-regulation signals that regeneration has started the second stage of healing. The therapy also reduced M.I.P., MCP-1, and IL-8 levels. TNF-α was similarly reduced following heated treadmill activity. Lower IL-8 levels may also indicate recovery after exercise stress [1,80].

The molecular structure of β-glucan appears to play a role in their efficacy. Yeast β-glucan have a more branched-like network than other glucans, responsible for a more significant increase in biological activity [75]. This has been demonstrated when oat β-glucan did not achieve the same effects as its yeast counterparts. However, oat β-glucan

does have other health benefits but displays different structures [5]. Yeast β-glucan was shown in studies to reduce URTIs' number, duration, and impact. Oat β-glucan was found not to affect upper respiratory infections or other effects on immune function. Yeast β-glucan, as well as mushroom β-glucan, will induce trained immunity in macrophages, which is correlated to their side branching [4,79,81,82].

6.2. Immune-Modulatory Effects of Black Yeast β-Glucan

Aureobasidium pullulans produce a β-glucan extracellularly. A study by Tanioka et al. (2013), analysed the effects of β-glucans isolated from *A. pullulans* on intestinal immune systems in normal and immunosuppressed mice. After treatment, cells from the Peyer's patch (P.P.) secrete higher IL-5, IL-6, and IgA levels. Dendritic cells from the Peyer's patch secreted more elevated levels of IL-6 when treated with the β-glucans. After oral administration, IgA production was higher in the intestine. This work demonstrated that β-glucans have the potential to activate dendritic cells in the Peyer's patches and induce IL-6 and IgA from the Peyer cells [83].

No et al. (2021), investigated a low molecular weight β-glucans isolated from *A. pullulans* and their anti-inflammatory ability by measuring reducing LPS-activated Nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase pathway (MAPKs) in LPS-stimulated RAW 264.7 cells. β-glucans isolated from *A. pullulans*, despite numerous potential benefits, have not translated to clinical application. A reason for this is the high viscosity of the extracellular polysaccharide; therefore, in this study, the authors reduced the thickness and molecular weight using mechanochemical ball-milling and named the extract LMW-AP-FBG. Results demonstrated that LMW-AP-FBG reduced LPS-induced nitric oxide, IL-1β, TNF-α, and IL-6 secretion, with more significant effects observed in the higher doses used. The extract also decreased LPS-induced inflammation by inhibiting NF-κB and MAPK signalling pathways. Other studies using β-glucans *A. pullulans* found that the extract induced the production of IL-5, IL-6, and IgA in the Peyer's patches [1].

The pathophysiology of COVID-19 is characterised by the presence of endothelial dysfunction that characterises pulmonary injury in both epithelial and endothelial cells of the alveolar-capillary barrier [84].

The immunological profile of COVID-19 from pathogenesis through progression to severe illness has been described as distinct, with a cytokine storm measured by elevation of biomarkers such as IL-6 assessed by elevation of markers such as D-Dimer. In this pilot clinical study, the authors describe the positive benefits of β-glucans generated from two strains of *A. pullulans* on biomarkers for cytokine storm in COVID-19 patients. In either of the groups, there was no mortality or need for ventilation of the participants. The combination of β-glucans was effective in lowering D-Dimer levels; they were maintained on day 30. Levels rose in the control group. In COVID-19, IL-6 levels were considerably high and related to poor clinical outcomes. In the current study, IL-6 levels were reduced from levels that predicted more significant mortality due to COVID-19. On day 30, it returned to normal levels in the β-glucans groups exclusively, but it climbed to levels predictive of more significant mortality in the control groups. The addition of β-glucans has aided in preserving the primary biomarkers of clinical severity and mortality of COVID-19 [85]. This study is an excellent prediction of the potential benefits of clinical administration of β-glucans. As this was pilot research with few participants, validation in more extensive multi-centric clinical studies would be required [85].

7. Anticancer Properties

β-glucans do not directly affect cancerous cells and tumours; their anti-cancer effects are elicited through stimulation of the immune response [86]. β-glucans achieve their anti-tumour outcomes by forming a complement complex. After systemic uptake, they are bound by endogenous plasma anti-β glucan antibodies (A.B.A.). This complex activates complement with the complement protein iC3b binding to the A.B.A. [87,88]. This secondary complex binds to immune cells and triggers different immune responses, including

CR3 phagocytosis, which accelerates the killing of antibody-targeted tumour cells [87,88]. Most medicinal β-glucans contain a (1–3) backbone with (1–6) links [89]. Complexity in structure increases anti-cancer properties [90].

