Microbiological Research 274 (2023) 127424

Contents lists available at ScienceDirect

Microbiological Research

journal homepage: www.elsevier.com/locate/micres

Sustainable production and pharmaceutical applications of β-glucan from microbial sources

Emma J. Murphy [a,b,*], Emanuele Rezoagli [c,d], Catherine Collins [a], Sushanta Kumar Saha [a], Ian Major [b], Patrick Murray [a]

[a] LIFE – Health and Biosciences Research Institute, Midwest Campus, Technological University of the Shannon, Limerick V94EC5T, Ireland
[b] PRISM Research Institute, Midlands Campus, Technological University of the Shannon, Athlone N37 HD68, Ireland
[c] Department of Emergency and Intensive Care, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[d] School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

ARTICLE INFO

Keywords:
β-glucan
Micro-algae
Yeast
Fungi
Bacteria
Immune-modulation

ABSTRACT

β-glucans are a large class of complex polysaccharides found in abundant sources. Our dietary sources of β-glucans are cereals that include oats and barley, and non-cereal sources can consist of mushrooms, microalgae, bacteria, and seaweeds. There is substantial clinical interest in β-glucans; as they can be used for a variety of diseases including cancer and cardiovascular conditions. Suitable sources of β-glucans for biopharmaceutical applications include bacteria, microalgae, mycelium, and yeast. Environmental factors including culture medium can influence the biomass and ultimately β-glucan content. Therefore, cultivation conditions for the above organisms can be controlled for sustainable enhanced production of β-glucans. This review discusses the various sources of β-glucans and their cultivation conditions that may be optimised to exploit sustainable production. Finally, this article discusses the immune-modulatory potential of β-glucans from these sources.

1. Introduction

Natural polysaccharides have been utilized to treat numerous human diseases (Ranjbari et al., 2017). Recently, there has been a growing interest in identifying natural compounds with the potential to reduce chronic illnesses and prevent infections (Ahnen et al., 2019; Lordan et al., 2011). Among these, β-glucans, which are abundant polysaccharides composed of glucan monomers, possess unique bioactive properties (Murphy et al., 2021) that differentiate them from other glucose molecules. Their therapeutic potential for a range of diseases has been well established (Pogue et al., 2021), and the US Food and Drug Administration recommends a daily intake of three grams of β-glucan-containing oats, which have been recognized as a cholesterol-reducing food ("Food Labeling: Health Claims; Soluble Fiber from Certain Foods and Risk of Coronary Heart Disease. Final Rule.," 2008).

Understanding the structural classification of β-glucans is crucial in determining their biological activity, and with their unique properties, β-glucans have been identified as promising natural compounds for reducing chronic illnesses and preventing infections. The structure and biological activity of β-glucans are significantly influenced by their origin, with glucose units serving as the fundamental building blocks for all β-glucans (Friedman, 2016; H. Zhang et al., 2018).

All beta-glucans have a backbone composed of linked glucose units, with a 1–3 β linkage fundamental to their activity (E. L. Adams et al., 2008a). However, there are variations in branching along the backbone, with some molecules branched at various positions and others not branched at all (Kataoka et al., 2002). Beta-glucans can be categorized as cereal or non-cereal, with differing branching structures, lengths, and variations depending on the source. Cereal-derived beta-glucans are typically branched at the 1,4 position, while most fungal and yeast derived beta-glucans have branching at the 1,6 position (Manners et al., 1973; Tosh et al., 2004; Yehia, 2022; Zeković et al., 2008). Some beta-glucans, such as Curdlan from Agrobacterium sp., have no side branching (Kataoka et al., 2002). Cereal-based beta-glucans primarily affect metabolism, such as altering gut microbiota and reducing cholesterol, with potential benefits for cardiovascular health. In contrast, non-cereal beta-glucans often impact the immune system, with

* Corresponding author at: LIFE – Health and Biosciences Research Institute, Midwest Campus, Technological University of the Shannon, Limerick V94EC5T, Ireland.
E-mail address: emma.murphy@tus.ie (E.J. Murphy).

https://doi.org/10.1016/j.micres.2023.127424
Received 3 March 2023; Received in revised form 14 May 2023; Accepted 3 June 2023
Available online 5 June 2023

anti-inflammatory, anti-cancer, and anti-infective properties (Murphy et al., 2020, 2022).

Despite the vast potential of β-glucans, there is significant variability in their biological activity that arises from differences in sources, growth conditions, extraction, and purification methods. Biotechnological processing, which involves manufacturing products from living organisms in controlled environments, presents a promising approach to mitigate source variability. Microbial or non-cereal sources of β-glucans, such as yeast, microalgae, bacteria, and mycelium, offer a diverse range of sources for extraction. This article provides a comprehensive review of natural sources of β-glucans, explores various methods to influence their growth, and concludes with a focus on their immuno-modulatory properties. To our knowledge, this is the first article to incorporate biotechnological processes of β-glucans from diverse sources and examine their biological activities.

2. Bitechnological sources of β-glucans

The use of biotechnological processing can offer more control and reproducibility over the production of β-glucans derived from microorganisms. β-glucans are derived from abundant sources, including microorganisms– bacteria, yeast, microalgae, and fungal mycelium. Biotechnological processing enables control and reproducibility of environments like growth conditions, pH, additives, foam, and aeration, which depending on the system, can all be automated. The conditions can also be manipulated to influence production. Elicitors in this context are physical or chemical factors that can enhance desirable products from cell culture, including microorganisms such as bacteria, fungi, yeast, and algae (H. Park et al., 2014a). Oxygen concentration has been observed to influence β-glucan content positively. Oxygen concentration accelerates the cell division of yeast and bacteria, thus increasing growth and cell mass (Baez and Shiloach, 2014). Co-production strategies involve the fermentation process of microorganisms that can simultaneously produce two or more valuable products, for example, vitamins and polysaccharides. This is a way to achieve sustainable microbial biomass production (Nair et al., 2020).

Technologies using microbial products replace synthetic production because of their numerous technical and economic advantages. These products include but are not limited to nutrition supplements, vitamins, enzymes, and pharmaceutical products (Singh et al., 2017). According to Business Communications Company (BCC) Research, the global β-glucan market is expected to reach 576.28 million USD by 2025 (Byrtusová et al., 2020).

2.1. Yeast

Yeasts are unicellular fungi that reproduce asexually (budding or fission) and sexually (spore formation). There are 500 species of yeasts that are currently known. The most commonly used are baker's yeast or *Saccharomyces cerevisiae*, which are used in wine making and brewing (Joseph and Bachhawat, 2014). This is also used for the production of various nutraceutical products (Padilla et al., 2015; Rai et al., 2017).

Yeast was instrumental in the discovery of the bio-activity of β-glucan. Pillemer et al. (1954) used zymosan, a crude mixture of yeast cell wall materials, to investigate the complement system, specifically the role of Properdin. Zymosan was used as an immune stimulant. Riggi and Diluzio identified a polysaccharide with 1–3 β linkage to be the stimulatory component in Zymosan (RIGGI and DI LUZIO, 1961). Thus, the research on β-glucan began and is still progressing today with numerous commercially available β-glucans available., such as Yestimun, which is an insoluble 1–3, 1–6 β-glucan derived from spent brewer's yeast. This yeast is a natural byproduct of the beer fermentation process (Stier et al., 2014).

β-glucan from yeast is mainly found in the cell wall, a bi-layered structure. However, some species of black yeast, such as *Aureobasidium pullulans*, secrete β-glucans extracellularly (Muramatsu et al., 2012; Suzuki et al., 2021). In *S. cerevisiae* the cell wall contains a 1–3 β-glucan, mannoprotein and 1–6 β-glucan (Teparić and Mrša, 2013; Yamaguchi et al., 2011). β-1, 3-glucan is the principal cell wall constituent and forms 50–55% of the cell wall of yeast, and 1–6 β-glucan account for 10–15% of the total cell wall polysaccharide (Aimanianda et al., 2009; Teparić and Mrša, 2013). 1–3 β-glucan forms a network in the cell wall of yeast by attaching to the heavily branched 1–6 β-glucan (Lesage and Bussey, 2006). Cell wall β-glucan content depends on yeast species and their growth conditions (Jaehrig et al., 2008). Extraction of β-glucans from the cell wall can be tedious as cell wall contaminants such as proteins and other polysaccharides are present. This can often result in variances between samples. It is thus more beneficial if β-glucans are secreted extracellularly into the growth media.

In terms of β-glucan synthesis, three members associated with 1–3 β-glucan synthases from *S. cerevisiae* have been identified. The genes related to 1–3 β-glucan production in *S. cerevisiae* are regulated through the MAP kinase Mpk1p of the Cell-Wall Integrity Signaling (CWIS) pathway (Jung and Levin, 1999). The synthesis of 1–3 β-glucan and 1–6 β-glucan is controlled by the expression of RHO1, FKS1 and FKS2 genes (Kondoh et al., 1997). The proteins FKS1, FKS2 and RHO1 form the glucan synthase complex or GS complex. Overexpression of the genes of RHO1 and FKS2 that transcribe these proteins increases β-glucan content. The gene for FKS2 undergoes transcription in reply to stress factors and response to carbon sources (Borovikova et al., 2016; Smits et al., 2001; Xu et al., 2016). Studies also suggest that genes belonging to the KRE family are heavily involved in 1–6 β-glucan synthesis (Chavan et al., 2003). This was demonstrated through the deletion of *kre5Δ,kre6Δ,* and *skn1Δ* genes in *Cryptococcus neoformans* which subsequently showed less 1–6 β-glucan cell wall synthesis (Gilbert et al., 2010).

