



Beta-Glucan in barley as a natural immunomodulator: mechanisms and therapeutic potential

Hafiz Ghulam Muhi Din Ahmed^{1,2} · Li'E Yang² · Xiaomeng Yang² · Jiazhen Yang² · Sajid Hussain³ · Muhammad Danial Shafiq⁴ · Muhammad Irfan Akram⁵ · Muhammad Sajad¹ · Yawen Zeng²

Received: 28 April 2025 / Accepted: 2 October 2025 / Published online: 11 October 2025
© The Author(s), under exclusive licence to Springer Nature B.V. 2025

Abstract

Barley (*Hordeum vulgare* L.) is a major cereal crop recognized for its abundant β -glucan content, a soluble dietary fiber exhibiting significant nutritional and immunomodulatory properties. Structurally composed of mixed-linkage (1 \rightarrow 3) (1 \rightarrow 4)- β -D-glucopyranosyl units, barley β -glucans possess unique physicochemical attributes underpinning their biological activity. Their biosynthesis is primarily governed by cellulose synthase-like (Csl) genes, notably *HvCslF6*, while environmental conditions, agronomic practices, and genetic diversity further modulate β -glucan accumulation. β -glucans act as natural immunomodulators, engaging pattern recognition receptors such as Dectin-1, Toll-like receptor 2 (TLR2), and CR3, thereby activating key innate and adaptive immune pathways, including the MyD88 and Syk cascades. This results in enhanced macrophage, dendritic cell, activate natural killer (NK) cells, and T-cell functions, along with modulation of inflammatory and oxidative stress responses. Barley β -glucans also exert antiviral, anti-inflammatory, antioxidant, and metabolic regulatory effects, contributing to the management of chronic conditions including cardiovascular diseases, diabetes, cancer, and inflammatory disorders. Recent advancements in pretreatment (germination, fermentation, ultrasonic-assisted extraction), molecular breeding (QTL mapping, GWAS, MAS), and genome editing (CRISPR/Cas9 targeting Csl genes) have accelerated efforts to optimize β -glucan yield and functionality. Emerging applications extend beyond nutrition to biomedical materials and vaccine adjuvants, driven by β -glucan's ability to induce trained immunity and enhance vaccine responses. Nonetheless, structural heterogeneity and incomplete mechanistic insights pose challenges to clinical translation. This review critically integrates molecular, immunological, and biotechnological perspectives on barley β -glucans, emphasizing the need for multidisciplinary strategies to unlock their full therapeutic and functional potential in advancing human health and sustainable food systems.

Keywords Beta-glucan · Immunomodulation · Barley · Innate · Therapeutics · Inflammation

Hafiz Ghulam Muhi Din Ahmed, Li'E Yang and Xiaomeng Yang contributed equally to this work.

✉ Hafiz Ghulam Muhi Din Ahmed
ahmedbreeder@gmail.com

✉ Yawen Zeng
zengyw1967@126.com

¹ Department of Plant Breeding and Genetics, Faculty of Agriculture and Environment, The Islamia University of Bahawalpur, Bahawalpur, Punjab 63100, Pakistan

² Biotechnology and Germplasm Resources Institute, Yunnan Academy of Agricultural Sciences, Kunming, Yunnan 650205, China

³ Department of Agronomy, Faculty of Agricultural Sciences and Technology (FAST), University of Layyah, Layyah, Punjab 31200, Pakistan

⁴ School of Environmental and Rural Science, University of New England Armidale, Armidale, NSW 2351, Australia

⁵ Department of Entomology, Faculty of Agriculture and Environment, The Islamia University of Bahawalpur, Bahawalpur, Punjab 63100, Pakistan

Introduction

Barley is a significant cereal crop due to the presence of beta-glucan, a substance that carries multiple health benefits like cholesterol lowering and improved glycemic control [1]. Beta-glucan, a soluble fiber, plays a crucial role in both food and animal feed applications, as it significantly influences the quality of barley-based products [2]. Beta-glucan is a soluble type of dietary fiber present mostly in barley (*Hordeum vulgare* L.) and due to its health-promoting and functional benefits, has received considerable attention. Barley possesses a variable beta-glucan content of between 3.57% and 5.34% depending on variety as well as environmental conditions [3].

Barley, particularly hull-less barley, is a rich source of β -glucan, the content of which is determined genetically as well as by the environment. Studies have established that barley β -glucan content varies from 2.56% to 11.73% due to genotype as well as environmental conditions [4]. Its molecular structure consists of linear chains of β -D-glucopyranosyl residues linked by 1,3 as well as 1,4 glycosidic bonds, which are responsible for its solubility as well as for its viscoelasticity [5]. Extraction methods, such as controlled pH and temperature water extraction, offer beta-glucan a spectrum of molecular weights that affect the functional characteristics such as water binding capacity and emulsification [6]. Beta-glucan possesses antimicrobial action against a spectrum of disease-causing microorganisms and acts as a prebiotic for promoting the growth of healthy bacteria within foods [7]. Generally, nutritional as well as functional characteristics of barley beta-glucan have rendered it a popular ingredient for application within foods as well as health products.

Structure, composition, and factors influencing Beta-glucan content

Structure of barley β -glucan is reported as having a mixed-linkage (1 \rightarrow 3)(1 \rightarrow 4)-linked β -d-glucan with markedly diverse molecular weights, for example, 201,000 Da for Qingke barley [8]. Thermal stability as well as barley variety rheological traits determine physicochemical attributes of β -glucan, some of which have non-Newtonian flow as well as diverse binding capacity [9, 10]. It serves as a thickener, a stabilizer, as well as a prebiotic with extensive application as a foodstuff for promoting gut health as well as modulation of starch digestibility [11]. The beta-glucan content of barley is extremely variable as per genotype as well as agricultural practice ranging from 3.18% to 7.7% under regular conditions. Beta-glucan content of hulled barley accessions varies between 3.18% as well as 4.51%, while naked barley can range up to 5.21% [12]. High beta-glucan as well

as protein content genotypes, i.e., ‘Nudum 155’ as well as ‘Nudum 95’, are suitable for food as well as feed purposes [13, 14]. Besides, genetic basis for high beta-glucan content was determined with two Quantitative Trait Loci (QTL) at chromosomes 1 H as well as 7 H, accounting for about 27.9% as well as 27.4% of the phenotype’s variance, respectively [15].

Barley beta-glucan content is the result of an interaction between environmental factors, genotype, and agricultural practice. Climatic factors, particularly temperature and rainfall at specific phases of development, are significant; cooler temperatures during tillering and higher kernel weights are positively correlated with β -glucan content, and excessive rain during the grain-filling stage is negatively correlated with it [5]. Genotypic differences are involved as well, with different cultivars of barley with different content of β -glucan, which is environment- as well as year-dependent [16]. Agronomic traits such as test weight, seed yield, as well as percentage of plump kernels are connected with content of β -glucan, indicating that both genetic as well as environmental interactions need to be addressed for maximizing content of β -glucan of barley [17]. Further, farming systems influence the content of β -glucan, with no-treatment and organic farms containing more than conventional farms [18]. Quantitative trait loci (QTL) for β -glucan content have been determined through research carried out using genetics that have identified important genes participating in its biosynthesis as well as metabolism that can be utilized for breeding for barley improvement for diverse uses [4].

Role of Beta-glucan as a natural Immunomodulator

Beta-glucan from barley is a strong natural immunomodulator with superior bioactivities, accelerating immune stimulation. Barley β -glucan acts as a natural immunomodulator through its role in promoting the activities of CAT and GPx, decreasing MDA content, as well as significantly enhancing IgG and IgM content within immunosuppressed rats, leading to restoration of overall immune response as well as hematological tests, e.g., due to arsenic trioxide poisoning, hence proving to have the ability to boost immunity. These polysaccharides activate immune receptors like Dectin-1 and Toll-like receptor 2 (TLR2) to facilitate co-localization for activation of immune signaling cascades, a critical infection resistance mechanism [19]. Barley β -glucans have also been shown to activate innate as well as adaptive immune functions and are hence functional food components for triggering health as well as immunity in both humans as well as animals [20, 21]. They are immune response mediators through dendritic maturation stimulation as well as secretion of cytokines, hence impacting both innate as well as adaptive immunity [22]. Beta-glucans boost the adaptive

immune response through augmented antigen presentation as well as activation of T cells, hence increased antibody levels upon vaccination [23]. They are immune-modulating

Table 1 Selected products and applications of β -Glucan as a therapeutic agent

Product Name/Type	Source	Form	Therapeutic Potential	Health Focus	Reference(s)
OatWell®	Oat β -glucan	Cereal ingredient	Lowers LDL cholesterol, reduces post-prandial glucose	Cardiovascular, metabolic syndrome	EFSA, 2010; Wood, 2007
Barliv™	Barley β -glucan	Concentrated extract	Improves insulin sensitivity, supports immune balance	Diabetes, immune regulation	Tosh & Chu, 2015
Nutra-Barley™	Barley β -glucan	Functional fiber	Promotes gut health, reduces cholesterol	Digestive health, lipid metabolism	Keenan et al., 2007
Wellmune®	Yeast β -glucan	Supplement/beverage	Enhances innate immune response, reduces URT infections	Immunity, respiratory health	Talbott & Talbott, 2009
Imunoglukan P4H®	Fungal β -glucan	Syrup/tablets	Stimulates immune defense, reduces infection frequency	Pediatric immunity	Jesenak et al., 2013
BetaHeart®	Oat β -glucan	Powder supplement	Maintains healthy cholesterol levels	Heart health	EFSA, 2010
Barley-Max™	Barley β -glucan	Whole grain flour	Antioxidant-rich, supports weight management	Obesity, chronic inflammation	Topping et al., 2003
BetaVia™	Algal β -glucan	Immune supplement	Activates macrophages, improves resistance to pathogens	Immune health, viral defense	Friedman & Juneja, 2010

agents with great strength, especially against viral diseases, where they can stimulate antiviral action as well as provide a protective action against the pathogen [23, 24]. Furthermore, beta-glucans have proved beneficial for the healing and prevention of allergic diseases through the restoration of the equilibrium of the TH1/TH2 lymphocyte response, which is typically altered in such diseases [25]. Their role in “trained immunity” implies that beta-glucans can regulate immune memory that may result in a positive impact on injury healing as well as chronic disease healing [26]. Altogether, the multimodal immunomodulatory effects of beta-glucans hint at their importance in therapeutic applications as well as health maintenance.