Autophagy is a physiological cellular process that degrades and eliminates misfolded proteins and damaged organelles. It is an intracellular degradative process caused by organelle damage, aberrant proteins, and nutritional shortage. Autophagy regulation is involved in both tumour suppression and tumour promotion. Autophagy also modulates the features of cancer stem cells, contributing to their stemness, recurrence, and resistance to anti-cancer treatments [91]. Proteins, damaged mitochondria, and other organelles swallowed by autophagosomes can be destroyed and recycled in autolysosomes by lysosomal hydrolases [92–94].

A study by Wang et al. (2020), discovered an anti-tumour mechanism of water-soluble yeast β-glucan. This study demonstrated that glucans are a natural autophagy inhibitor with high potential in liver cancer treatment for the first time. The polysaccharide inhibited autophagic breakdown by rising lysosomal pH and decreasing the activity of lysosomal cathepsins, resulting in the buildup of damaged mitochondria and the formation of ROS. Additionally, the sugar inhibits hepatocellular carcinoma cell (HCC) metabolism in the glycolysis and tricarboxylic acid (TCA) cycles and induces cell death without nutrients. Further, yeast β-glucan effectively reduced tumour development in a xenograft mouse model and a primary HCC model produced by DEN/CCl4 (diethylnitrosamine/carbon tetrachloride) without any damage.

The data also indicate that β-glucan is a new autophagy inhibitor with solid anti-tumour activity and potential therapeutic use in the clinical treatment of HCC. In immunodeficient BALB/c nude mice, yeast β-glucan exerted significant anti-tumour activity. The mice lack a thymus and are unable to produce T-cells. This data suggests yeast β-glucan exerted direct anti-tumour effects that were not dependent on the immune system [2].

To ultimately establish the yeast β-glucan putative mechanism of autophagy suppression, autolysosome production and lysosomal activity were investigated. The lysosome's low luminal pH (4–5) is required for lysosomal enzyme activation and cargo breakdown. Increased lysosomal pH has been shown to hinder lysosomal autophagosome fusion. The data in this study suggest that yeast β-glucan limits autophagic flux by rising lysosomal pH and reducing cathepsin activity without impacting autophagosome-lysosomal fusion. Autophagy enhances tumour cell survival under stressful conditions such as hypoxia, food deprivation, and treatment resistance. The results of this study demonstrate yeast β-glucan sensitised apoptosis in nutritional deficient HCCs [2].

Studies are ongoing to find a cure for myelosuppression and boost the immune systems of individuals suffering from chemotherapy-induced myelosuppression. A study by Chae et al. (2019) investigated the level of damage to myeloid and lymphoid cell growth induced by chemotherapy medications. The effect of yeast β-glucan on alleviating immunosuppression was studied. I.P. administered gemcitabine at 30 mg/kg was used to reduce red blood cells, white blood cells, and platelets. The treatment also inhibited lymphocyte activity and damaged bone marrow tissue. In gemcitabine-induced immunosuppressed mice, yeast β-glucan treatment increased the activity of immunological effector cells (splenocytes) and hematopoiesis. The therapy also increased the transcription of myelopoiesis-related cytokines in lymphoid organs. β-glucan also boosted splenic natural killer (NK) cell activity against YAC-1 tumour cells. The results suggest that oral yeast β-glucan improves the recovery of immunosuppressed mice from myelosuppression and immunosuppression, typical side effects of chemotherapy. In-vitro work in this study also indicates that β-glucan could restore NK cell activity. This may support the use of β-glucan as adjuvants in cancer treatment to reduce chemotherapy-induced immunosuppression and improve the quality of life for cancer patients [95].

β-glucan, used as an adjuvant, can improve 5-year survival in hepatocellular carcinoma, gastric cancer, and colorectal cancer by up to 15% and reduce recurrence by up to 43%. Oral yeast-derived β-glucan enhances the anti-tumour efficacy of anti-tumour adoptively

transplanted T cells and redirects Myeloid-derived suppressor cells towards an M1-like phenotype, enabling dendritic cell and macrophage recruitment to malignancies [96].