The growth and environmental conditions in which the yeast cells are grown will significantly affect cell wall components and heterogenicity (Novak and Vetvicka, 2008). The conditions must be suitable for the organism to grow, but they can also be manipulated to produce β-glucans (Galinari et al., 2017; Jaehrig et al., 2008).

Genomic studies have demonstrated that when yeast cells are challenged with various environmental factors, there is up- and down-regulations of the genes associated with cell wall synthesis (Becerra et al., 2002; Ter Linde and Steensma, 2002). Thus, yeast will activate mechanisms responsible for cell survival under stress conditions by modifying the cell wall (Borovikova et al., 2016; Bzducha-Wróbel et al., 2018; Xu et al., 2016). Stages of growth will influence the quantity of β-glucan. The logarithmic phase is the optimum phase for β-glucan production in yeast cells. Cell number is high in this phase; thus, β-glucan content is high (Aimanianda et al., 2009; Papaspyridi et al., 2018; Yoshimi et al., 2017).

Species of the microorganism are vital to consider as there are interspecies differences concerning the degree of branching and distribution of the branches (Wasser, 2002). Environmentally, the dry mass and subsequent polysaccharide content are hugely dependent on carbon source, nitrogen limitation, pH, temperature, and aeration (Aguilar-Uscanga and François, 2003). The β-glucans cell wall is responsible for osmotic stability and is designed to protect the cell from outside environments, including preventing the cell from dehydrating (Dalonso et al., 2015; Utama et al., 2021). The cell wall also acts as an energy and food reserve in nutrient and food depletion. In the yeast cell, the role of β-glucan is to provide structure and strength to the cell wall (Ruiz-Herrera, 1991a). Thus, biotechnological processes with the aim of β-glucan production must stimulate the cell wall polysaccharide biosynthesis. This can be done by strategies that aim to gain higher cell biomass, which is achieved by selecting the correct culture medium composition and growth conditions.

2.1.1. Culture conditions of yeast to influence β-glucan production

The growth medium, Yeast Bacto Glycerol (YBG), is considered the model media for the growth of yeast cells (Bzducha-Wróbel et al., 2018). Glucose is an essential ingredient required for development and

β-glucans production as yeast cells use glucose as a constituent in their cell walls (Bashir and Choi, 2017).

The β-glucan synthesis pathway in *S. cerevisiae* involves several steps. Phosphoglucomutase converts glucose-6-phosphate to glucose-1-phosphate, which is then used by UDP-glucose pyrophosphorylase to synthesise UDP-glucose from UTP. Glucan synthases FKS1, FKS2, and FKS3 associated with RHO1 polymerise UDP-glucose into the β-glucan molecule (Castro et al., 1999).

Zhou et al. (2019) engineered this pathway in *S. cerevisiae* to enhance β-glucan accumulation by expressing bacterial 1–6 β-glucan synthase and overexpressing phosphoglucomutase and RHO1. This resulted in a 43% increase in β-glucan content (Zhou et al., 2019). Media have also been shown to affect β-glucan content and activity. For instance, different media such as wort, yeast peptone, and glucose were assessed by Jaehrig et al. (2008) who observed differences in β-glucan content and bioactive properties, including antioxidative activities (Jaehrig et al., 2008). Other studies have found that the use of N-peptone sources and molasses as the carbon source can increase β-glucan range and content (Rizal et al., 2020; THONTOWI et al., 2007).

Aguilar-Uscanga et al. investigated how growth conditions affected cell wall composition and β-glucan content in yeast cells. They considered factors such as carbon source, temperature, pH, and aeration, and compared shake flask cultivation to controlled batch reactors. Results showed that carbon source had an impact on β-glucan production, with variations observed in shake flask cultures compared to batch fermenters. Changes in pH during growth caused a decrease of up to 40% in β-glucan levels, highlighting the importance of maintaining a consistent pH throughout the fermentation process (Aguilar-Uscanga and François, 2003).

Initiators can also be added to influence growth and bioactive production. In a study, *S. cerevisiae* was cultured with sole additives (SDS, EDTA, and NaCl), including SDS combined with NaCl and EDTA as initiators to enhance β-glucan production. This study showed that all different media supplemented with additives enhanced β-glucan output by 7–40%. Yeast supplemented in YBD medium with 100 ppm SDS produced the highest levels of β-glucan content. SDS was the best additive to enhance production compared to control. Also, when extracted, this β-glucan had low proteins and higher branching levels than that of the control (Naruemon et al., 2013). This experiment showed that initiators induce β-glucan production and can change structure concerning branching. Side branching is very often associated with biological activity, with some studies demonstrating that branched β-glucans appear to have a stronger affinity to immune cell receptors (E. L. Adams et al., 2008b).

Industrial wastes from food sources are an environmental concern. Disposal and reuse methods are constantly being explored. Potato juice and glycerol are two by-products of the food industry. These two by-products contain valuable nutrients and can be recycled digestate for microorganisms.

Bzducha-Wróbel et al. (2015) repurposed waste to cultivate yeast and increase the yield of functional β-glucans. The combination of deproteinated potato juice, YBD media, and 5–10% glycerol increased β-glucans production from 31% to 44% (Bzducha-Wróbel et al., 2015).

A similar study by Bzducha-Wrobel et al. used deproteinated potato juice supplemented with glycerol, a carbon source. Glycerol is also exploited as a substrate as it stimulates the activity of 1–3 β-glucan synthase, the enzyme responsible for the synthesis of β-glucans. Other substances for the activation of this enzyme include beef albumin and Mn^{2+}, Ca^{2+}, and Mg^{2+} ions. However, when glycerol exceeded 15%, yeast growth was restricted and glucan content reduced. The optimal pH for β-glucan synthesis was found to be between pH 5 and 7, resulting in thicker cell walls (Bzducha-Wróbel et al., 2018). Other authors stated optimal maximum growth of yeast with 2–6% glycerol (Ochoa-Estopier et al., 2011).

A recent study explored the use of tannic acid, a by-product from the brewing industry, to produce β-glucan from *Saccharomyces carlsbergensis* (Fumi et al., 2011). Tannins interact with the yeast cell wall, causing polysaccharides to precipitate and inducing stress in the cells. In response, the cells create a thicker β-glucan-chitin layer (W. Zhang et al., 2015). The study found that adding 0.1% w/v tannic acid to the growth medium significantly increased β-glucan production by 42.23% and that stirring the culture increased production by 1.4 fold compared to shake flask culture (Chotigavin et al., 2021).

The positive results from these studies demonstrate that by-products from waste streams can be repurposed to produce bioactive molecules and thus used as a bioresource. This conversion of waste streams into bioactive molecules is fundamental to a circular economy, emphasising the use of biotechnological processes. Table 1 provides additional methods to enhance β-glucan production in yeast.

2.2. Fungal mycelium

Mushroom mycelia, comprised of hyphae, are essential components of fungi. They are a group of higher fungi that grow on dead organic matter, including trees that extend from the spore to collect nutrients (Ongpeng et al., 2020). Mushroom mycelium has gained industrial interest as it can be cultured with foods to increase nutritional value (Park and Kim, 2018).

The medicinal properties of mushrooms have well been documented. Polysaccharides from mushrooms are macromolecules with various biological functions, including immunomodulatory, anti-tumour, anti-inflammatory and hypoglycemic, and hepatoprotective activities (Taofiq et al., 2016). The fungal cell wall is a complex structure mainly composed of polysaccharides, including α-, β-glucan, chitin, and galactomannan (Beauvais et al., 2014; Latgé, 2010; Yoshimi et al., 2016). β-glucans structure from mycelium sources is species dependent. Diverse examples include; *Poria cocos*, for instance, which produces 1–3 β-glucan.

Lentinus edodes produces 6-branched 1–3 β-glucan, and *Sarcodon aspratus* produces 3-branched 1–6 β-glucan (Morales et al., 2019; Smiderle et al., 2013; Synytsya and Novák, 2013).

Species of mushrooms will also dictate β-glucan content. *Sparassis* species contain higher amounts of β-glucan compared with other mushrooms (Li et al., 2020; Nishioka et al., 2020). In *Sparassis crispa* species, 43.6% of dry weight in the fruiting bodies contains β-glucans (Ohno et al., 2000). Other studies have shown structural differences in the polysaccharides found in the fruiting body compared to those found in the mycelial biomass of the mushroom *Pleurotus ostreatus var. florid* (Komura et al., 2014). Demonstration of variance between β-glucan bioactivity in inflammatory lung injury models between mushroom species, with some species exasperating the immune response and some species reducing inflammatory biomarkers has also been reported (Murphy et al., 2022).

While some species of mushroom fruiting body can be expensive to cultivate, mushroom mycelia have shorter growth periods and is easier to produce using solid and liquid cultures (M. Park and Kim, 2017). Mycelial cultivation is also more reliable and economically friendly for mass production of biomolecules. The bioactive properties of *Ganoderma lucidium* can be maintained through mycelium cultivation, which is cheaper than cultivating its fruiting body (Park and Kim, 2018). To cultivate mycelium, the fungi are first grown on a solid agar such as potato dextrose agar, and then transferred to liquid broth after seven days. The mycelium can then form pellets, which can be gently sheared and moved to larger vessels for continued culture (Park and Kim, 2018).

The enzyme that is responsible for β-glucan production in fungi is 1–3 β-glucan synthase (GLS), which is a plasma membrane-associated enzyme with multiple transfer domains (Lesage and Bussey, 2006). For β-glucan production, this enzyme must be expressed, which can be affected by environmental triggers and specific molecules (Papaspyridi et al., 2018).

Cytoplasmic uridine diphosphate glucose (UDPG) is the substrate used by GLS and acts as a sugar donor. Beauvis et al., (1993) state that

Table 1
Temperature, medium and other condtions used to faciltiate the biotechnological production of β-glucans from Yeast.