Source variability of β -Glucan

There are different sources of β -glucan that have unique structural characteristics that result in different biological activity or therapeutic potential. Cereal β -glucans, notably from barley, contains mixed-linkage β -(1,3)(1,4)D-glucans that have primarily been associated with benefits for metabolic health, including glycemic control, cholesterol lowering, and modulation of gut microbiota. β -glucans from yeast and fungi have β -(1,3)(1,6) linkages that have been shown to have stronger immunomodulatory effects via direct stimulation of innate immune response signaling pathways, such as activation of macrophages and natural killer (NK) cells [27]. The structural differences pertain to solubility, molecular weight, and interaction with specific receptors that impact the clinical and functional benefit of β -glucan. Understanding these source-driven structural variations is relevant when considering the health benefits of β -glucan. This review highlight the potential of barley β -glucan as a natural immunomodulator, focusing on mechanisms of action and relevant therapeutic implications in the promotion of immune health. Table 1 highlights commercially available products and formulations containing β -glucan derived from various sources, including barley, oats, yeast, fungi, and algae. These products demonstrate the diverse therapeutic potential of β -glucan, ranging from cardiovascular and metabolic health to immune system support and gut microbiota modulation. Notably, barley-derived β -glucan shows promising multifunctional properties as a natural immunomodulator, making it a strategic focus in health food innovation and personalized nutrition.

Scope and objectives of the review

The review addresses *Hordeum vulgare* (barley) β -glucan immunomodulatory activity and therapeutic application, emphasizing the pivotal importance of thorough mechanistic investigations as well as of translational studies. Barley

β -Glucans are bioactive polysaccharides with documented anti-inflammatory, anti-tumor, and immune-stimulating effects through the regulation of innate as well as adaptive immune mechanisms including dendritic maturation, macrophage activation, as well as the elaboration of cytokines [27]. Therapeutic significance is underscored through the development and the use of β -glucan medicines, such as those put to use for cancer. While promising results exist, therapeutic utilization of β -glucans is thwarted by extensive structural heterogeneity, source-dependent variation, and a dearth of knowledge regarding the immunological action involved [28, 29]. This review summarizes the current understanding of the physicochemical properties, immunological interactions, and health-promoting activities of barley β -glucans, and identifies key areas for future research. Special attention is focused on their possible future application as immunotherapy against gastrointestinal cancer as well as for the development of functional foods or nutraceuticals. It combines current advancements with a view of providing a scientific framework to impending multidisciplinary studies for the improvement of the formulation of β -glucan for immunomodulation as well as therapeutic efficacy.

2. Biosynthesis and genetic regulation

Biosynthesis as well as genetic regulation of barley β -glucan are performed through complex interactions of multiple proteins as well as genes. Comparative proteomics of hullless barley cultivars have shown that proteins of differentially expressed carbohydrate metabolism as well as β -glucan biosynthesis are quite different for cultivars with varying levels of β -glucan [30, 31]. Biosynthetic mechanisms of barley beta-glucan (BG) are the outcome of a synergy of enzymatic activities and proteins that facilitate its deposition within the cereal grains. Central proteins involved with the biosynthesis of BG are the cellulose synthase-like (Csl) genes, specifically CslF/H/J, which are responsible for polymerization of BG in aleurone and endosperm tissue [32].

Biosynthesis pathways of β -Glucan in barley

Biosynthesis of (1 \rightarrow 3)(1 \rightarrow 4)- β -D-glucan occurs throughout the plant, within vegetative as well as reproductive (grain) tissue, but with tissue-specific regulation as well as functional specialization (Fig. 1). These Csl family members, namely the CslF, CslH, and CslJ subfamilies, code for the Csl proteins that are responsible for synthesizing the mixed-linkage β -glucans, with their associated glycosyltransferases polymerizing the UDP-glucose-derived glucose

units into the β -(1 \rightarrow 3) and β -(1 \rightarrow 4) glycosidic linkages that form the backbone of the β -glucan polymer [32].

Gene Activation and Transcriptional Regulation.

The Csl genes are expressed variably in a range of plant tissues. *HvCslF6* is expressed universally and is the principal gene for biosynthesis of β -glucan in vegetative as well as grain tissue. More specifically, *HvCslF3*, *HvCslF9*, and *HvCslH1* are expressed preferentially in vegetative parts such as expanding stems and young leaves, suggesting a role for cell wall biosynthesis early in growth [1, 16].

Translation and Enzyme Targeting.

Following transcription, Csl mRNAs are translated into membrane-bound synthase proteins destined for targeting to the Golgi apparatus and plasma membrane for the most part, where polymer assembly is performed. Proper targeting and insertion within these membranes are of importance for enzymatic activity [33, 34].

Polymer Synthesis and Linkage Formation.

The elongation of the β -glucan chain through the sequential addition of β -(1 \rightarrow 4) and β -(1 \rightarrow 3) glycosidic linkages is mediated by the Csl enzymes. Solubility, viscosity, and bioactivity of the resultant β -glucan polymer are established by the ratio and arrangement of these linkages [2, 34].

Subcellular Transport and Deposition.

The newly synthesized β -glucan is transported and deposited in the primary cell wall, where it takes part in wall structure, water status, and mechanical properties. β -glucan plays a structural role in vegetative tissues, controlling cell growth and mechanical strength, but in seeds it plays a role in the storage of energy and dietary fiber [5, 8, 27].

Developmental and Environmental Regulation.

Both developmental signals and environmental signals such as light, temperature, drought, as well as infection with pathogens, regulate β -glucan synthesis actively. For instance, deposition of β -glucan can be strengthened within vegetative tissues to reinforce the cell wall under biotic stress [6, 8, 26].

Tissue-Specific Functions.

In leaves and stems, β -glucans are linked with cell wall firmness and are more transient, with a tendency to be restructured as tissues mature. They occur less often in roots but may be linked with symbiosis interactions or tolerance of physical stress. Beta-glucan is a rich source of nutritional as well as pharmaceutical importance as a source of dietary fibre in seeds [4, 7].

The biosynthesis of barley β -glucan is regulated both temporally and spatially through a complex network of enzymes, with multiple active genes present within the plant. While seeds are of first importance due to nutritional content, vegetative β -glucans have crucial physiological functions as well as structural functions, so biosynthesis

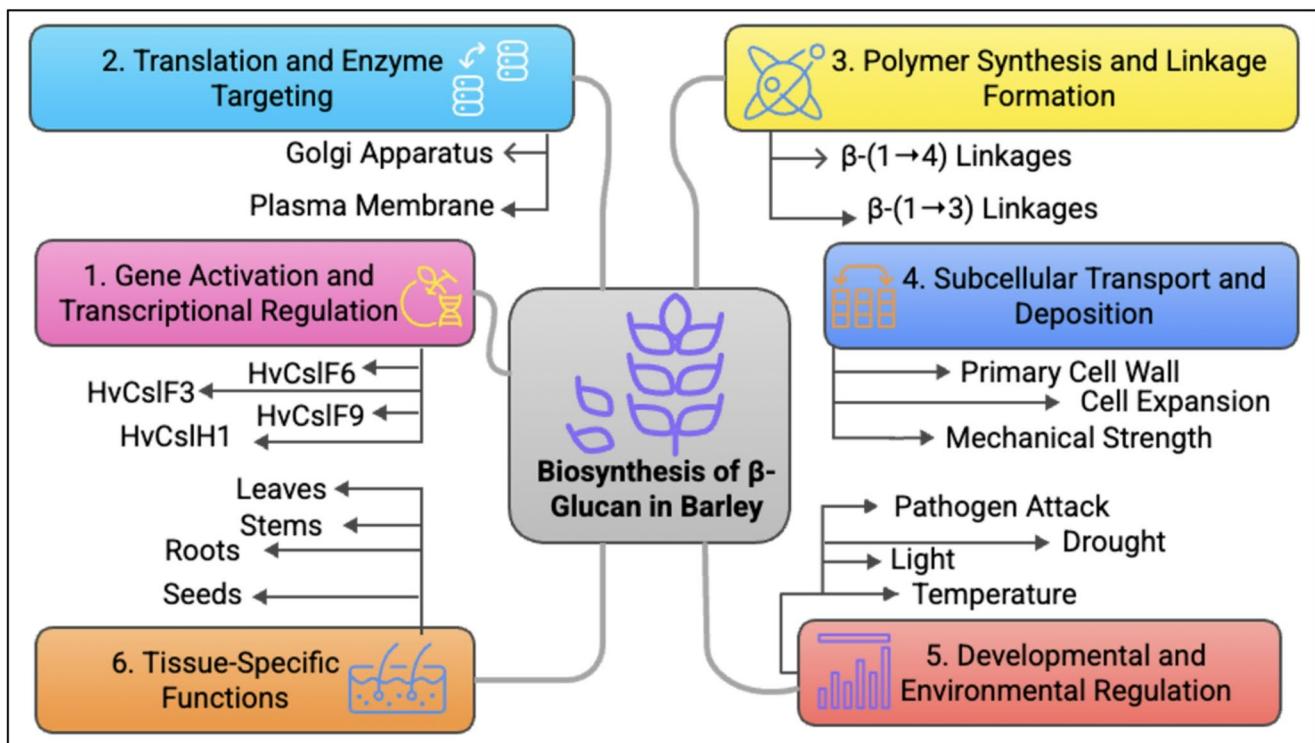


Fig. 1 Schematic representation of β -glucan biosynthesis in barley, encompassing six interconnected stages: (1) genetic regulation by *HvCsl* genes; (2) protein translation and targeting to the plasma membrane; (3) synthesis of β -(1→4) and β -(1→3) linkages; (4) deposition of β -glucan in the primary cell wall, contributing to cell expansion and structural integrity; (5) modulation by developmental and environmen-

tal cues such as light, temperature, pathogen attack, and drought; and (6) functional diversification across various tissues, including leaves, stems, roots, and seeds. Figure prepared using Microsoft PowerPoint (Office 365, updated 2023), Canva (Version 2024.1), and Adobe Photoshop (Adobe Creative Cloud, 2024 release)

of the entire-plant β -glucan is of significance for barley growth, defense, and flexibility.