β-glucan boosts the ability of CR3 to destroy tumours bound with iC3b from naturally occurring antibodies and combining β-glucan with complement-fixing anti-cancer mAb augments this action in mice tumour models and humans [97]. The other route through which β-glucan exerts anti-cancer activity is by inducing anti-tumour T cell immunity. Numerous studies have demonstrated the activation or improvement of T cell immunity via the release of suppressor cells generated from myeloid cells, macrophage phenotype 2, or Tregs, and the stimulation of D.C., to be more effective antigen-presenting cells [98,99].

Additional anti-cancer effects of β-glucan have been documented, mediated through the C-type lectin receptor Dectin-1; in these studies, β-glucan therapy affects the balance of stimulation vs immunosuppression in ways that favour anti-tumour immunological responses [98,100].

Alexander et al. (2018) investigated the immunologic pathways underpinning anti-tumour immunity mediated by yeast-derived β-glucan particles. The data establish a unique function for inflammatory monocytes in β-glucan-mediated anti-cancer effectiveness and suggest that this immunomodulator might be an adjuvant to boost immune responses against metastatic illness. The results demonstrate that particulate β-glucan therapy has an anti-cancer impact in a mouse model of pulmonary-metastatic melanoma independent of previously described β-glucan anti-tumour pathways. These findings establish a unique monocyte-dependent mechanism by which β-glucan exerts anti-cancer activity against metastatic pulmonary illness. Additionally, the data indicated that prophylactic β-glucan administration significantly reduced pulmonary tumour burden but had no effect on engraftment, indicating an early innate immune-driven mechanism. The first is the well-established process by which β-glucan binds to and primes CR3 for more significant phagocytosis and cytotoxicity of target cells opsonised with iC3b [101]. The mice model used in this study lacked functional mature B cells, and thus, the authors suggest the CR3-iC3b model is not how this anti-tumour activity is achieved [102].

While monocytes are sensitive to β-glucan, tumour studies have not precisely examined their function in mediating β-glucan anti-cancer effects. To confirm or refute this, the group employed CCR2.DTR animals and allowed them to deplete inflammatory monocytes during the β-glucan therapy period, seeing an abrogation of β-glucan efficiency. These well-established models of inflammatory monocytes insufficiency reveal that β-glucan impact is dependent on inflammatory monocytes [102].

Oral and IV soluble β-glucans boost the immune response's tumoricidal effectiveness, with soluble glucan delivered directly to the bone marrow and tissue macrophages. Macrophages take up intact β-glucans, divided into a 25-kDa active fragment. This active fragment binds to neutrophil CR3, priming effector cells to destroy tumour cells via a CR3-Syk-PI3K signalling cascade, demonstrating that immunological modulation requires β-glucan breakdown into active fragments [103]. Additionally, although I.P. injection of β-glucans has been investigated less than oral administration, several findings demonstrate that I.P. injection has more influence over immunological activity than oral administration [104,105].

Delivery of β-Glucans for Cancer Therapy

β-glucans have also been studied as a delivery vehicle for cancer targeted therapies through dectin-1 signalling. Particle yeast-derived β-glucans are hollow, porous 24 m spheres with an outer shell that induce macrophage phagocytosis. β-glucans have been studied for their hollowness as an encapsulation vehicle to deliver medicines to the tumour microenvironment and, more specifically, macrophages [106].

Studies have also shown that combining β-glucans with tumour antigens may boost innate and adaptive immune responses [107]. β-glucans were used to conjugate a peptide antigen for a well-known cancer biomarker, MUC1. After four vaccinations, only the

conjugate generated high levels of cancer biomarker IgG antibodies. The biomarker binding to β-glucans was required to stimulate immunological responses [89].

Clinical trials have demonstrated that Pembrolizumab with Imprime P.G.G. for chemotherapy-resistant metastatic triple-negative breast cancer showed promising results with a 64.2% 12-month patient survival [108]. Adaptive immunological resistance and the co-stimulatory marker of T cell activation are significantly increased in M2 macrophages and D.C.s treated with Imprime P.G.G. β-glucans [109]. In a phase II clinical study for relapsed Indolent Non-Hodgkin Lymphoma, Imprime P.G.G. with rituximab boosted the production of pro-inflammatory cytokines associated with an M1-macrophage phenotype and expanded activated tumour-infiltrating T cells [110].