Organisms	Medium	Temperature	Other Conditions	β-glucan Content	Reference
Yeast					
S. cerevisiae	Malt extract agar	28 °C	Samples cultured with Soybeans at 32 for 40 h	0.6% w/w	(Rizal et al., 2021)
S. cerevisiae	Sabouraud dextrose agar containing chlorampREhenicol (0.005%) then transferred to YPG broth (yeast extract 1%, peptone 2%, and glucose 2%)	30 °C	Agitated in the shaker at 150 rpm	27.5% of wall dry weight	(Shokri et al., 2008)
S. cerevisiae	Fermentation medium	30 °C	Nitrogen source – Peptone 2%	933.33 mg/L	(THONTOWI et al., 2007)
S. cerevisiae	Fermentation medium	30 °C	Nitrogen source urea (0.2%), Diammonium and hydrogen phosphate	733.33 mg/L.	(THONTOWI et al., 2007)
S. cerevisiae	Yeast Extract-Glucose broth (YG broth) (15 g/L glucose, 5.2 g/L K_2HPO_4, 3.18 g/L KH_2PO_4, 0.12 g/L $MgSO_4$, 0.5 g/L Yeast extract, and 0.54 g/L NH_4Cl	30 °C	Agitation at 200 rpm	3.72 ± 0.31 g/L	(Pengkumsri et al., 2017)
S. cerevisiae	Potato dextrose agar (PDA) Transferred to yeast extract glucose (YG) broth containing 15 g/L glucose, 5.2 g/L K_2HPO_4, 3.18 g/L KH_2PO_4, 0.12 g/L $MgSO_4$, 0.5 g/L yeast extract and 0.54 g/L NH_4Cl	30 °C	Agitation speed of 200 rpm	3.945 ± 0.05	(Utama et al., 2021)
C. utilis	Synthetic yeast extract-peptone-glucose medium (YPD) composed of (g/L): 20 g peptone, 20 g glucose, and 10 g yeast extract. Deproteinated potato juice water, 5% and 10% glycerol concentrations as a carbon source.	28 °C	Reciprocating shaker at a frequency of 200 cycles/min.	YPD alone 31% YBD Potatoe Juice mixture at 5% and 10% 45%	(Bzducha-Wróbel et al., 2015)
S. cerevisiae	YPD (10 g/L) yeast extract, 20 g/L bactopeptone and 20 g/L glucose	30 °C	pH 5 200 rpm	18%	(Aguilar-Uscanga and François, 2003)
S. cerevisiae	Yeast Nitrogen Base media (YNB) 1.7 g/L yeast nitrogen without amino acid and ammonium, 5 g/L ammonium sulphate, 20 g/L glucose	30 °C	pH 5 200 rpm	18%	(Aguilar-Uscanga and François, 2003)
S. cerevisiae	YBD medium with 100 ppm SDS			40% w/w content	(Naruemon et al., 2013).
S. cerevisiae	Yeast Extract-Glucose broth (YG broth) 15 g/L glucose, 5.2 g/L K_2HPO_4, 3.18 g/L KH_2PO_4, 0.12 g/L $MgSO_4$, 0.5 g/L Yeast extract, and 0.54 g/L NH_4Cl	30 °C	Agitation of 200 rpm 0.8 vvm (dm3/min) aeration for 48 h/ round	49.21 ± 3.96%	(Pengkumsri al, 2017)
Saccharomyces carlsbergensis	3% w/v molasses and 0.1% w/v diammonium sulfate (MDS) medium supplemented with 150 mL of 0.1% w/v tannic acid Scale-up of the culture - 7.5 L bioreactor in MDS medium supplemented with 0.1% w/v tannic acid	30 °C	Agitation at 400 rpm	17.08% w/w	(Chotigavin et al., 2021)
S. cerevisiae	YPG medium (g/L: 20 g peptone, 20 g glucose and 10 g of yeast extract).	28 °C	200 rpm pH 5	19.9 ± 0.6	(Bzducha-Wróbel et al., 2018)
S. boulardii	YPG medium (g/L: 20 g peptone, 20 g glucose and 10 g of yeast extract).	28 °C	200 rpm pH 5	17.9 ± 0.5	(Bzducha-Wróbel et al., 2018)
S. cerevisiae	Deprotonated waste potatoe juice + 5% glycerol	28 °C	200 rpm carbon source, pH 7	22.2 ± 0.6 g/100 g	(Bzducha-Wróbel et al., 2018)
S. boulardii	Deprotonated waste potatoe juice + 20% glycerol	28 °C	200 rpm pH 7	22.2 ± 0.6 g/100 g	(Bzducha-Wróbel et al., 2018)
A. pullulans	Glucose-sucrose (GS) medium containing 2.5% glucose, 2.5% sucrose, 0.2% ascorbic acid, 0.1% K_2HPO_4, 0.2% $MgSO_4{\cdot}7\ H_2O$, and 1.0% corn steep liquor. Media for -glucan production - 8% molasses, 0.2% ascorbic acid, 3% amino acid fermentation waste and 88.8% soybean powder.	25 °C	200 rpm	15.45 ± 0.07%	(Sekar et al., 2018)

factors that influence the activity of GLS include; the age of the culture, guanosine-5'-triphosphate, sodium fluoride, sucrose, and ethylenediaminetetraacetic acid (EDTA). The activity of GLS is also correlated to the stage of growth of the organism. The highest levels of activity of GLS are seen in the early exponential (log) phase of development (Beauvais et al., 1993; Papaspyridi et al., 2018).

The process of β-glucan synthesis in fungi includes; initiation, elongation of the glucan chains, and the branching step (Bowman and Free, 2006; Papaspyridi et al., 2018; Ruiz-Herrera, 1991b). β-glucan chains are synthesised in the cytoplasm, composed of glucose monomers up to 1500 subunits in length. After synthesis, they are transferred by a transmembrane enzyme complex to the periplasmic space, where further modifications can occur to construct the cell wall. 1–6 β-glycosidic side branches are then added, which connect the 1–3 β-glucan chains together (Bowman and Free, 2006; Papaspyridi et al., 2018; Ruiz-Herrera, 1991b).

Gene expression of filamentous fungi can be induced by adding various nutrients to the liquid cultivation (Miyazawa et al., 2020). Filamentous fungi can also grow in different forms, all influenced by the growth environment, including agitation speed, pH, and medium composition (Krull et al., 2013; Papagianni, 2004). When 1–3 α-glucan in the inner cell wall is covered with either 1–3 β-glucan or chitin, the degree of hyphal aggregation is reduced. Hyphal aggregation contributes to pellet formation (Crognale et al., 2007; Miyazawa et al., 2018, 2020). It is important to carefully consider the growth conditions and nutrient availability when cultivating mycelium to produce desired biomolecules.

2.2.1. Culture conditions of fungal mycelium to influence β-glucan production

Numerous factors can affect the growth of filamentous fungi during liquid cultivation. These include a carbon source, carbon concentration, Manganese content, surfactants, oxygen, agitation and tank design (Cairns et al., 2019). Nitrogen is also essential for forming cell wall constituents, including β-glucan (Yoshimi et al., 2017). Mycelium will naturally produce β-glucan. Initiators can be added to the media to influence production.

Several studies have explored various methods to enhance β-glucan production in fungi. Talc has been added to media in mycelium cultivation of *Grifola frondosa*, which has been shown to significantly alter polysaccharide production through interaction with enzymes related to biosynthesis (Tao et al., 2018).

Enzymes such as chitinase, β-glucuronidase, and a lysing enzyme complex have also been administered to elicit β-glucan production, resulting in increased concentration of up to 31% compared to the control (Park et al., 2014a). Additionally, alginate oligosaccharides extracted from brown algae have been investigated for their elicitation effects on β-glucan production in the cauliflower mushroom (*Sparassis latifolia*), and the results demonstrate their effectiveness in enhancing the nutritional value of mushrooms (Li et al., 2020).

Waste products have also been utilised for β-glucan production in mycelium cultivation. Gern et al., 2008 stimulated *Pleurotus ostreatus* to produce both endo and exopolysaccharides using waste material. Media was prepared using corn steep liquor, generated as a waste residue in the corn industry. Media was also designed using wheat extracted as a residue of the mushroom spawn industry. Results demonstrated that yeast extract at 5 g/L and glucose extract at 40 g/L was effective for polysaccharide production. The maximum biomass was achieved with 20 g/L of Corn starch liquor (CSL) and 40 g/L of glucose in the growth media. Nitrogen levels at higher concentrations increased the productivity of polysaccharides, and glucose increase had a significant effect on overall biomass. Results also demonstrate that the organism took longer to adapt to media that contained CSL, shown by a more prolonged lag phase. This study shows that material generally discarded as waste is suitable for mycelium growth (Gern et al., 2008). In this context, other waste products used for β-glucan production include olive mill solid waste (OMSW). The mushroom *Pleurotus eryngii* was cultivated on substrates containing different concentrations of OMSW. Results show that β-glucan content was directly correlated to the amount of OMSW in the growing substrate (Vetvicka et al., 2019). There is an abundance of waste products that can be used to increase β-glucan production in fungi. Additional methods are presented in Table 2.

2.3. Bacteria

Curdlan is the designation given to β-glucans isolated from *Agrobacterium* species. These specific β-glucans contain no side branching, just a 1–3 β- D backbone (Kataoka et al., 2002). The backbone consists of 1–3 β-linked glucose residues with the unusual physiochemical property of forming an elastic gel when heated in aqueous suspensions (Zeković et al., 2005). It is a high molecular weight water-insoluble, alkali-soluble extracellular polysaccharide. In som species *Alcaligenes faecalis* and *Agrobacterium radiobacter* it is a secondary metabolite synthesised under nitrogen-limiting conditions (Kalyanasundaram et al., 2012a). The yield of β-glucans from bacteria can be quite low at 6–7% compared to fungal/yeast sources (Kalyanasundaram et al., 2012a). Certain bacterial species such as *Bacillus subtilis* can produce up to 3 g/L of β-glucans (Kalyanasundaram et al., 2012a).