Key gene families involved in Beta-glucan synthesis in barley

The primary gene families involved in barley (*Hordeum vulgare*) beta-glucan biosynthesis are predominantly represented by the Cellulose synthase-like (Csl) gene superfamily with CslF and CslH subfamilies (Table 2). Interestingly, *HvCslF6* was found to be a central enzyme for (1,3;1,4)- β -glucan biosynthesis because mutations of the gene imposed a complete loss of polysaccharide from the grain, whereas other relatives *HvCslF9* did not affect the content of β -glucan but had impacts on the other components of the cell wall [15]. The most differentiated core gene is *HvCslF6* with high expression levels in vegetative tissues as well as reproductive tissues with a direct correlation with endosperm development due to β -glucan accumulation. Functional validation through TILLING mutants as well as transgenic mutants established that *HvCslF6* down-regulation leads to near-total depletion of β -glucan deposition, positioning it at a pivotal position. The other CslFs

in CslF, *HvCslF3*, *HvCslF9*, and *HvCslF4* are expressed most highly in elongating vegetative tissues of stems and leaves, suggesting ancillary functions for primary cell wall biosynthesis and tissue-specific regulation. The *HvCslH* subfamily, specifically *HvCslH1*, is a backup enzyme for β -glucan construction with generally lesser efficacy compared to *CslF6*. Products of the enzyme are both targeted to the plasma membrane as well as the Golgi apparatus, where the polymers of the β -glucan are positioned together by the formation of β -(1→4) as well as β -(1→3) bonds. Moreover, the barley genome houses a very extensive set of genes, 116 BAHD family acyltransferases, whose indirect effects are potentially involved in the metabolism of polysaccharides as well as cell wall composition whereas direct functions within the assembly of β -glucans are less obvious [35]. Additionally, the XTH gene family, with a minimum of 42 members, can contribute to the modification of the components of the cell wall, hence indirectly causing the synthesis of β -glucan [36]. Comparative genomics and promoter studies have also recently uncovered evolutionary divergence and functional divergence in the Csl gene family, providing the potential for precise manipulation via the application of CRISPR/Cas9 and gene editing for the alteration of

Table 2 Key gene families involved in β -Glucan synthesis in barley and their function

Gene/Family	Main Function	Tissue-Specific Expression	Notes/Impact on β -Glucan Synthesis
HvCslF6	Primary enzyme for (1,3;1,4)- β -glucan biosynthesis	Reproductive tissues (grain), vegetative tissues (leaves, stems)	Essential for β -glucan accumulation; loss-of-function mutants show near-complete β -glucan absence
HvCslF3	Contributes to cell wall biosynthesis	Young leaves and elongating stems	Minor role in β -glucan content; involved in vegetative growth
HvCslF9	Modulates cell wall components	Vegetative tissues	Little direct impact on β -glucan content, but influences cell wall structure
HvCslF4	Auxiliary role in polysaccharide biosynthesis	Elongating stems and leaves	Possible supportive function in primary cell wall modification
HvCslH1	Supplementary β -glucan synthesis	Reproductive tissues	Complementary role to HvCslF6; less impact overall
BAHD Acyltransferases	Polysaccharide metabolism modulation	Various tissues	Indirect influence on cell wall structure; impact on β -glucan under investigation
XTH (Xyloglucan endotransglycosylase/hydrolase)	Cell wall remodeling	Broad expression	May modify or impact β -glucan via remodeling of polysaccharide networks
CslF Family (General)	(1,3;1,4)- β -glucan synthesis	Diverse tissues	Evolutionary specialization; targets for bioengineering β -glucan traits
CslH Family (General)	Cell wall polysaccharide synthesis	Mainly reproductive	Less dominant compared to CslF; complementary role in β -glucan biosynthesis
Promoter Regions (Csl genes)	Regulation of gene expression	Tissue-specific regulation	Important for transcriptional control and trait optimization via genetic editing

β -glucan content for nutritional, industrial, and therapeutic uses. Collectively, the gene families have a multifaceted role in the control of barley content with Csl.

Genetic variability and breeding for high Beta-Glucan content

Plant breeding and biotech are the key drivers in increasing the content of beta-glucan in barley, a cereal of high genetic diversity with desirable traits. Recent studies have determined key genetic loci and candidate genes for the synthesis of beta-glucan, which facilitate precision breeding programs. For example, genome-wide association studies (GWAS) identified robust marker-trait associations, pointing to genes HORVU6Hr1G088380 at the center of beta-glucan accumulation [2, 37]. Several studies have identified the main loci associated with increased barley beta-glucan content. Two Quantitative Trait Loci (QTL) on chromosomes 1 H and 7 H were found to contribute a combined percentage of around 55.3% to the variation of beta-glucan content, with HvCslF9 and Horvu_PLANET_7H01G069300 being candidate genes associated with these loci [12]. Furthermore, a genome-wide association study (GWAS) detected

14 stable marker-trait associations (MTAs) for beta-glucan content [2]. Besides that, a wild barley study detected 13 QTL on all seven chromosomes targeting genes involved in carbohydrate metabolism as well as cell wall modification, for example, callose synthase [4]. Quantitative trait loci (QTL) of large effect for increasing the content of β -glucan in barley were identified on chromosomes 2 H, 3 H, 4 H, and 7 H, which are of great importance for understanding and manipulating β -glucan development in barley grains [32, 38]. These results together provide a strong platform for barley breeding for increased beta-glucan content. Among the primary genetic loci for creating increased beta-glucan content of barley are a gene cluster located on chromosome 2 H, for instance, HvCslF3, HvCslF4, HvCslF8, HvCslF10, HvCslF12, and HvCslH1, revealed through QTL and GWAS mapping [15]. With the inclusion of molecular techniques such as RNA-seq and SNP evaluation, breeding schemes are more specific with the improvement of barley cultivars for functional foods with regard for the requirements of malt manufacture [4, 39]. This holistic approach is centered around biotechnology as a means of barley simplification for health purposes.

Immunomodulatory mechanisms

Barley β -glucan possesses strong immune-modulating mechanisms through immune receptor binding as well as immune response induction. Barley β -glucan activates Toll-like receptor 2 (TLR2) as well as Dectin-1, leading to co localization of the receptors as well as immune signaling, which is of great significance for the control of infection such as *Leishmania donovani* [19]. Aside from the above, barley β -glucan was also found to improve hematological parameters as well as the rate of immunoglobulins (IgG and IgM) in immunosuppressed models, reflecting its effect for bolstering overall immunity. Low molecular weight barley β -glucan was, in another instance, found to strongly activate dendritic cell maturation associated with their enhanced function to stimulate adaptive immune responses (Fig. 2).

Interaction with pattern recognition receptors (PRRs)

Beta-glucans, especially from barley, are known to possess strong immunomodulatory effects through their action against pattern recognition receptors (PRRs) for example, Dectin-1, as well as Toll-like receptors (TLRs). These polysaccharides preferentially bind to Dectin-1, causing co-localization of the receptor with TLR2, stimulating downstream signaling pathways such as MyD88 and Syk, resulting in enhanced inflammatory responses as well as immune protection against *Leishmania donovani* and other microorganisms [19, 40]. When bound, Dectin-1 stimulates downstream signaling molecules, such as MyD88 and Syk, that are involved in the induction of inflammation as well as immune cell activation [41]. B-glucans stimulate multiple immune cells, such as macrophages as well as dendritic cells, to trigger internalization of these ligands as well as subsequent immune responses [42]. This multistep process unearths the therapeutic benefits of barley β -glucans as