8. Administration to Livestock

The European Union outlawed antibiotics as feed additives in 2006, demanding rapid research and development of antibiotic alternatives [111]. With several studies showing β-glucan immunostimulant properties, and the restriction on growth and immunity-promoting antibiotics, they are now being fed to farm animals [112,113]. Antibiotics were routinely used to protect livestock from illness and to stimulate appetites. Resistance to antibiotics and antibiotic residues in food products are frequent effects of antibiotic usage. As a result, there is a persistent need for antibiotic replacement. β-glucan is one such replacement possibility [114].

Vaccinating all animals is time-consuming and costly, so one of the critical benefits of β-glucan is that it may be provided orally and elicit the same effects as if it was administered via another method.

The effects of *S. cerevisiae* yeast on the cell walls of *Salmonella* and *Campylobacter* infected turkeys were studied in-vivo. Fresh faeces were taken for *Salmonella* and *Campylobacter* counts as well as iliac tissue for histomorphological analysis. The group administered yeast cell wall had lower levels of Salmonella and larger villus surface ratios than the control group [115]. The ileum of broilers fed yeast cell walls enhanced *Lactobacillus* and *Bifidobacterium* while decreasing *Clostridium perfringens* [116].

To examine the effect of sulphated yeast β-glucan on immunosuppression, 11-day-old hens were randomly allocated to five groups and given cyclophosphamide once daily for three consecutive days, except for the standard control group. Cyclophosphamide was administered to induce immunosuppression. At 14 days, chickens in three experimental groups received oral sulphated yeast β-glucan from *S. cerevisiae* in three doses for 14 days. At 4 mg/kg, β-glucan significantly increased the bursa index, I.F.N-γ and IL-6 concentrations, decreased TGF-β1 concentration, and promoted lymphocyte proliferation; it also considerably decreased bursa histopathological changes, and improved gut *Bifidobacterium* and *Lactobacillus* populations in chicken caecal digesta compared to the model control group. This demonstrated that G.S.C. might successfully reverse immunosuppression and maintain a healthy gut microbiome [117].

By producing a healthy gut microbiome and encouraging gut development, yeast-derived products have been demonstrated to boost body weight, body weight growth, and feed conversion ratio in broiler diets. In another study, the presence of β-glucan dramatically enhanced the number of goblet cells in chick jejunum, indicating that β-glucan supports gut health. Other studies, on the other hand, discovered no difference [118–122]. A study by Ding et al. (2019) administered yeast β-glucan to investigate growth performance, immunity, and intestinal morphology in chicks. Results demonstrated that growth performances increased after administration. However, the mechanisms by which these effects were achieved are not fully elucidated. White blood cells and lymphocytes were increased in chicks fed the β-glucan diet. These cells are crucial for defence against infection and help restore damaged tissues in the body [123].

9. Extraction and Characterisation of β-Glucans

The yeast cell wall's rigidity avoids external tension, and β-glucans are cell wall components so it is difficult to extract them. A single extraction technique is not always adequate to remove β-glucans from yeast. Because of this, a variety of procedures are frequently employed to extract β-glucans, including heat treatment, ultrasound, and enzymes [124].

The extraction method must not affect the molecule's structure as this is correlated to activity. Aggressive extraction methods can degrade the chains and degree of branching [125]. Therefore, it is better to use gentler methods over a single step aggressive plan to avoid destroying the molecule and reducing its effect. Methods can be chemical, physical, and enzymatic; glass beads can be used to physically rupture the cell wall on specific enzymes and be used to break down the cell wall. Freezing and unfreezing are other methods used to rupture the cell wall [126].

β-glucans exhibit a wide range of properties, including solubility, primary structure, molecular weight, branching, and polymer charge. All of which affect biological activities. Low purity and variability of materials prevent understanding polysaccharide structure-function interactions with cells [127,128]. The correct extraction method is fundamental for activity.