2.3.1. Culture conditions of bacteria to influence β-glucan production

When exposed to new environmental conditions, microorganisms undergo adaptation phases that can delay β-glucan production, especially if the conditions are unfavourable (Falcone and Mazzoni, 2016). A study comparing adaptation phases of bacteria and yeast found that *Xanthomonas campestris* and yeast had a 72-hour lag phase, while *Bacillus natto* had a shorter lag phase of 24 h (Stratford et al., 2014).

Factors that determine the lag phase include the number of cells inoculated, cultivation media, growth environment, temperature, incubation time, pH, and sub strate content (Brooks et al., 2011; Haruta and Kanno, 2015). In the post-stationary growth phase, nitrogen levels deplete, and excess carbon sources increase, with some bacteria (*X. campestris* and *B. natto*) showing optimal β-glucan output at 120 h after inoculation (Mihalcescu and Stan, 2018; Utama et al., 2021).

β-glucans are synthesized through secondary metabolites in the bacteria *B. natto* and *X. campestris*, making an increase in population or biomass ineffective in increasing yield (Tan et al., 2016). These bacteria synthesize glucose, which is used as a secondary metabolite in the formation of β-glucan (Dhivya et al., 2014; Zeković et al., 2005), while pH also plays a critical role in mass cell generation with optimal β-glucan production occurring at a pH range of 5.5–7.0 (Kalyanasundaram et al., 2012a).

A study by Kalyanasundaram et al. (2012b) studied the production of the Curdlan specifically in chemically induced mutant strains in both shake flask and bioreactors. Mutant strains were obtained by chemical mutagenesis using N-methyl-N-nitro-nitrosoguanidine (MNNG) at 1 mg/mL. Curdlan producing colonies appeared blue on aniline blue agar plates and were selected for shake flask cultures. Two strains were

Table 2
Temperature, medium and other condtions used to faciltiate the biotechnological production of β-glucans from Fungi.

Organisms	Medium	Temperature	Other Conditions	β-glucan Content	Reference
Fungi					
R.oligosporus	Potatoe Dextrose Agar	30–35 °C	Samples cultured with soybeans 32 for 40 h	0.25% w/w	(Rizal et al., 2021)
G. lucidium	Potatoe Dextrose Agar Mycelium transferred to Potatoe Dextrose Broth	25 °C	Cocultued with *Rhynchosia nulubilis*	13.26% w/w	(Park and Kim, 2018)
P. ostreatus	Wheat extract infused yeast (5 g/L) extract and glucose (40 g/L) pH of 6.0	30 °C	Agitation at 120 rpm	Total polysaccharide activity = 17.12 ± 0.97 mg/L Day	(Gern et al., 2008)
P. ostreatus	Wheat extracts infused corn steep liquor (20 g/L) extract and glucose (40 g/L) pH of 4.5	30 °C	Agitation at 120 rpm	Total polysaccharide activity = 17.01 ± 4.15 mg/L Day	(Gern et al., 2008)
Aspergillus oryzae	Potato dextrose broth medium (PDB) supplemented with a yeast extract (2 g/L)	25 °C	Dark on a rotary shaker at 120 rpm.	18.41% g/100 g	(Sutter et al., 2016)
Aspergillus sojae	Potato dextrose broth medium (PDB) supplemented with a yeast extract (2 g/L)	25 °C	Dark on a rotary shaker at 120 rpm.	20.71% g/100 g	(Sutter et al., 2016)
Rhizopus oryzae	potato dextrose broth medium (PDB) supplemented with a yeast extract (2 g/L)	25 °C	Dark on a rotary shaker at 120 rpm.	6.99% g/100 g	(Sutter et al., 2016)
Rhizopus oligosporus	Potato dextrose broth medium (PDB) supplemented with a yeast extract (2 g/L)	25 °C	Dark on a rotary shaker at 120 rpm.	2.52 g/100 g	(Sutter et al., 2016)
P. linteus	Yeast malt extract glucose (YMG) agar.	30 °C	pH 4–5 40–50 rpm 1050–1650 NI/min	14.16 ± 6.27% w/w	(Shin et al., 2021)

determined. They used a two-stage culture technique for optimal conditions, including pH for Curdlan production. The two-step culture method is used to understand the effects of variables on the production of metabolites such as Curdlan. Results showed an increase in pH-induced cells to consume more sucrose and thus produce more Curdlan. They found pH 5 optimal for Curdlan production (Kalyanasundaram et al., 2012a). In a similar study, as pH increased, *Agrobacterium* sp. ATCC 31750 absorbed more sucrose and produced more Curdlan (Kalyanasundaram et al., 2012b). Additional methodologies for the production of β-glucans from bacteria can be found in Table 3.

2.4. Microalgae

Microalgae are mostly unicellular, microscopic photosynthetic organisms, but some microalgae are multicellular due to their complex cellular structures. Microalgae are predominantly photoautotrophic organisms, but certain microalgae can be cultivated in heterotrophic (dark) and mixotrophic (light) conditions with readily available carbon sources. Based on available research, microalgae can be considered an important source of β-glucans (Ibarra et al., 2017; Pignolet et al., 2013; Schulze et al., 2016; Vogler et al., 2018a).

A biodiscovery screening study by Schulze et al. (2016) found a wide range (1.7–24.2% dry weight biomass) of β-glucan content in 40 tested species of freshwater and marine microalgae when cultivated under standard laboratory growth conditions. Interestingly, microalgae appear to produce two different structures depending on the species. The most common species of β-glucan, which is 1 − 3 structure is produced by microalga *Euglena gracilis*. Another species of microalga *Nannochloropsis gaditana* produces β-glucan similar to that of mushrooms with limited 1–6 branching (Vogler et al., 2018b).

The microalga *Euglena gracilis* is a well-reported microalgal source of β-glucans (Evans et al., 2019a; Krajčovič et al., 2015; Yasuda et al., 2020a). *Euglena gracilis* is a unicellular photosynthetic protist species of microalgae that stores a 1–3 β-glucan called paramylon as a storage reserve polysaccharide (K. Suzuki et al., 2015). Paramylon is a linear unbranched 1–3 β-glucan polymer with high- molecular weight (Barsanti et al., 2011a). The estimated molecular weight is between 100 and 500 kDa (Gissibl et al., 2019). This microalga species accumulates large amounts of Paramylon, up to 90% of its cell mass (Monfils et al., 2011).

Paramylon is receiving industry attention, and its market is predicted to increase (Gissibl et al., 2019). β-glucans isolated from this source are purer than those isolated from the mushroom. This is because there is a lack of contamination from cellular components of the cell wall, for example, proteins and other sugars. Also, Paramylon has a high level of crystallinity which enables it to be isolated at a very low cost by disrupting the cell wall and subsequent recovery of crystal granules (Russo et al., 2017).

Paramylon content will, like other microorganisms, be dependent on growth conditions such as light or dark or carbon sources. Studies have suggested that the highest concentration of polysaccharides is reached after 24 h. Higher values are obtained in the dark, and glucose is the best carbon source (Barsanti and Gualtieri, 2019).

2.4.1. Culture conditions of microalgae to influence β-glucan production

The microalga *E. gracilis* accumulates Paramylon during photoautotrophic (PT), heterotrophic (HT), and mixotrophic (MT) growth (Grimm et al., 2015). Studies have also shown that light can be detrimental to the accumulation of Paramylon. The highest paramylon titres have been reported at 16 g/L, obtained through culturing in the dark (Šantek et al., 2012). This species of microalga *E. gracillis* grow faster to higher biomass concentrations while producing higher levels of Paramylon under heterotrophic cultivation conditions compared with photoautotrophic or mixotrophic ones (Chae et al., 2006; Fujita et al., 2008).

Sun et al. (2018) compared the production of paramylon in two Euglena strains, *E. gracilis Z* and *E. gracilis var saccharophila*, and found that both strains produced higher levels of paramylon when cultivated in a dark environment, with the *var saccharophila* strain producing a higher concentration of 8.1 ± 0.3 g/L than the *Z* strain at 7.5 ± 0.4 g/L, and the *Z* strain requiring a longer cultivation period to reach maximum paramylon levels possibly due to residual glucose depletion. The authors suggest that the difference in paramylon levels between species may be due to their sensitivity to light or a photoinduced reaction to light (Sun et al., 2018). *Euglena* can be cultivated heterotrophically or photo autotrophically, with nutrient sources such as molasses, corn steep, and yeast extracts used for polysaccharide accumulation, and cultivations are usually performed under heterotrophic conditions in the dark to avoid photo-inhibitory effects (Ivušić and Šantek, 2015; Ogawa et al., 2015; Rodríguez-Zavala et al., 2006; Šantek et al., 2012).

In their study, Šantek et al. (2012) utilized pre-treated protein liquor, which included nitrogen (5%) and carbon (31.8%), glucose, vitamin B1

Table 3
Temperature, medium and other condtions used to faciltiate the biotechnological production of β-glucans from Bacteria.