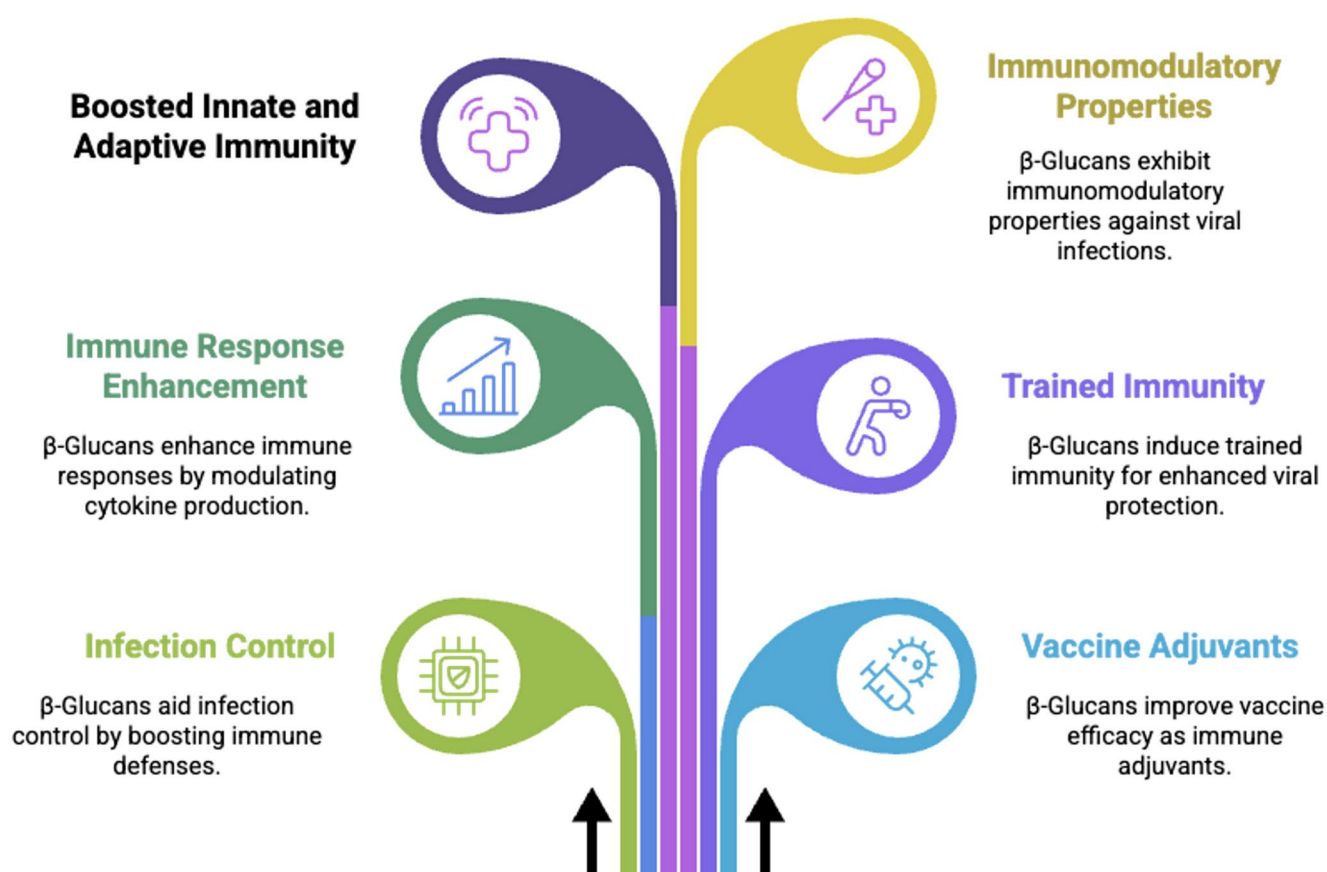


Fig. 2 Unveiling the Immunomodulatory Power of Barley β -Glucans. This figure illustrates the six primary mechanisms by which β -Glucans enhance immune function: Boosted Innate and Adaptive Immunity (comprehensive defense); Immunomodulatory Properties (regulation against viral infections); Immune Response Enhancement (modulating cytokine production); Trained Immunity (inducing innate immune

memory for enhanced viral protection); Infection Control (boosting immune defenses); and functioning as Vaccine Adjuvants (improving vaccine efficacy). Figure prepared using Microsoft PowerPoint (Office 365, updated 2023), Canva (Version 2024.1), and Adobe Photoshop (Adobe Creative Cloud, 2024 release)

immunostimulant agents for uses against infections as well as potentially for cancer. Beta-glucans activate autophagy cascades through NOX-2, triggering the generation of reactive oxygen species crucial for immune activation [43, 44]. They also play a role in B cell differentiation and cytokine secretion, modulating adaptive immunity via Dectin-1 activation [40]. They also induce type I interferon responses via Dectin-1 activation by β -glucans, inducing antiviral immunity and suggesting a general immunomodulatory function [45]. Also, β -glucan binding to Dectin-1 was shown to induce pro-inflammatory cytokine secretion from a number of immune cells, including bovine monocytes, thereby establishing its immunopotentiating potential for general use [46–48].

Modulation of innate and adaptive immunity

Innate immunity is a rapid, generally nonspecific, immediate defense, while adaptive immunity is a slow, more specific, and targeted defense mechanism which improves with repeated exposures to the same pathogen (Table 3). Both the innate and acquired branches of the immune system as a whole form a complete immune mechanism against infections [19]. Beta-glucans, specifically barley-derived

beta-glucans, are significant regulators of innate as well as acquired immunity because they can activate important immune cells such as macrophages, natural killer (NK) cells, as well as T-cells. It is noted from research that barley β -glucan can stimulate macrophage differentiation of M0 to M1 phenotype as well as enhance their pro-inflammatory response along with activation of NK cells, which are crucial for antitumor immunity [49]. Additionally, β -glucans interact with Toll-like receptor 2 (TLR2) as well as with the receptor Dectin-1 to facilitate co-localization that triggers immune signaling pathways, thereby augmenting the immune response against infections such as *Leishmania* [19]. Additionally, β -glucans have been found to create innate immune memory, capable of regulating macrophage activation by different environmental stimuli, potentially making it more effective against infection [50]. Overall, the immunomodulating activity of β -glucans suggests their application as nutritional supplements for immune response improvement in humans as well as animals [20, 23]. Barley beta-glucans are polysaccharides with strong immune-stimulating effects, particularly through macrophage stimulation, activation of natural killer (NK) cells, as well as T-cell activation. It is suggested through studies that activation of macrophages creates innate immune memory with reprogramming of the function reducing inflammation but enhancing immunity to infection and tumors [51, 52]. Specifically, barley β -glucans polarize macrophages to the M2 phenotype responsible for tissue repair as well as anti-inflammatory response, promoting healing of wounds in immunosuppressed models [53, 54]. Overall, barley β -glucans are potent immunostimulant compounds that activate both innate and adaptive immune mechanisms [20]. Even more recent studies have addressed the use of barley-derived β -glucans as adjuvants for immune stimulation by vaccines due to their ability to provoke humoral as well as cellular immunity. The therapeutic applications of β -glucans have immense potential for their clinical uses in immune-mediated diseases, autoimmunity, cancer immunotherapy, as well as chronic inflammatory diseases [55–57]. Thus, barley β -glucans have a pivotal role as a component of the plant's defense chemical arsenal as well as a beneficial adjuvant to augment immune function in man through their strictly regulated modulation of innate as well as adaptive immunity.

Anti-Inflammatory and antioxidant effects

Beta-glucan of barley possesses strong anti-inflammatory and antioxidant effects through modulation of cytokine levels and alleviation of oxidative stress. Evidence indicates barley β -glucan plays a therapeutic action against inflammation of the airway by down-regulating pro-inflammatory

Table 3 Immunological mechanisms targeted by Barley-Derived β -Glucans in innate and adaptive systems

Aspect	Innate Immunity Modulation	Adaptive Immunity Modulation
Key Immune Cells Activated	Macrophages (M1/M2 polarization), Natural Killer (NK) cells	T-cells (CD4+, CD8+ activation)
Receptors Involved	Dectin-1, Toll-like receptor 2 (TLR2)	Dectin-1 interaction, enhanced antigen presentation
Mechanism of Action	Induction of innate immune memory; enhanced phagocytosis and cytokine production	Augmentation of antigen-specific responses and memory T-cell generation
Phenotypic Changes	Macrophage differentiation (M0 \rightarrow M1/M2 states)	Increased T-cell proliferation and activation
Impact on Infections	Improved pathogen clearance (e.g., <i>Leishmania</i>)	Enhanced long-term immunity after infections or vaccinations
Role in Tumor Immunity	NK cell activation and tumor cytotoxicity	Activation of tumor-specific adaptive immune responses
Use as Vaccine Adjuvants	Priming of innate immune pathways, boosting vaccine responses	Enhanced antibody production and cellular immunity
Therapeutic Applications	Wound healing, anti-inflammatory treatments	Cancer immunotherapy, modulation of autoimmune diseases
Clinical Implications	Immunonutrition, infection control strategies	Chronic disease prevention and management

cytokines as well as oxidative stress markers such as malondialdehyde (MDA) and up-regulating antioxidant enzymes such as glutathione peroxidase and catalase [58]. Barley is rich in bioactive phytochemicals including flavonoids and phenolic acids, which are accountable for its antioxidant activity [59, 60]. Barley's anti-inflammatory constituents involve NF- κ B and JNK pathway inhibition as well as pro-inflammatory mediators, particularly with fermentation, enhancing their effectiveness [61, 62]. Moreover, highland barley β -glucan was also shown to ease ulcerative colitis symptoms in mice, indicating its application for gastrointestinal health through control of inflammatory reaction and improvement of intestinal barrier [63, 64]. Additionally, barley β -glucan inhibited the generation of nitric oxide as well as the expression of inducible nitric oxide synthase and cyclooxygenase-2 in macrophages, again demonstrating its anti-inflammatory action [53, 65]. Moreover, barley β -glucan fermentation increases its anti-inflammatory activity, consistent with high levels of beneficial metabolites promoting gut health [63]. All of these findings are testaments to the therapeutic potential of barley-derived β -glucans for inflammation modulation as well as disease associated with oxidative stress [23, 66].