Crude polysaccharides can be extracted using water, physical means (ultrasound and radiation), chemical methods (hot alkali and acid-alkali), natural ways (enzyme method), or a combination of the preceding techniques. Deproteinisation procedures include trichloroacetic acid (T.C.A.), enzymes, and polysaccharide purification by column chromatography or ultrafiltration [129–133].

Ultrasound-assisted extraction (UAE) is a green extraction technique that avoids using strong solvents [134]. UAE accelerates the extraction of molecules but also preserves the structural and molecular characteristics [135].

Ultrasounds (US) are mechanical waves having a frequency over 20 kHz. Two types of US exist: low-intensity and high-intensity US. The low-intensity US is used to test physicochemical properties in the food industry. For the extraction of chemicals of interest, high-intensity ultrasounds are used at frequencies of 20–100 kHz [135].

The effect of operational variables on the UAE β-glucans from barley was investigated in a study by Benito-Román et al. (2013). The operational variables used in this investigation were amplitude, time, and cycles in conjunction with varied ultrasonic powers to increase extraction performance and molecular weight in beta-glucan extraction. The extraction performance is closely related to amplitude and time. When compared to conventional extraction, UAE reduces extraction times and energy usage. The data show that extraction yield relies on amplitude and time, whereas molecular weight decreases with time. The highest extraction yield (66%) is obtained by supplying the most energy (962.5 kJ/L), resulting in the lowest molecular weight (269 kDa). Reduced treatment intensity (energy output of 170 kJ/L) reduces extraction yield to 44.3% but raises molecular weight to 461 kDa. However, while the UAE process improves the extraction yield and molecular weight of β-glucans over stirred tank extraction (3 h, 55 °C, 1000 rpm), the main effect of ultrasounds is the reduction in process time and energy consumption (3 min versus 3 h and 170 kJ/L versus 1460 kJ/L) [136].

Another similar study determined parameters of UAE of polysaccharides from white button mushrooms (*A. bisporus*). The efficient extraction parameters were 230 W ultrasonic power, 70 °C extraction temperature, 62 min extraction duration, and 30 mL/g W/M ratio, yielding 6.02% *A. bisporus* polysaccharides (ABPS). ABPS had a molecular weight of 158 kDa [137].

Additionally, combining ultrasonic waves with microwave-assisted extraction (MAE) for the separation of molecules of interest might yield even more significant advantages [135]. MAE uses microwave energy to heat the extraction solvent directly. The increased pressure and temperature that microwave extraction provides keep the water in a liquid state and above the boiling point. In addition to reduced CO_2 emissions and reduced usage of polluting solvents, this technique is deemed environmentally friendly because

of its improved efficiency and lower energy use. In addition to being more effective and selective, this non-contact heat source may also speed up energy transfer, start-up, and reaction to heating control, and eliminate temperature gradients [138].

Studies have shown that the highest yield of β-glucans from mushrooms using MAE was obtained at 180 °C and 30 min [139]. Other studies have demonstrated that MAE had high reproducibility and was efficient and fast at β-glucan extraction from mushrooms [138]. MAE can be used alone as an extraction technique or combined with other methods such as UAE.

A study characterised four proprietary yeast 1,3/1,6 β-glucan sources. The number of β-glucans and glycogen in each sample established its purity. Each sample's side chain length distribution was determined using an alkaline degradation test followed by ion chromatography. In addition, the purity profile, branching, and linking patterns of each proprietary source of yeast-glucan varied [140].

Glycogen, a 1,4-glucan comparable to starch, is a frequent component co-isolated with yeast β-glucans and downstream purification processes find it challenging to eliminate. It negates the β-glucans' intended health benefit. β-glucan samples from various sources have varying amounts of glycogen. Extraction methods must therefore remove any additional resides which can also affect activity. For example, mannoproteins inside the cell wall are coupled indirectly by 1,6 β-glucans via a glycosylphosphatidylinositol (GPI) anchor and directly by 1,3 β-glucans via linkages that can be broken in alkalis [141].

The manufacturing method can influence the formation structure. It is widely accepted that processing alters the physicochemical properties of β-glucans. Following extraction, linkage analysis is a widely used technique for establishing the relative percentages of each form of linkage in a sample from which % branching may be determined [142,143].