Organisms	Medium	Temperature	Other Conditions	β-glucan Content	Reference
Bacteria					
X. campestris	Nutrient agar (NA) then transferred to yeast extract glucose (YG) broth containing 15 g/L glucose, 5.2 g/L K_2HPO_4, 3.18 g/L KH_2PO_4, 0.12 g/L $MgSO_4$, 0.5 g/L yeast extract and 0.54 g/L NH_4Cl	30 °C	Agitation speed of 200 rpm	0.785 ± 0.06	(Utama et al., 2021)
B. natto	Nutrient agar (NA) Transferred to yeast extract glucose (YG) broth containing 15 g/L glucose, 5.2 g/L K_2HPO_4, 3.18 g/L KH_2PO_4, 0.12 g/L $MgSO_4$, 0.5 g/L yeast extract and 0.54 g/L NH_4Cl	30 °C	Agitation speed of 200 rpm	1.345 ± 0.08	(Utama et al., 2021)
Agrobacterium sp.	Two-stage culture technique YP medium contained sucrose 20 g/L, yeast extract 5 g/L and peptone 5 g/L Cells then washed with 0.1 M citrate buffer, pH 5.5 and suspended in 25 mL of the buffer containing 1 mg/mL of N-methyl-N-nitro-nitrosoguanidine (MNNG). After incubation for 2 days at 30 °C, colonies showing darker blue than the wild strain were isolated for further studies. Seed medium contained; sucrose 20 g/L, yeast extract 5 g/L and peptone 5 g/L, pH 7.0 then inoculated into fermentation medium - sucrose 100 g/L, $(NH_4)2HPO_4$ 2.3 g/L, KH_2PO_4 g/L, $MgSO_4.7\ H_2O$ 0.4 g/L and 10 mL of trace element solution (5 g $FeSO_4.7H2O$, 2 g $MnSO_4{\cdot}H_2O$, 1 g $CoCl_2.6\ H_2O$, 1 g $ZnCl_2$ g/L of 0.1 N HCl, 0.3% (w/v) calcium carbonate in 7.5 L bioreactors	30 °C	7.5 L bioreactors aeration rate and the agitation speed were maintained at 1.0 vvm and 700 rpm	66 g/L	(Kalyanasundaram et al., 2012b)

(0.6 mg/L) and B12 (0.05 mg/L). They conducted shake flask cultures with 100 mL of medium, containing 5 mL of a previous shake-flask culture, in a dark environment on a rotary shaker at 150 min^{-1} and a temperature of 27.5 °C. Additionally, fed-batch bioreactors with a total volume of 30 L and a working volume of 14 L were used, with oxygen saturation maintained at 40%. The cultures had an initial pH but was not controlled. The bioreactor was fed with 14 L of 25% potato liquor, 15 g g/L glucose, and vitamins, and the stirrer speed increased gradually from 200 to 260 min^{-1}. This process yielded a paramylon content of 15.6 g/L.

The study also involved repeated batch cultivation in a 7 L total volume bioreactor with a working volume of 5 L. The cultures were inoculated into 5 L of medium containing 25% potato liquor, 15 g/L glucose, and vitamins at 27.5 °C. The second cycle was initiated by replenishing the working volume with new media and no vitamins, and the stirrer speed increased from 280 to 350 min^{-1}. The paramylon concentration obtained was 15.64 g/L when the initial glucose was at 25 g/L and the volume of potato liquor at 80%. Increasing the initial glucose concentration to 30 g/L with the same volume of potato liquor at 80% raised the concentration of paramylon to 16.07 g/L (Šantek et al., 2012).

Another similar study investigated the use of complex medium ingredients that would be suitable for use in large-scale heterotrophic cultivation of *E. gracilis* and the resulting production of Paramylon. The study examined various sugars industrial by-products such as corn steep, beef extract, and yeast extract. Inorganic nitrogen, phosphorus, and plant growth hormone were also compared. The highest Paramylon concentrations were found when media consisted of 20 g/L glucose and 30 g/L corn steep solid. The work also demonstrated that beef extract increase was correlated to higher biomass concentrations (Ivušić and Šantek, 2015).

The study by Kim et al. (2021) investigated the optimal carbon source and concentration to produce Paramylon. A food processing by-product – spent tomato by-product (STB) was used as a carbon source for its nutrients. The biomass production increased when STB was used compared with a synthetic medium (1.6-fold higher at pH 3 and 2-fold higher at pH 8). When 15 g/L glucose was administered as a carbon source, 1.2 g/L of Paramylon was obtained. (Kim et al., 2021). Like other microbial sources, by-products from waste streams can also be added to influence the microalgae to produce β-glucans.

There are numerous abiotic factors that can be optimised to improve β-glucan production in microalgae. The factors that are most frequently reported as affecting the amount of polysaccharides in microalgal biomass are starvation and/or nutrition restriction, saline stress, light intensity, CO_2 concentration, temperature, and metabolic types (Hsueh et al., 2009; Ibarra et al., 2017). Understanding the effects of altering parameters is important as β-glucan content can be maximised. Additional information on methods used to manipulate β-glucan production in microalgae can be found in Table 4.

3. Co-cultivation methods

This article has mainly discussed enhancing microorganisms by biotic means. Compounds of interest, particularly β-glucan, can also be enhanced by abiotic means such as physical elicitation and enzyme treatments. Microorganisms can also be co-cultured to influence β-glucan production. If β-glucan producing microorganisms are co-cultured with food products, the nutritional value increases (Narayani and Srivastava, 2017; Park et al., 2014b; Pettit, 2011; Ryoo et al., 2018).

The yeast *S. cervisiase* can be added to soybean fermentation to produce a product with higher levels of β-glucan content and thus improve the functional properties of the food (Rizal et al., 2021). Previous studies have shown that yeast can grow well in soybean fermentation when added as a carbon source (Rizal et al., 2020). When a variety of black bean *Rhynchosia nulubilis* are cultured with mycelial from *Ganoderma lucidium*, they demonstrate higher antioxidant and anti-inflammatory activity than when cultured alone (M. Park and Kim, 2017).

Other studies also have fermented mycelium with probiotic bacteria, including lactic acid bacteria, to benefit from both microorganisms. Also, β-glucan can promote the proliferation of lactic acid bacteria (Nishioka et al., 2020). When the bacterium *Vibrio natriegens* was co-cultured with the microalga *E. gracilis*, there was an increase in Paramylon production by 35%. Significant increases in cellular biomass were also observed (Kim et al., 2019). A study by Nishioka et al., 2020 investigated the effects of a product lactic acid bacteria-fermented *Sparassis crispa* (SCL). The study examined the impact of SCL on innate immunity. Mice were orally administered SCL. The study found that oral administration of SCL increased immune cells in the jejunum and spleen, as well as enhanced monocytes and macrophages. The mRNA expression levels of innate immune genes in human monocyte cells also increased, and phagocytosis levels were higher. Overall, the study demonstrated that SCL enhances the innate immune responses in the intestine (Nishioka et al., 2020).

Rubiyatno et al., 2021 screened, isolated and characterised microalgae growth-promoting bacteria to enhance the production of Paramylon in *E.gracilis* under mixotrophic conditions under a 12 hr light cycle and a 12-hour dark process. Their previous studies identified that sewage effluent promoted the growth of *E. gracilis* because of the microbial content. After *E. gracilis* was cultured with sewage effluent, bacteria that showed micro-algae promoting abilities were screened, characterised, and analysed for their Paramylon promoting skills. Results show that an *Enterobacter* species (CA3) increased *E. gracilis* biomass production by 1.8-fold and paramylon production by 3.5-fold. An *Emticicia* bacterial species (CN5) increased *E. gracilis* biomass production by two-fold and Paramylon by 4.1-fold (Rubiyatno et al., 2021).

In addition to biotic means,abiotic methods can enhance β-glucan production. Microorganisms can be co-cultured with food products to increase nutritional value. Studies have demonstrated that waste by-products contain microorganisms that promote the contents of bioactive molecules, which supports a circular economy process for biotechnology.

4. Modification of β-glucans using enzyme synthesis

β-glucans production can be manipulated using the outlined cultivation techniques. Polysaccharides can also be modified after extraction to change their basic structure and intermolecular forces, which impact their bioactivity. Modification can be done using chemical, physical and biological methods, and it can alter the degree of polymerisation at both the chain and side branches. Larger structural polysaccharides and medium-chain length oligosaccharides can be hydrolysed and structurally modified by the action of carbohydrate hydrolytic enzymes into modified structures that can have different structure functional activity and cell recognition properties. β-Glucanase is an enzyme that can decrease the molecular weight of the polysaccharide and increase water solubility (Yuan et al., 2020).

Cell wall β-glucans are generally found to be insoluble, creating absorption and distribution limitations. Enzymatic preparations can increase solubility, decrease molecular weight and increase bioactivity. As the structure is dependent on the source and, ultimately, activity, modification can improve any restrictions caused by the primary structure. As often insoluble high molecular weight β-glucans are not suitable for pharmaceutical administration, they require hydrolysis but the β-glucan molecules must not be hydrolysed to an extent where bioactive properties are lost. Studies have shown that low molecular weight can be correlated to a reduction in activity (Li et al., 2016).

A study by Xin et al., 2022 enzymatically biotransformed yeast β-glucans into a water-soluble form. They performed immunomodulatory experiments to determine if the bioactivity was maintained. According to the findings, treatment with water-soluble β-glucans dramatically triggered immune response activation and accelerated the migration of keratinocytes without insolubility limitations (Xin et al.,

Table 4
Temperature, medium and other condtions used to faciltiate the biotechnological production of β-glucans from Microalgae.