Therapeutic potential and clinical applications

Beta-glucan from barley holds immense therapeutic value for a wide range of clinical uses, the most obvious of which are its metabolic and immunological uses (Fig. 3). Its role in regulating lipid as well as glucose metabolism makes it a promising drug candidate for the management of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), where research documents its ability to boost expenditure of energy as well as normalize bile acid metabolism to avert fat deposition in mice [64, 67]. Additionally, its immunomodulatory effects have been highlighted in cancer therapies, where β -glucan has been shown to be efficient as an adjuvant in the treatment of gastrointestinal tumors, improving the quality of life of patients and minimizing chemotherapy side effects [45]. Additionally, barley β -glucan had the potential to enhance immune effects in immunosuppressed models, making it a potential functional food ingredient for enhancing immunity. Cumulatively, the findings demonstrate the diversity of mechanisms through which barley-derived β -glucan can be involved in controlling disease and health [27, 68].

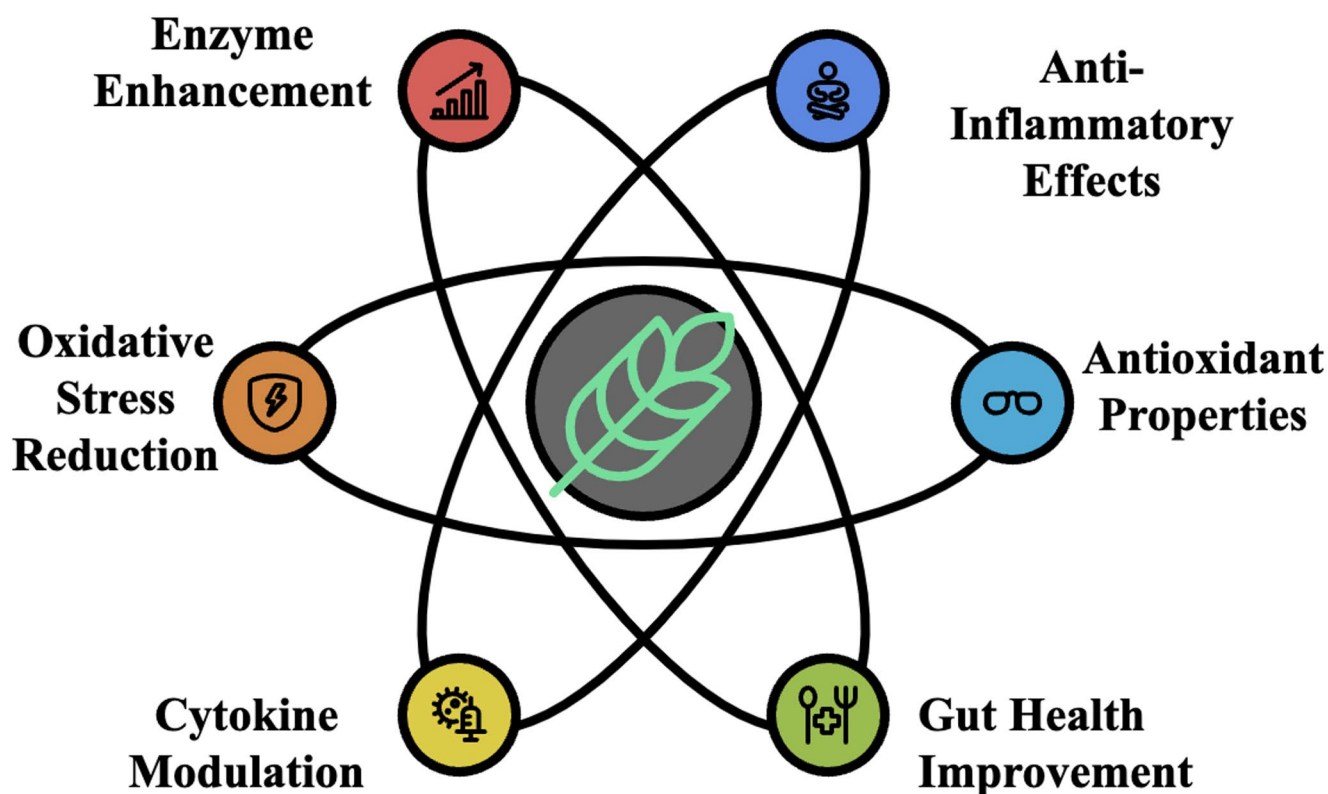


Fig. 3 This figure illustrates the six primary health benefits of β -glucan: Enzyme Enhancement, Anti-Inflammatory Effects, Antioxidant Properties, Gut Health Improvement, Cytokine Modulation, and Oxidative Stress Reduction, highlighting its multifaceted positive impact on

human health. Figure prepared using Microsoft PowerPoint (Office 365, updated 2023), Canva (Version 2024.1), and Adobe Photoshop (Adobe Creative Cloud, 2024 release)

Prevention and management of chronic diseases

Beta-glucan, particularly barley-derived beta-glucan is of huge promise for the control of chronic diseases including cancer, diabetes, as well as cardiovascular disease. Research indicates that low-molecular-weight β -glucan is capable of inducing apoptosis of cancer cells of the colon, inhibiting tumor growth, as well as enhancing therapeutic efficacy against cancer [68, 69]. β -Glucans' capacity to form a gel-like substance retards gastric emptying and reduces postprandial peaks of glucose by enhancing insulin sensitivity and glycemic control. Mechanistically, it acts on the expression of the glucose transporters (GLUT) and modulates incretin hormones such as GLP-1, leading to enhanced glucose homeostasis. β -glucan enhances insulin sensitivity and lowers the level of blood glucose by enhancing the viscosity of the dietary fiber so that gastric emptying is slowed [70]. More importantly, the impacts on the cardiovascular realm are significant; β -glucan lowers total and LDL cholesterol and elevates HDL cholesterol, lowering the cardiovascular

risks of heart disease [71]. Overall, the addition of barley β -glucan as a food ingredient not only contributes positively towards metabolic health but also represents a holistic solution for the management of chronic disease through its antioxidant potential and modulation of the profiles of lipids and blood glucose [72].

Role in infection control and vaccine adjuvants

Barley beta-glucans contribute towards infection defense as adjuvants for vaccines by promoting immunity and preventing infection. Barley β -glucans are reported to promote immunity by elevating immunoglobulin levels and regulating the production of cytokines, and may prove particularly useful in immunocompromised subjects (Fig. 3). They have also proven to improve innate and adaptive immunity and improve the effectiveness of influenza A virus vaccines [73]. β -glucans have also been reported to cause "trained immunity," meaning that innate immune cells are more responsive on repeated exposure and offer a protective advantage for viral disease [74, 75]. Studies demonstrated that the effectiveness of vaccines is enhanced by β -glucans due to increased antibody titers within vaccinated models upon pre-exposure of β -glucans [24, 76]. Aside from this, β -glucans possess immunomodulatory effects that enhance innate and adaptive immunity and are thus effective against viral diseases like COVID-19 [77]. Barley β -glucans have also proven effective at elevating the functionality of immunity in immunosuppressed models and barley can be utilized as a food ingredient for common immunity [23, 78]. The use of barley-derived β -glucans thus holds great promise for significantly improving resistance to infection.

Applications in autoimmune and inflammatory disorders

Barley beta-glucan can be used as a treatment for autoimmune and inflammatory diseases particularly inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) as demonstrated by Table 4. β -Glucan of barley was also reported to mitigate symptoms of UC in mice models by decreasing disease activity indices, improving the health of the intestine, and by modulating the inflammatory cytokine levels [61, 79]. β -glucan was revealed to cause innate immune memory within macrophages by decreasing the activation of the NLRP3 inflammasome and the production of IL-1 β , and this finds application in conditions such as cryopyrin-associated periodic syndromes (CAPS) [51]. Additionally, its usage includes veterinary medicine where β -glucans have also displayed immunomodulatory activity towards the treatment of inflammatory bowel disease in dogs and cats, a sign of its wider utility as a

Table 4 Applications of Barley-Derived β -Glucans in autoimmune and inflammatory disorders

Disorder/Condition	Mechanism of Action	Key Outcomes	Notes/Implications
Ulcerative Colitis (UC)	Modulation of inflammatory cytokines	Reduced disease activity, improved gut health	Mouse model studies show symptom alleviation
Crohn's Disease (CD)	Regulation of immune responses	Inflammation reduction	Potential therapeutic candidate
Cryopyrin-Associated Periodic Syndromes (CAPS)	Inhibition of NLRP3 inflammasome activation	Decreased IL-1 β secretion	Targets innate immune pathways
Inflammatory Bowel Disease (IBD) in Animals	Immunomodulation in gut mucosa	Symptom management in dogs and cats	Veterinary applications expanding
General Autoimmune Disorders	Induction of innate immune memory	Improved immune regulation	Broad anti-inflammatory benefits
Intestinal Inflammation	Enhancement of autophagy and ROS production	Strengthened immune defenses	Critical for gut immune homeostasis
Ulcerative Colitis (Highland Barley β -Glucan)	Cytokine balance modulation	Reduced intestinal inflammation	Specific effect of highland barley varieties
Chronic Inflammatory Disorders	Activation of immune receptor pathways	Controlled immune responses	Promising for clinical translation
General Inflammatory Disorders	Anti-inflammatory cytokine modulation	Alleviation of chronic symptoms	Supports use in functional foods or supplements

therapeutic agent that crosses species [80]. Generally speaking, β -glucan is a potential clinical therapy for the management of various inflammatory and autoimmune diseases due to its broad variety of mechanisms. Subsequently, highland barley β -glucan was demonstrated to improve the symptoms of ulcerative colitis in mice by enhancing the health of the intestine, restraining inflammation, and balancing the cytokines [61, 81]. Additionally, β -glucans engage the immune receptors and provoke pathways that initiate autophagy and production of reactive oxygen species necessary for enhanced immune responses [82]. Overall, the evidence suggests the therapeutic utility of β -glucans treatment of inflammatory disease conditions as well as enhancement of the immune system [83].