Cell wall β-glucans are insoluble in hot alkaline solutions because they are covalently linked to chitin and other polysaccharides, for example, hydrogen bonds between hydroxyl glucose groups in the main chain. The 1,3 β-glucans solubility is affected by chain length or polymerisation. However, the degree of branching of 1,6 reduces the solubility [125,144].

Together, these factors can enable β-glucans isolated from the same source to take on significantly differing immune-modulating properties [13,145]. Extraction techniques can also have huge effects on β-glucans. Many investigators' uses of high or low pH and temperature settings in extraction procedures also results in molecules altered from their original conformation, changing their immune-stimulatory capabilities [146,147].

There are numerous extraction methods widely available. Brewer's yeast has not been fully utilised as a source of β-glucan because of its low water solubility [148]. J. liepins et al. (2015) analysed the effects of air-drying on the immunologic activity of β-glucan from spent brewers' yeast. Results showed that β-glucan content was not reduced after desiccation, positively impacting the quality of β-glucan extracted. This study also demonstrated that drying improved the immunogenic properties of spent brewers' yeast compared to new biomass β-glucan [148].

A study by Hromadkova et al. (2003) isolated particulate β-glucan from S. cerevisiae cell walls retrieved as water-insoluble particles from an aqueous medium using three distinct drying methods: solvent exchange (G.E.), lyophilisation (G.L.), and spray drying (G.S.). The immunological activity of the glucan samples was determined using mitogenic and comedogenic assays. The results indicated that the physical state of the differentially dried particulate β-glucan samples had a considerable effect on their immunomodulatory activity, which was about double that of the G.L. and G.E. samples. Thus, the authors suggest that it is necessary to adopt spray-dried preparations when using particle 1,3 β-glucan as immunomodulator/adjuvants in aqueous suspension. Other reports indicate that if aqueous β-glucan suspensions are desired, it is advised to spray-dry the samples after isolation [149].

Enzymes can be applied externally to degrade the cell wall and increase cell death and lysis. These enzymes include zymolyase, peptidase, and lysozyme [150,151]. However, enzymes produced by the yeast itself can be used to rupture the cell wall. This process is

called autolysis, in which enzymatically cell death occurs and the cell wall is destroyed, thus releasing the β-glucan [152]. Autophagy is a metabolic process that essentially consumes its own tissue, which happens during famine or illness. In this process, the digestive enzymes are released into the cytoplasm. There are three separate phases: stationary phase, anaphase, and autolysis stage. Due to this enzymatic activity, the cytoplasmic material is entirely liberated by the breakdown of the cell membrane [24]. If left for long periods after the cell undergoes autolysis, the enzymes can begin to alter the polymer in the cell wall.

After cell lysis, the intracellular contents must be removed using a variety of alkaline and acidic chemicals. As the cell wall no longer shields the β-glucan at this point in the removal process, these actions must not damage the β-glucan. Degradation of components necessitates chromatography, filtering, and centrifugation techniques. The extraction of 1-butyl-3-methylimidazolium chloride with an additional precipitation step using water, followed by separation using filtering or centrifugation, is another approach that has been utilised [153]. More detailed and summarised extraction methods can be found in [14,154].

10. Concluding Remarks

Many molecules can interact with the immune system and β-glucans are well established to have immune-modulating abilities. They can also be resourced from waste materials or byproducts. Sustainable, eco-friendly raw material sources have been prioritised to protect the global environment, particularly in the food and cosmetics industries. The fermentation of ethanol using yeast is an innovative process that generates a significant quantity of beneficial byproduct debris. For instance, byproduct yeast from waste material is both safe and valuable. It is an excellent source of protein, vitamin, chitin, and, most significantly, β-glucan. For example, spent yeast is a byproduct and waste material of beer production. Often used as animal feed and substrate for biogas production [152], it can also be utilised as a source of β-glucan. Extraction, separation, and purification are all necessary steps in the production of β-glucan but the extraction and purification processes are critical to its activity [155]. Potential applications to animals and people are numerous, and new ways of exhibiting novel mechanisms of action are continually being developed. Additionally, new mechanisms of action for how β-glucans achieve their effects are constantly unfolding. In a world where waste must be reduced or minimised, it is essential to look at both industrial and agricultural food wastes as sources or mediums for functional bioactive molecules such as β-glucans.

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