Organisms	Medium	Temperature	Other Conditions	β-glucan Content	Reference
Microalgae					
E. gracilis Z strain	Euglena liquid medium (EM) which consists of (per liter): 1 g sodium acetate, 1 g peptone, 2 g tryptone, 2 g yeast extract and 0.01 g $CaCl_2$·2 H_2O. Paramylon production media - 7.7 g glucose, 10 g yeast extract, 0.2 g $CaCO_3$, 0.5 g $MgSO_4$, 0.4 g $(NH_4)2HPO_4$, 0.2 g KH_2PO_4, 1.81 g NH_4Cl, 2 mL of trace mineral stock A and 1 mL of trace mineral stock B. Trace mineral stock A was made by dissolving 2.2 g $ZnSO_4$•7H2O, 2 g $MnSO_4$•4H2O, 0.5 g Na_2MO_4•2 H_2O, 0.04 g $COCl_2$•6 H_2O in 3 mL of concentrated HCl and the solution was diluted with double distilled H_2O to 50 mL.	22 °C	120 rpm Cultured in Dark or Diurnal cycle (12:12 h light: dark), 1500 lumens Strains were first grown with no carbon for 72 h addition of glucose on day 3	Cultured in Dark 7.5 ± 0.4 g/L Diurnal cycle 3.6 ± 0.1 g/L	(Sun et al., 2018)
E. gracilis var. saccharophila	Euglena liquid medium (EM) which consists of (per liter): 1 g sodium acetate, 1 g peptone, 2 g tryptone, 2 g yeast extract and 0.01 g $CaCl_2$·2 H_2O. Paramylon production media - 7.7 g glucose, 10 g yeast extract, 0.2 g $CaCO_3$, 0.5 g $MgSO_4$, 0.4 g $(NH_4)2HPO_4$, 0.2 g KH_2PO_4, 1.81 g NH_4Cl, 2 mL of trace mineral stock A and 1 mL of trace mineral stock B. Trace mineral stock A was made by dissolving 2.2 g $ZnSO_4$•7H2O, 2 g $MnSO_4$•4 H_2O, 0.5 g Na_2MoO_4•2 H_2O, 0.04 g $CoCl_2$•6 H_2O in 3 mL of concentrated HCl and the solution was diluted with ddH_2O to 50 mL.	22 °C	120 rpm Cultured in Dark or Diurnal cycle (12:12 h light:dark), 1500 lumens Strains were first grown with no carbon for 72 h addition of glucose on day 3	Cultured in Dark 8.1 ± 0.3 g/L Diurnal cycle 4.9 ± 0.4 g/L	(Sun et al., 2018)
E. gracilis	Pre- treated potato liquor - 32.8 g/L containing 5% nitrogen and 31.8% carbon, glucose, 0.6 mg/L of vitamin B1 and 0.05 mg/L of B12	27.51 °C	Fed-batch cultivation Stirrer speed initially 200 min^{-1} increased gradually to 260 min^{-1} 1ST Step- in the dark on a rotary shaker at 150 min^{-1} 2nd step – 5% culture added to 30 L bioreactors - Turbines with a diameter of 79 mm and 4 baffles used. Oxygen saturation maintained at 40%. Starting pH 5. Bioreactor medium 14 L of 25% potatoe liquor, 15 g/L glucose and vitamins. Undiluted potatoe liquor supplemented with 66.7 g/L glucose was fed during the operation.	13.66 g/L	(Šantek et al., 2012)
E. gracilis	Pre- treated potato liquor - 32.8 g/L containing 5% nitrogen and 31.8% carbon. Glucose, 0.6 mg/L of vitamin B1 and 0.05 mg/L of B12 were also added.	27.51 °C	Repeated batch Glucose 30 g/L Potatoe liquor 80% 1ST Step initially operated at a speed of 270 and 280 min^{-1}, - gradually increased during repeated-batch operation to a final 320 and 350 min^{-1}, depending on the oxygen supply required in the dark on a rotary shaker at 150 min^{-1} 2nd step Media which composed of 5 L of medium – composed of 25% potatoe liquor, 15 g/L glucose and vitamins inoculated in a 7 L bioreactor with Rushton turbines with a diameter of 70 mm and 4 baffle – second cycle media was replenished but did not contain vitamins	16.07 g/L	(Šantek et al., 2012)
E. gracilis	Cramer-Myers medium - 1 g KH_2PO_4, 1 g $(NH_4)2SO_4$, 0.2 g $MgSO_4$·7H2O, 0.2 g $CaCl_2$·2 H_2O, 0.758 g EDTA-2Na·2H2O, 3 mg $Fe(SO_4)2$·6 H_2O, 1.8 mg $MnCl_2$·4 H_2O, 1.5 mg $CoSO_4$·7 H_2O, 0.4 mg $ZnSO_4$·7 H_2O, 0.2 mg Na_2MoO_4·2 H_2O, 0.02 mg $CuSO_4$·5 H_2O, 100 µg vitamin B1, and 0.5 µg vitamin B12	27 °C	Light–dark period was 24:0. 15 g/L glucose and spent tomatoes by-product	1.2 g/L paramylon	(Kim et al., 2021)
Scenedesmus ovalternus SAG 52.80	Preculture - BG-11 media stock solution [g/100 mL] $NaNO_3$ (15 g), K_2HPO_4. 3 H_2O (0.4 g), $MgSO_4$. 7 H_2O (0.75 g), $CaCl_2$. 2 H_2O (0.36 g), citric acid (0.06 g), ferric ammonium citrate (0.06 g), EDTA (dinatrium-salt) (0.01 g), Na_2CO_3 (0.2 g), micronutrient solution; H_3BO_3 (61 g), $MnSO_4$·H_2O (169 g),$ZnSO_4$ 7 H_2O (287 g), $CuSO_4$. 5 H_2O (2.5 g), $(NH_4)_6Mo_7O_{24}$. 4 H_2O (12.5 g).	25 ± 2 °C	Preculture - OD_{750} was 0.1, irradiance was 50 µmol photons m^{-2} s^{-1} at 12/12 h light/dark cycle Nitrate starvation experiments – microalga resuspended in BG-11 medium, Nitrogen concentrations 100%, 75%, 50%, 40%, 35%, 30%, 25%, 20%, 15%, 10% and 5% of the standard concentration (1.5 g/L $NaNO_3$) - irradiance was 200 µmol photons m^{-2} s^{-1}	Standard preculture conditions – 24.2% DW Nitrate starvation – Nitrogren (30%) – 46%	(Schulze et al., 2016)

(*continued on next page*)

Table 4 (*continued*)

Organisms	Medium	Temperature	Other Conditions	β-glucan Content	Reference
Porphyridium purpureum SAG 1380–1d	Preculture - F/2 modified medium containing 2.45 g/L $MgSO_4$·7 H_2O and 1.2 g/L KCl	25 ± 2 °C	Preculture - OD_{750} was 0.1, irradiance was 50 µmol photons m^{-2} s^{-1} at 12/12 h light/dark cycle	Standard preculture conditions – 22.4% DW	(Schulze et al., 2016)
Scenedesmus obtusiusculus A 189,	Preculture - BG-11 media stock solution [g/100 mL] $NaNO_3$ (15 g), K_2HPO_4. 3 H_2O (0.4 g), $MgSO_4$. 7 H_2O (0.75 g), $CaCl_2$. 2 H_2O (0.36 g), citric acid (0.06 g), ferric ammonium citrate (0.06 g), EDTA (dinatrium-salt) (0.01 g), Na_2CO_3 (0.2 g), micronutrient solution; H_3BO_3 (61 g), $MnSO_4$·H_2O (169 g),$ZnSO_4$ 7 H_2O (287 g), $CuSO_4$. 5 H_2O (2.5 g), $(NH_4)_6Mo_7O_{24}$. 4 H_2O (12.5 g).	25 ± 2 °C	Preculture - OD_{750} was 0.1, irradiance was 50 µmol photons m^{-2} s^{-1} at 12/12 h light/dark cycle Light experiments cultivated under different irradiances (50, 100, 150, and 200 µmol photons m^{-2} s^{-1}) Nitrate starvation experiments – microalga resuspended in BG-11 medium, Nitrogen concentrations 100%, 75%, 50%, 40%, 35%, 30%, 25%, 20%, 15%, 10% and 5% of the standard concentration (1.5 g/L $NaNO_3$) - irradiance was 200 µmol photons m^{-2} s^{-1}	Standard preculture conditions – 7.8% DW Light experiments - 19% at 150 µmol m^{-2} s^{-1} Nitrate starvation – Nitrogren (30%) – 34%	(Schulze et al., 2016)
Phaeodactylum tricornutum	Grown indoors using autoclaved seawater (salinity 33 psµ) enriched with filter-sterilized f/2 nutrients	22 °C	Artificial daylight fluorescent light (150 µmol µEm^{-2}s^{-1}) Scaled up to outdoor photobioreactors 0–11 h of light, temperatures ranging from 10° to 22°C	47.3% reducing sugar	(Carballo et al., 2018)
Rhodosorus sp. SCSIO-45730.	ASW medium - $NaNO_3$ (1500 mg /L), K_2HPO_4 (120 mg /L), $NaHCO_3$ (40 mg /L), $FeCl_3$·6 H_2O (3.15 mg /L), $EDTANa_2$·2 H_2O (4.36 mg /L), $MnCl_2$·4 H_2O (0.18 mg /L), $ZnSO_4$·7 H_2O (0.022 mg /L), Na_2MoO_4·2 H_2O (0.006 mg /L), $CoCl_2$·6 H_2O (0.01 mg /L), and $CuSO_4$·5 H_2O (0.01 mg /L) in 28% sea water	25 °C	30–180 µmol photons m^{-2} s^{-1} (first 4 days) of cultivation and then kept at 180 µmol photons m^{-2} s^{-1}. Phosphate concentrations 0, 60, 120 and 240 mg/L Chitosan effects tested at 0, 1, 3, 5, 10, 20, 50, 80, and 120 mg/L	Phosphate optimisaiton at 120 mg/L- β-glucan content - 108.1 ± 4.0 mg/L day− 1 Chitosan flocculation at 3 mg/L– 90%	(Dai et al., 2020)

2022). Depol 667 P was used in this study which contains a standardised blend of glucanase from fungal *Trichoderma* species. Also, in this study, the β-glucans were pre-treated with heat to increase enzyme activity. Other studies have also determined that heat pre-treatment enhances enzymatic production of β-glucans oligosaccharides (Kumagai et al., 2016).