Strategies to enhance Beta-Glucan content

Enhancement of the beta-glucan content of barley also occurs through pretreatment, extraction, and utilization of improved breeding protocols. Germination and fermentation have also been shown to significantly enhance the beta-glucan level of barley such that germinated barley contains up to 5.66% beta-glucans as well as enhanced antioxidant capacity [9, 84]. Furthermore, ultrasonic-assisted extraction (UAE) optimizes the recovery of soluble dietary fibers up to the maximum of 5.21% beta-glucans under specific conditions, enabling environmentally-friendly food consumption habits [85]. Targeting the breeding of specific quantitative trait loci (QTL) for beta-glucan content will also facilitate the development of barley cultivars with higher beta-glucan content, such as the wild barley germplasm [4, 86]. All these strategies reflect the potential of the beta-glucan content of barley towards its value addition for health as well as for its functionality as a food ingredient [1].

Conventional and molecular breeding approaches

Conventional as well as molecular breeding strategies aiming towards enhancing beta-glucan content of barley have garnered interest due to the medicinal value of the compound as well as the range of end uses [87]. Marker-assisted selection (MAS) was the lead methodology as a prime strategy involving identified loci and candidate genes for beta-glucan production such as HORVU6Hr1G088380 and HvCslF9 that were implicated by genome-wide association studies (GWAS) and quantitative trait loci (QTL) [2]. A number of quantitative trait loci (QTL) have been linked with BG content in recent studies, with significant QTL located on chromosomes 1 H, 3 H, 4 H, 5 H, 6 H, and 7 H, which can be utilized in breeding programs to enhance BG content in both hull-less and conventional barley types. Recent studies

have identified quantitative trait loci (QTL) associated with beta-glucan content, allowing the possibility of undertaking breeding programs to enhance this trait [12, 88]. That is, two QTL located on chromosomes 1 H and 7 H were correlated with significant phenotypic variation of beta-glucan content and confirmed the genetic ability to develop barley cultivars idiosyncratically of beta-glucan content for specific uses, such as functional foods or malting. These QTL will enable backcrossing for increased β -glucan content utilizing specific alleles of Glacier AC38 and CDC Fibar [4, 89]. Genome-wide association analysis identified a number of consistent marker-phenotype associations between β -glucan content and identified 14 significant markers and candidate genes of which the cellulose synthase-like gene HvCslF6 was highly implicated for β -glucan production [90, 91]. Recent studies pinpoint 13 QTL for the β -glucan content of wild barley and recognize β -glucan synthases and hydrolases as marker genes for marker-assisted selection purposes, enabling classical and molecular backcrossing for the improvement of β -glucan content [4, 92]. Additionally, new methods of breeding like hybridization of waxy and non-waxy barley have also demonstrated promise towards the production of progeny having considerably higher BG content beyond the thresholds of the traditional methods of breeding. The integration of next-generation genomic tools like SNP markers and machine learning enables the detection of positive alleles that strengthen the efficiency of the breed program [67, 93]. Furthermore, the contrasting requirements of low β -glucan content for malting and high β -glucan content for food applications highlight the need for a balanced integration of these traits through targeted breeding strategies [1, 94]. Overall, the usage of traditional breeding methods supplemented by advanced molecular tools holds great promise of developing barley lines of enhanced beta-glucan quality for health and industrial needs [39].

Biotechnological interventions

Biotechnology methods of barley beta-glucan enhancement primarily include the manipulation of the cellulose synthase-like (Csl) gene family as well as more specifically HvCslF6 that plays a key role in the beta-glucan biosynthesis. Overexpression of HvCslF6 was reported as causing beta-glucan levels of over 80% improvement over the controls, demonstrated by transgenic barley [95]. Applications of biotechnologies involving CRISPR and gene editing tools have shown significant promise for enhancing beta-glucan biosynthesis of barley (*Hordeum vulgare*). The use of CRISPR/Cas9 has facilitated certain mutations of (1,3;1,4)- β -glucan synthases genes and affirmed HvCslF6 as a crucial factor for β -glucan level of the grains, proposing intricate interactions between beta-glucan level and grain morphology

where certain of the knock-out lines have varying effects on beta-glucan level [15]. Additionally, the advancements of molecular breeding have made possible the development of barley cultivars having higher beta-glucan content that finds application for health as well as industrially [1, 57]. Studies demonstrate the application of CRISPR/Cas9 genome editing for the production of barley lines harboring novel alleles of the Waxy gene that contribute towards increased β -glucan content (35.40% higher than the wild type), making the possibility of increased beta-glucan production among barley a reality [95, 96]. Quantitative trait loci (QTL) analysis also identified additional genes such as hydrolases that are associated with beta-glucan content as well as new targets like Patatin and Nudix hydrolase that would also facilitate barley beta-glucan content manipulation [4]. The use of this type of gene editing technology not just improves the nutritional quality of barley but also satisfies the dual market demand of producing lower beta-glucan levels for brewing purposes and higher levels for health-oriented food uses. Overall, these innovations represent a quantum leap towards a sustainable agriculture and enhanced food security.

Recent advances and future perspectives

Recent breakthrough on the use of beta glucan in barley acknowledges its vast health benefits and prospects for the creation of new food technology. Beta glucans present mainly in barley have the ability to decrease LDL cholesterol and manage the level of blood sugar, which are beneficial for the health of the heart [1, 97]. Research has centered on the molecular and biochemical aspects of the beta glucans, allowing for selection for increased beta glucan content in barley varieties, especially hullless barley, for food uses [67, 89]. Furthermore, beta glucans also have some physicochemical characteristics such as viscosity and gelation ability that make them suitable for a number of applications including intelligent packaging and hydrogel [57, 98, 99]. These developments not only enrich barley foods on the health front but also open up opportunities for delivery systems of biomedicine and environmentally friendly materials for packaging [45, 100] as mentioned in Table 5.

Insights from preclinical and clinical studies

A variety of preclinical investigations have provided convincing evidence of barley β -glucan's strong immunomodulatory, anti-inflammatory, hypoglycemic, and hypocholesterolemic effects in a broad array of in vitro and animal experiments [101, 102]. Experiments have identified β -glucan's interaction with a number of pattern recognition receptors like Dectin-1 and complement receptor 3

(CR3) as being responsible for orchestrating stimulation of the innate immunity, phagocytosis induction, and modulation of the production of cytokines. Modulation of the gut microbiota by induction of health-promoting genera such as *Bifidobacterium* and *Lactobacillus* are also implicated in the beneficial effects of β -glucans [103]. These have been supported by clinical trials, albeit smaller and less numerous. Supplementation of the diet with barley β -glucans leads to improved lipid profiles, improved glycemic control, decreased markers of inflammation, and improved vaccination responses in human subjects [104–106]. But variability of the source of β -glucan, molecular profile, and dosing regimens among the studies highlights the need for standardized clinical regimens as a prerequisite for the ability to reap its full therapeutic potential.

Future directions for functional foods and therapeutics

The future of barley β -glucan involves the precise application as a functional food and therapeutic intervention for immunonutrition and chronic disease care. Innovative biotechnology platforms, including nanodelivery systems, bioencapsulation, and precision fermentation, offer opportunities to optimize site-directed delivery and enhance the bioavailability of β -glucan [107, 108]. A combination of omics-based technologies like metabolomics, proteomics, and microbiome profiling will, in the future, allow individualized design of β -glucan interventions according to individuals' metabolic and immunological profiles. Regulatory approval of β -glucan health claims by the regulatory bodies of major markets also paves the path for the innovation of β -glucan-fortified breakfast cereals, drinks, and medical nutrition foods for the targeted populations at highest risk [109, 110]. Future work should target engineering of β -glucan having defined molecular characteristics for defined therapeutic purposes, for example, stimulation of anti-tumoral immunity, modulation of carbohydrate digestion, or lowering of cardiovascular disease [108]. Overall, these advances put barley β -glucan at the forefront of next-generation of functional foods and nutraceuticals addressing global health challenges.