Another similar study demonstrated that oat β-glucan hydrolysed to a lower molecular weight of 73,000 g/mol and showed hypercholesterolemic effects in-vivo and bile acid-binding capacity in-vitro, ultimately reducing the risk of cardiovascular disease (Bae et al., 2009, 2010). Cellulase was used to decrease molecular weight. The authors were interested in reducing molecular weight, ultimately decreasing viscosity. Advantages of enzyme modification include high specificity and high efficiency. Products of enzyme digestion or hydrolysis will always be homogeneous. The target site is usually dependent on the enzyme. However, the usual course is to degrade the backbone. Thus, an enzymatic synthesis is an attractive approach as it allows for highly synthetic precision with site-specific modifications (Nidetzky and Zhong, 2021; Pergolizzi et al., 2017). The process also offers a more sustainable green synthesis over chemical and physical means.

5. Immune modulation properties of β-glucans

Well-functioning immune systems are critical for disease reduction or reducing disease. β-glucans are natural substances that prime the immune system. The effects achieved through this interaction can be broadly classified as anti-inflammatory, anti-infective and anti-cancerous. The biological activity of β-glucans is correlated to structure. β-glucans have a defined structure-activity relationship. The 1–3 backbone is a fundamental requirement for all activity (Adams et al., 2008b). The variance in side-branching is species-specific and will also influence biological activity depending on 1–4 or 1–6 branching locations off the main backbone. The side-chain frequency and degree of polymerisation are also correlated to activity, with some studies demonstrating a higher degree of branching, and the higher molecular weight is associated with a higher level of biological activity (Driscoll et al., 2009) (Han et al., 2020; Sletmoen and Stokke, 2008).

β-glucans are found in the cell wall of microbial sources; thus, they are recognised by immune counterparts as foreign material or pathogen-associated molecular patterns (PAMPs) (Ausubel, 2005). Microbial based PAMPs are often referred to as MAMPs. These patterns are recognised and bound by specific receptors on immune cells and mucosal membranes called pathogen recognition receptors (PRRs).

Initially it was understood that complement receptor 3, could bind to both iC3b and zymosan (Ross et al., 1987). Further studies showed that CR3 also has specificity for β-glucans, based on several observations: 1) anti-CR3 monoclonal antibody inhibited the phagocytic and respiratory burst responses to particulate β-glucans, 2) cells from patients with CR3 deficiency did not respond to particulate β-glucans, and 3) solubilized CR3 was found to bind to β-glucans-sepharose (Ross et al., 1987). Later studies identified the αMβ2-Integrin (CR3) as the β-glucans receptor, which binds to β-glucans through one or more lectin sites located outside of the CDll b I-domain. This domain contains binding sites for other molecules such as iC3b, ICAM-1, and fibrinogen (Thornton et al., 1996). More recent studies have further explored the significance of CR3 in relation to specific pathways. Clark et al. (2018) investigated how neutrophils release a substance called Neutrophil extracellular trap (NET) which contains DNA and antimicrobial proteins, in response to activation by *Aspergillus fumigatus* hyphal extracts and curdlan. The study found that both *A. fumigatus* hyphal extracts and curdlan induced NET release in both humans and mice. Additionally, the study found that the β-glucan receptor CR3, but not Dectin-1, was necessary for NET formation (Clark et al., 2018).

For β-glucans to elicit their biological effects, they must be recognised by immune cells through binding to PRRs. The C-type lectin receptors (CLRs) are principal PRRs that recognise fungal markers (Tang et al., 2018). The 1–3 backbone is fundamental for this recognition (E. L. Adams et al., 2008a). Dectin-1 is often referred to as the β-glucan receptor. It is intrinsically present on immune cells, including macrophages, dendritic cells and neutrophils. The receptor is also present in mucosal immune cells where pathogens invade. Other receptors known to respond to β-glucans include lactosylceramide receptors, scavenger

receptors and Toll-like receptors (TLR), namely TLR2 (Murphy et al., 2021).

After binding to receptors, an immune response is initiated. Binding of TLR2 results in the production of reactive oxygen species (ROS), the release of pro-inflammatory markers and the initiation of phagocytosis for pathogen elimination (Ellefsen et al., 2021). Following Dectin-1 recognition of β-glucans, the innate immune system is usually activated. This results in the production of reactive oxygen species (ROS) and inflammatory cytokines (Kankkunen et al., 2010). 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.

Inflammation, a process to eliminate pathogens, is characterised by the activation of numerous cell types and mediators. The inflammatory response is the up-regulation of inflammatory activity (Medzhitov, 2008). The inflammatory response can also occur when there is no external challenge. This type of response is correlated to many inflammatory conditions and diseases. The regulation of inflammatory reactions is vital for the treatment and prevention of disease (No et al., 2021).

PAMPs can stimulate immune cells without the requirement of being attached to an infectious agent. Thus β-glucans have mainly been developed as adjuvants and immunotherapeutic (Camilli et al., 2018). Humans and vertebrate animals cannot synthesise β-glucans (Desamero et al., 2018). Thus they are recognised by immune cells and can activate and modulate the immune response.

5.1. *The immune-modulatory activity of β-glucans from natural sources*

5.1.1. *Yeast*

Yeast derived β-glucans have been shown to activate immune cells and initiate inflammation, thus reducing incidences of infection and inhibiting cancer progression (Alexander et al., 2018; Dellinger et al., 1999; Netea et al., 2017; Qi et al., 2011; Wojcik et al., 2009; Zhong et al., 2021). Potential bioactive properties of β-glucans are usually measured in macrophages. Phagocytosis is a method used for understanding if β-glucans are recognised by immune cells (Sutter et al., 2016).

Yeast β-glucans have been shown to upregulate the chemotaxis of innate immune cells. This priming can increase resistance to infection in animal models (Adams et al., 1997; Fuller et al., 2017; Ikewaki et al., 2007). PGG is a commercial source of yeast β-glucan; it has been demonstrated to enhance bacterial clearance from blood and thus reduce mortality in a preclinical model of intra-abdominal sepsis in rodents. These preclinical models have included antibiotic-resistant *Staphlococcus aureus* infection (Cisneros et al., 1996; Liang et al., 1998; Onderdonk et al., 1992; Tzianabos et al., 1998).

β-glucans from yeast have also been demonstrated to induce expression of the modulatory cytokine interleukin 1-receptor antagonist (IL-1Ra) in-vitro (Smeekens et al., 2015). A study investigated - β-glucan microparticles (GPs) derived from the yeast *S. cerevisiae* as antigen vehicles and analysed immune-stimulatory effects. The results showed that loaded particles induced a higher T-cell specific response than antigen alone (Baert et al., 2016). Encapsulation of antigens prevents degradation and encapsulation with β-glucan increases immunogenicity.

Pengkumsri et al. (2017) conducted a study to evaluate the immunomodulatory effect of β-glucans isolated from *S. cerevisiae* strains. The β-glucans were extracted from yeast grown in YG broth supplemented with various components. The study involved administering air-dried β-glucan to mice orally for seven days at different concentrations. The results showed that the extracts induced the expression of both pro-inflammatory and anti-inflammatory cytokines in serum analysis. Notably, a low dose was sufficient to stimulate the anti-inflammatory cytokine IL-10, while higher doses were required for the expression of IL-17, an inflammatory marker. No expression of IL-6 was observed. TGF-β was expressed at a higher amount, which is involved in regulating defence and inflammatory responses. This study indicated that consuming yeast β-glucans can alter cytokine expression profiles, and the authors also discussed the yeast's growth conditions for β-glucans extraction (Pengkumsri et al., 2017).

In humans, a multicentre, prospective, randomised, double-blind placebo-controlled clinical trial administered PGG glucan at a dose of 0.5 mg/kg or 1.0 mg/kg to patients after gastro-intestinal procedures found that PGG reduced postoperative infection and death (Dellinger et al., 1999). In a Phase II clinical study, patients with chronic lymphocytic leukaemia were administered mABs in combination with PGG glucan improved the duration of response of the mAbs (Zent et al., 2015). A similar study helped PGG with mAbs to treat small-cell lung cancer (NSCLC). The combination treatment improved the objective response rate and assessment of tumour burden (Thomas et al., 2017).

Ganda Mall et al. (2018) conducted a study on the effects of yeast β-glucan on mast cell-induced hyperpermeability in patients with Crohn's disease and noninflammatory bowel disease (IBD)-controls. The results showed that β-glucan significantly reduced paracellular hyperpermeability in Crohn's disease and transcellular hyperpermeability in the villus epithelium (Ganda Mall et al., 2018).

Aureobasidium pullulans, a black yeast-like fungus, produce β-glucan similar to mushroom fruiting bodies (Tanioka et al., 2013). These β-glucans have been shown to possess anti-tumour effects, prevent cancer progression, prevent viral influenza infection, prevention of food allergies, stimulate immune cells such as NK cells, monocytes and neutrophils and reduction in inflammation (Kim et al., 2007; Kimura et al., 2007, 2006; Muramatsu et al., 2012; Sekar et al., 2018; Tanioka et al., 2013; Větvička et al., 1996).

Yeast-derived beta-glucan has vast applications, including immune cell activation, infection reduction, cancer inhibition, bacterial clearance enhancement, cytokine induction, altered cytokine expression profiles, reduced postoperative infection and death, improved monoclonal antibody response duration, reduced hyperpermeability in Crohn's disease, and possession of anti-tumor effects, prevention of cancer progression and viral influenza infection, food allergy prevention, immune cell stimulation, and inflammation reduction.

5.1.2. *Mycelium*

β-glucans isolated from mycelium also have anticancer, immune-stimulatory and antioxidant effects (Park and Kim, 2017). *Ganoderma lucidium* is widely used to treat various conditions, including arthritis, bronchitis and high blood pressure (Lee et al., 2011). The mushroom also possesses anti-tumour and antioxidant properties (M. H. Park and Kim, 2018). The mycelium of *Phellinus linteus* (PLM) exerts antioxidant, anti-inflammatory, anti-viral, cytotoxic, and anti-diabetic effects (Kim et al., 2004; Nakamura et al., 2004).

The pharmacological efficacy of the products isolated from fermentation-cultivated mycelia is comparable to products isolated from wild fungal materials (Yan et al., 2014). Another species of *Ganoderma, G. sinense* has been used in China as a traditional medicine for more than 2000 years. The active ingredient in *G. sinense* is a polysaccharide that, in 2010, was developed and marketed into a tablet by the China Food and Drug Administration (SFDA) (Zhang et al., 2019).

The immunomodulatory activity of the fungi extracts from solid-state fermentation (SSF) and submerged fermentation was determined by their ability to activate blood neutrophils and influence cytokine production in human peripheral blood mononuclear cells (PBMC) and mouse bone marrow-derived macrophages (BMDM) in a study by Sutter et al. (2016). The extract activated blood neutrophils and significantly modulated the inflammatory cytokine IL-1β cytokine levels after lipopolysaccharide stimulations. In this study, a nitro blue tetrazolium (NBT) reduction assay estimated the activation of neutrophils. The activity measured by this assay correlated with the amount of β-glucan in the mycelium biomass of the filamentous fungi (Sutter et al., 2016).

IL-1Ra is a natural inhibitor of the IL- 1β, a cytokine associated with inflammation. Particulate β-glucan has been demonstrated to induce IL-1Ra, potentially inhibiting IL-1β (Sutter et al., 2016). Other studies have

shown that 1–3 β-glucan decreased the IL-1β/IL-1Ra ratio without generating any significant production of IL-1β, IL-6, TNF-α or IFN - γ all inflammatory cytokines (J Luhm, 2006). Another study demonstrated that PLM elicited immuno-modulatory effects by increasing the INF-γ/IL4 ratio. The extract also displayed anti-inflammatory properties through the inhibition of inflammatory mediators (Shin et al., 2021).

β-glucans isolated from the mushroom cultured on olive mill solid waste (OMSW) substate were administered in an in-vivo model of inflammatory bowel disease. Results demonstrated that intestinal cytokines were downregulated. and there was a reduction in CD14/CD16 monocytes. (Vetvicka et al., 2019).

Sparassis crispa mushroom has been shown to possess immune cells activation, including NK cell stimulation and cytokine inducing activity and anticancer effects, including tumour angiogenesis inhibitory activity, with the majority of activity correlated to β-glucans content (Nishioka et al., 2020; Yamamoto et al., 2009; Yoshikawa et al., 2010).

5.1.3. Bacteria

Curdlan has been shown to increase the population of *Lactobacillus* in the gut (Shi et al., 2018). A healthy gut microbiome is required for a healthy immune system. When administered in an in-vivo mouse model of cyclophosphamide (CTX)-induced immunosuppression, Curdlan increases nitric oxide release, increases cytokine expression and splenic lymphocyte proliferation (Tang et al., 2019).

Curdlan sulfate, a sulphated glycoconjugate, was investigated as a potential treatment for malaria. *In-vitro*, it inhibited erythrocyte rosette formation in *Plasmodium falciparum* laboratory strains and clinic isolates (Kyriacou et al., 2007). Curdlan also increased the immunogenicity of the hepatitis B vaccine. This was achieved by promoting antibody response to hepatitis B surface antigen (HBsAg) (Li et al., 2014). Paramylon has been demonstrated to have anti-tumour activity (Barsanti et al., 2011b). Curdlan derivatives were also shown to inhibit HEp-G2 tumour cell growth (Bădulescu et al., 2009).

5.1.4. Microalgae

Paramylon isolated from *E. gracilis* was found to have decreased abdominal fat accumulation in obese mice. There was also a dose-dependent decrease in postprandial glucose levels, serum low-density lipoprotein (LDL)-cholesterol, and serum secretory immunoglobulin A (IgA) concentrations (Aoe et al., 2019). When investigated for their anti-fibrotic effect in mice with liver fibrosis - Paramylon dampened the CCl4-induced loss of weight. It prevented the increase of aspartate aminotransferase (AST) typical of hepatocyte damage and reduced the overall alteration of tissue parenchyma. The lobular architecture was like that non-damaged liver (Barsanti and Gualtieri, 2019). Paramylon can stimulate Dectin-1(Nakashima et al., 2017; Russo et al., 2017; Yasuda et al., 2020b).

Paramylon has also been shown to reduce the severity of upper respiratory tract infections (URTIs) compared to placebo, inhibit the development of atopic dermatitis mice, possess anti-allergy effects, activate leukocytes and increase ROS production in neutrophils and monocytes and activate IL-1β-mediated inflammatory response in human primary macrophages (Evans et al., 2019b; Russo et al., 2017; Sonck et al., 2010; Sugiyama et al., 2010). In wounds, film dressing prepared with Paramylon speeds up wound healing in mice facilitated through regulation of the immune response. (Yasuda et al., 2018).

A study by Russo et al. (2017) investigated the activation details of human lymphocytes stimulated by different β-glucans, including Paramylon. Results demonstrated that sonicated and alkalised Paramylon upregulates inflammatory factors (NO, TNF-α, IL-6, and COX-2) in lymphocytes (Russo et al., 2017). Paramylon nanofibers treatment in human peripheral blood mononuclear cells (PBMC) increased transactivation of NF-κB increase in pro-inflammatory mediators (TNF-α, IL-6, COX-2, and iNOS) (Barsanti and Gualtieri, 2019).

A study by Ishibashi et al. (2019) investigated the immunity-enhancing function of Paramylon in humans. They analysed the reactivity of human serum and salivary antibodies against Paramylon. Participants were healthy men between 30 and 70 years old. Subjects were given test food with an ingestion amount of 500 mg/day and a placebo for four weeks. Results demonstrated induction of antibodies specific against Paramylon in test groups suggesting activation of mucosal immune response after oral administration (Ishibashi et al., 2019).

In a preclinical model of atopic dermatitis (AD)-like skin lesions induced by repeated application of 2,4,6-trinitrochlorobenzene (TNCB), oral administration of Paramylon inhibited AD development skin lesions, reduced the infiltration of inflammatory cells to the skin and serum IgE levels. The serum levels of IL-4 and IFN-γ and IL-18 and IL-12 in skin lesions were also reduced. The authors suggest the effects are achieved through suppression of T-helper (Th) 1 and Th 2 cell responses (Sugiyama et al., 2010).

A clinical trial administered Paramylon food in a randomised, double-blind, placebo-controlled, parallel-group comparison study in 66 healthy men and women. Participants were administered Paramylon daily for four weeks. The treatment group showed significantly lower levels of physical and mental fatigue sensations. The treatment group also had higher serum biological antioxidant levels than the placebo group (Kawano et al., 2020).

Preclinical in-vivo models demonstrated that when Paramylon was administered, survival increased after *Escherichia coli* injury through oral administration, NK cell cytotoxicity and stimulation of dendritic cells in Peyer patches after intraperitoneal injection of Paramylon. Antibacterial activity against *E. coli* and *Staphylococcus aureus* has also been shown (Gissibl et al., 2019; Watanabe et al., 2013; Yasuda et al., 2020b).

Paramylon, derived from *E. gracilis*, has demonstrated numerous beneficial effects, including reducing abdominal fat accumulation, improving glucose and cholesterol levels, and stimulating immune cells. It has also shown promise in treating liver fibrosis, upper respiratory tract infections, atopic dermatitis, and fatigue. Additionally, it exhibits antibacterial and anti-allergy effects.

6. Conclusion

β-glucans are one of the most common biomolecules and have played an important role in the treatment of a wide range of human diseases. Natural polymers are preferred over synthetic polymers because they are less expensive, more widely available, cost-effective because they are biodegradable, and biocompatible with a few exceptions. Biotechnological processing environments, growth conditions, pH, and so on can all be automated, and controlled. These same processes can have an impact on the production of β-glucans. One of the many benefits of these processes is that no genetic modification or post-translational modifications are required as these microorganisms already produce the compound of interest. All that is required is that the environments be changed to manipulate production. As a result, the future of β-glucan production for improved animal and human health appears bright. β-glucans from microbial sources possess a range of immune-modulating functions. Yeast-derived beta-glucan has numerous applications, including immune cell activation, infection reduction, cancer inhibition, and inflammation reduction. β-glucans isolated from mycelium and mushrooms such as *Ganoderma lucidum* and *Phellinus linteus* have anticancer, immune-stimulatory, and antioxidant effects. Curdlan has beneficial effects on the gut microbiome, boosts the immune system, and has anti-tumour properties. Paramylon derived from *Euglena gracilis* has anti-fibrotic, antibacterial, and anti-allergy effects, and shows promise in treating various health conditions, including upper respiratory tract infections, atopic dermatitis, and fatigue. The biotechnological processing of microorganisms to produce naturafl β-glucans offers a promising avenue for improving animal and human health through the wide range of immune-modulating functions they possess.

Data Availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.micres.2023.127424.

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