Conclusion

Barley β -glucan is a complex bioactive molecule of considerable health significance due to its immunomodulatory, anti-inflammatory, and metabolic regulation activity. Its unique (1 \rightarrow 3)(1 \rightarrow 4)- β -D-glucan structure that results through the collective action of the CslF and CslH gene families forms the groundwork of its activity. Genomic tools

Table 5 Past, Current, and future directions for β -Glucan research

Era	Research Focus Areas	Key Scientific Advances	Identified Limitations and Challenges	Future Research Directions and Opportunities
Past (Before 2000 s)	- Discovery and structural elucidation of β -glucans from barley	- Characterization of β -(1 \rightarrow 3) and β -(1 \rightarrow 4) linkages unique to cereal β -glucans	- Limited understanding of molecular mechanisms of action	- Advanced biochemical profiling (e.g., NMR, mass spectrometry)
	- Early investigations into dietary fiber roles	- Establishment of β -glucan as a functional fiber in human nutrition	- Lack of distinction between β -glucans from different sources (e.g., yeast vs. barley)	- Source-specific functional comparisons (barley vs. oat vs. fungal β -glucans)
	- Initial studies on cholesterol-lowering effects	- Basic health claims related to lipid regulation recognized	- Poor extraction and purification methods leading to inconsistent bioactivity	- Development of optimized, standardized extraction techniques
Current (2000–2025)	- Exploration of immunomodulatory, anti-inflammatory, and anti-cancer activities	- Clinical trials showing reductions in LDL-cholesterol, glycemic control, immune enhancement	- Significant heterogeneity in β -glucan preparations (molecular weight, solubility)	- Standardization of β -glucan products (purity, molecular weight profiles)
	- Clinical validation of metabolic benefits (anti-diabetic, cardioprotective)	- β -glucan identified as a potential vaccine adjuvant	- Variability in clinical outcomes	- Large-scale, multi-ethnic clinical trials
	- Mechanistic studies on immune signaling pathways (e.g., dec- tin-1, CR3)	- Advances in food processing technologies preserving β -glucan bioactivity	- Lack of consensus on optimal dosing and formulations	- Integrating β -glucans into medical nutrition therapy protocols
	- Gut microbiota modulation and prebiotic effects	-	- Regulatory challenges for health claims in some countries	- Investigating structure-activity relationships in immunomodulation
Future (Post-2025 and beyond)	- Personalized nutrition and precision medicine applications	- Development of β -glucan-loaded nanoparticles for targeted immunotherapy	- Regulatory approval for novel delivery systems	- Systems biology-guided β -glucan research
	- Nanotechnology and bioengineering approaches for targeted delivery	- Artificial modulation of β -glucan biosynthesis pathways in barley for enhanced yield and bioactivity	- Long-term safety and efficacy data required	- Development of designer β -glucans for disease-specific applications
	- Synthetic biology for enhanced production of β -glucans with tailored structures	- Exploration of β -glucan–gut microbiome–immune axis	- Bioavailability optimization remains a challenge	- Expansion into veterinary and aquaculture immunotherapies
	- Integration with multi-omics technologies (genomics, metabolomics, microbiomics)	- Use in combination therapies (e.g., immuno-oncology drugs, vaccines)	- Potential variability in patient response (genetic and microbiota-driven)	- Functional food innovations targeting specific disease risks (e.g., functional cereals for cancer survivors)

like QTL mapping, GWAS, and CRISPR/Cas9 genome editing have facilitated the development of barley lines with enhanced β -glucan levels and new opportunities are developing for the development of functional foods. Agronomic as well as environmental factors also determine β -glucan

composition and point towards the need for genotype-by-environment strategies. Mechanistically, barley β -glucan engages innate immune receptors such as Dectin-1 and TLR2, initiating signal transduction pathways that reinforce macrophage, dendritic cell, NK cell, and T-cell responses

while also triggering trained immunity and modulation of inflammatory and oxidative stress pathways. These intricate applications confirm its therapeutic significance in infectious disease, cancer immunotherapy, autoimmune disease, as well as chronic metabolic disease such as diabetes and cardiovascular disease. However, the challenges of molecular heterogeneity, standardization of the extract, as well as partial mechanistic elucidation at present hold back its clinical actualization. Future directions should dwell on optimizing the methods of extraction, structural elucidation from a bioactivity point of view, and rigorous clinical evaluation with a view towards the production of standardized therapeutic regimes. The use of novel biotechnology tools and omics-based personalized modalities holds promise towards personalizing β -glucan interventions for health needs. Barley β -glucan represents the intersection of sustainable agriculture, nutrition science and immunotherapy as a frontier platform for the next generation of functional foods and biotherapeutics upon which the health resilience of the world can be built.

Acknowledgements This research was supported by Talent Introduction and Training Program of Yunnan Academy of Agricultural Sciences (2024RCYP-22) and the China Agriculture Research System of MOF and MARA (CARS-05-04 A).

Author contributions Conceptualization, Hafiz Ahmed and Xiaomeng Yang; Data curation, Hafiz Ahmed, and Muhammad Danial Shafiq; Formal analysis, Sajid Hussain, Jiazhen Yang and Li'E Yang; Funding acquisition, Yawen Zeng; Investigation, Hafiz Ahmed; Methodology, Sajid Hussain, Xiaomeng Yang and Muhammad Danial Shafiq; Project administration, Hafiz Ahmed and Yawen Zeng; Resources, Hafiz Ahmed; Software, Jiazhen Yang, Muhammad Sajad; Supervision, Yawen Zeng; Validation, Hafiz Ahmed and Muhammad Akram; Visualization, Yawen Zeng; Writing – original draft, Hafiz Ahmed and Xiaomeng Yang; Writing – review & editing, Sajid Hussain, Jiazhen Yang, Muhammad Sajad, Li'E Yang and Yawen Zeng.

Funding Not Applicable.

Data availability Data is provided within the manuscript file.

Declarations

Competing interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

AI tools We declare that no AI or automated writing tools were used in drafting this manuscript.

Consent to participate and publish All authors participated and approved the final manuscript to be published.

References

- Kumar D et al (2020) Barley grain beta glucan enrichment: status and opportunities. Elsevier, Wheat and barley grain biofortification, pp 295–308
- Geng L et al (2021) Identification of genetic loci and candidate genes related to β -glucan content in barley grain by genome-wide association study in international barley core selected collection. *Mol Breeding* 41:1–12
- Popov VS et al (2024) weight method for determination of soluble β -glucans in barley grain
- Walling JG et al (2022) Quantitative trait loci impacting grain β -glucan content in wild barley (*Hordeum vulgare* ssp. spontaneum) reveals genes associated with cell wall modification and carbohydrate metabolism. *Crop Sci* 62(3):1213–1227
- Khaleghdoust B (2024) Barley and wheat beta-glucan content influenced by weather, fertilization, and genotype. *Front Sustain Food Syst* 7:1326716
- Sujithra S et al (2024) Isolation, purification and characterization of β -glucan from cereals-a review. *Int J Biol Macromol* 256:128255
- Schmidt M (2022) Cereal beta-glucans: an underutilized health endorsing food ingredient. *Crit Rev Food Sci Nutr* 62(12):3281–3300
- Nie C et al (2021) Structure of β -glucan from Tibetan hull-less barley and its in vitro fermentation by human gut microbiota. *Chem Biol Technol Agric* 8:1–14
- Yang Y et al (2024) Understanding the mechanisms of β -glucan regulating the in vitro starch digestibility of Highland barley starch under spray drying: structure and physicochemical properties. *Food Chem* 441:138385
- Trivedi R, Upadhyay TK (2024) Preparation, characterization and antioxidant and anticancerous potential of Quercetin loaded β -glucan particles derived from mushroom and yeast. *Sci Rep* 14(1):16047
- Hu J et al (2020) Purification, preliminary structural characterization, and in vitro inhibitory effect on digestive enzymes by β -glucan from Qingke (Tibetan hullless Barley). *Adv Polym Technol* 2020(1):2709536
- Gianinetti A (2024) QTL analysis of β -glucan content and other grain traits in a recombinant population of spring barley. *Int J Mol Sci* 25(12):6296
- Kaur A et al (2024) Unraveling the hidden potential of barley (*Hordeum vulgare*): an important review. *Plants* 13(17):2421
- Utama GL et al (2020) Microorganism-based β -glucan production and their potential as antioxidant. *Sys Rev Pharm* 11:868–873
- Garcia-Gimenez G et al (2020) Targeted mutation of barley (1, 3; 1, 4)- β -glucan synthases reveals complex relationships between the storage and cell wall polysaccharide content. *Plant J* 104(4):1009–1022
- Abdel-Haleem AMH (2020) Characterization of β -glucan gum for food applications as influenced by genotypic variations in three hullless barley varieties. *J Food Sci* 85(6):1689–1698
- Desta KT et al (2024) Comprehensive characterization of global barley (*Hordeum vulgare* L.) collection using agronomic traits, β -glucan level, phenolic content, and antioxidant activities. *Plants* 13(2):169
- Marginean R et al (2024) Comparative study on Beta-Glucan content and proximate composition of spring. *Barley Seeds Genotypes Obtained in Different Crop Systems*
- Patidar A et al (2020) Barley beta-glucan and zymosan induce Dectin-1 and Toll-like receptor 2 co-localization and anti-leishmanial immune response in *leishmania donovani*-infected BALB/c mice. *Scand J Immunol* 92(6):e12952

20. Menkovska M, Ibrahim O (2022) A review on the impact of the plant bioactive compound β -glucans as phytochemicals for boosting human and animals' immune response— β -glucans as immunostimulants. *Adv Biosci Biotechnol* 13(7):298–315
21. Zhong X et al (2023) Immunomodulatory effect and biological significance of β -glucans. *Pharmaceutics* 15(6):1615
22. Renke G (2022) B-glucan trained immunity immunomodulatory properties potentiate tissue wound management and accelerate fitness recover. *Immunotargets Ther*. <https://doi.org/10.2147/ITT.S381145>
23. Ikewaki N et al (2022) Controlled modulation of all the arms of the immunity including innate immunity by biological response modifier glucans, a simple yet potential nutritional supplement strategy to fight COVID-19. *J Food Biochem* 46(7):e14156
24. Ajit J (2025) B-glucan induced trained immunity enhances antibody levels in a vaccination model in mice. *PLoS One* 20:2024.2004. 2011.588932
25. Cerletti C et al (2021) Edible mushrooms and beta-glucans: impact on human health. *Nutrients* 13(7):2195
26. Xin Y (2022) Immune-enhancing effect of water-soluble beta-glucan derived from enzymatic hydrolysis of yeast glucan. *Biochem Biophys Rep* 30:101256
27. Murphy EJ (2020) β -glucan metabolic and immunomodulatory properties and potential for clinical application. *J Fungi* 6(4):356
28. Yuan H et al (2019) Effect of the modifications on the physicochemical and biological properties of β -glucan—A critical review. *Molecules* 25(1):57
29. Al-Altaie DM, Addai ZR (2021) Determination of antioxidant compounds, antibacterial activity and minerals content of broccoli. *Indian J Forensic Med Toxicol* 15:123–130
30. Zhang G et al (2020) Quantitative proteome profiling provides insight into the proteins associated with β -glucan accumulation in hull-less barley grains. *J Agric Food Chem* 69(1):568–583
31. Fauziyah B, Yuwono M (2021) Analysis of powder properties and pharmacopeial specifications of Bagasse cellulose isolated from *saccharum officinarum* L in Indonesia. *Indian J Forensic Med Toxicol* 15(3)
32. Sun L et al (2021) Molecular Characteristics, Synthase, and food application of cereal β -Glucan. *J Food Qual* 2021(1):6682014
33. Singla A et al (2024) Beta-glucan as a soluble dietary fiber source: Origins, biosynthesis, extraction, purification, structural characteristics, bioavailability, biofunctional attributes, industrial utilization, and global trade. *Nutrients* 16(6):900
34. Malunga LN et al (2021) Beta-glucan from barley attenuates post-prandial glycemic response by inhibiting the activities of glucose transporters but not intestinal brush border enzymes and amyloysis of starch. *Front Nutr* 8:628571
35. Yuan Z et al (2022) Systematic identification and expression profiles of the BAHF superfamily acyltransferases in barley (*Hordeum vulgare*). *Sci Rep* 12(1):5063
36. Koc HA et al (2022) In silico analysis of XTH gene family from barley (*Hordeum vulgare* L.) and their comparative expression analysis during germination. *Turk J Bot* 46(2):92–108
37. Revheim I (2024) The acute effect of a β -glucan-enriched oat bread on gastric emptying, GLP-1 response, and postprandial glycaemia and insulinemia: a randomised crossover trial in healthy adults. *Nutr Metab (Lond)* 21(1):13
38. Kim I-S et al (2024) Effect of barley on postprandial blood glucose response and appetite in healthy individuals: a randomized, double-blind, placebo-controlled trial. *Nutrients* 16(22):3899
39. Finocchiaro F et al (2023) Barley: from molecular basis of quality to advanced genomics-based breeding. *Compendium of crop genome designing for nutraceuticals*. Springer, pp 1–38
40. Vuscan P et al (2024) Potent induction of trained immunity by *Saccharomyces cerevisiae* β -glucans. *Front Immunol* 15:1323333
41. Mata-Martínez P et al (2022) Dectin-1 signaling update: new perspectives for trained immunity. *Front Immunol* 13:812148
42. Bai Y et al (2025) B-glucan induced plasma B cells differentiation to enhance antitumor immune responses by Dectin-1. *BMC Immunol* 26(1):2
43. Jeong J-H et al (2024) Investigating the immune-stimulating potential of β -glucan from *aureobasidium pullulans* in cancer immunotherapy. *Biomol Ther (Seoul)* 32(5):556
44. Hossain MM et al (2025) Oat Beta-glucan consumed at breakfast improves glucose tolerance acutely and after a subsequent Lunch-A randomized dose response study in healthy young adults. *Food Funct*
45. Wang J et al (2024) Yeast β -glucan promotes antiviral type I interferon response via dectin-1. *Vet Microbiol* 295:110107
46. Pedro AR et al (2021) Dectin-1-mediated production of pro-inflammatory cytokines induced by yeast β -glucans in bovine monocytes. *Front Immunol* 12:689879
47. Park M et al (2023) Effects of barley β -glucan on postprandial blood glucose responses: a systematic review and meta-analysis. *Korean J Food Sci Technol* 55(4):282–291
48. Adachi Y (2023) Potentiation of antitumor activity by antibody drugs and mushroom-derived β -glucans in natural killer cell-mediated tumoricidal activities against non-Hodgkin's B-cell lymphoma. *Int J Med Mushrooms*. <https://doi.org/10.1615/IntJMedMushrooms.2022047219>
49. Zhu Z et al (2023) Yeast β -glucan modulates macrophages and improves antitumor NK-cell responses in cancer. *Clin Exp Immunol* 214(1):50–60
50. Stothers CL et al (2021) β -glucan induces distinct and protective innate immune memory in differentiated macrophages. *J Immunol* 207(11):2785–2798
51. Camilli G (2020) β -Glucan-induced reprogramming of human macrophages inhibits NLRP3 inflammasome activation in cryopyrinopathies. *J Clin Invest* 130(9):4561–4573
52. Ibrahim HK, Mahdi MS (2020) Antioxidant effect of Beta-glucan extract from *Saccharomyces cerevisiae*. *Indian J Forensic Med Toxicol* 14(4)
53. He X (2021) Barley β -glucan gelatin sponge improves impaired wound healing in diabetic and immunosuppressed mice by regulating macrophage polarization. *Mater Today Commun* 29:102744
54. Shvachko NA et al (2021) Bioactive components in oat and barley grain as a promising breeding trend for functional food production. *Molecules* 26(8):2260
55. Braian C et al (2023) Selected β -glucans act as immune-training agents by improving anti-mycobacterial activity in human macrophages: a pilot study. *J Innate Immun* 15(1):751–764
56. Binou P et al (2021) Enrichment of bread with beta-glucans or resistant starch induces similar glucose, insulin and appetite hormone responses in healthy adults. *Eur J Nutr* 60:455–464
57. Fatemi R et al (2023) Screening barley genotypes in terms of some quantitative and qualitative characteristics under normal and water deficit stress conditions. *Asian J Agric Biology* 2023(02).
58. Abdelmawgood IA (2024) β -glucan mitigates ovalbumin-induced airway inflammation by preventing oxidative stress and CD8+ T cell infiltration. *Int Immunopharmacol* 132:111985
59. Eid O et al (2023) Comprehensive overview: the effect of using different solvents for barley extraction with its anti-inflammatory and antioxidant activity. *Chem Biodivers* 20(3):e202200935
60. Gordeeva E et al (2022) Fine points of marker-assisted pyramiding of anthocyanin biosynthesis regulatory genes for the creation of black-grained bread wheat (*Triticum aestivum* L.) lines. *Agronomy* 12(12):2934

61. Chen M et al (2021) B-glucan extracted from Highland barley alleviates dextran sulfate sodium-induced ulcerative colitis in C57BL/6J mice. *Molecules* 26(19):5812
62. Sutariati GAK, Muhidin M (2025) Characterization of saline soil rhizobacteria from coastal lands in dissolving Phosphate, nitrogen fixing and synthesizing IAA growth hormone. *J Glob Innov Agric Sci* :995–1002
63. Cheng J (2024) Anti-inflammatory activity of β -glucans from different sources before and after fermentation by fecal bacteria *in vitro*. *J Sci Food Agric* 104(2):1116–1131
64. Singh RP, Bhardwaj A (2023) B-glucans: a potential source for maintaining gut microbiota and the immune system. *Front Nutr* 10:1143682
65. Han J et al (2023) Nulichal barley extract suppresses nitric oxide and pro-inflammatory cytokine production by lipopolysaccharides in RAW264. 7 macrophage cell line. *Prev Nutr Food Sci* 28(3):370
66. Yüce H et al (2024) Effect of beta-glucan on oxidative stress, inflammation, hormonal and histopathological changes in dehydroepiandrosterone-induced polycystic ovary syndrome
67. Liu H et al (2022) Highland barley β -glucan alleviated Western diet-induced non-alcoholic fatty liver disease via increasing energy expenditure and regulating bile acid metabolism in mice. *Food Funct* 13(22):11664–11675
68. Kim JH et al (2023) Low-molecular-weight β -1, 3–1, 6-glucan derived from *aureobasidium pullulans* exhibits anticancer activity by inducing apoptosis in colorectal cancer cells. *Biomedicines* 11(2):529
69. Shoukat M, Sorrentino A (2021) Cereal β -glucan: a promising prebiotic polysaccharide and its impact on the gut health. *Int J Food Sci Technol* 56(5):2088–2097
70. Chiozzi V et al (2021) Biotechnological addition of β -glucans from cereals, mushrooms and yeasts in foods and animal feed. *Processes* 9(11):1889
71. Niazi MK et al (2023) Therapeutic Effect of Barley on Cardiovascular Diseases. *Frontiers in Clinical Trials: IntechOpen*
72. Olawale RA (2023) Beta-Glucans: one for you. One for me
73. Khan N et al (2025) β -glucan reprograms neutrophils to promote disease tolerance against influenza A virus. *Nat Immunol*. <https://doi.org/10.1038/s41590-024-02041-2>
74. Geller A, Yan J (2020) Could the induction of trained immunity by β -glucan serve as a defense against COVID-19? *Front Immunol* 11:1782
75. Fu YJ (2023) All-natural immunomodulatory bioadhesive hydrogel promotes angiogenesis and diabetic wound healing by regulating macrophage heterogeneity. *Adv Sci* 10(13):2206771
76. Purushotham P et al (2022) Mechanism of mixed-linkage glucan biosynthesis by barley cellulose synthase-like CslF6 (1, 3; 1, 4)- β -glucan synthase. *Sci Adv* 8(45):eadd1596
77. Córdova-Martínez A et al (2021) B-glucans could be adjuvants for SARS-CoV-2 virus vaccines (COVID-19). *Int J Environ Res Public Health* 18(23):12636
78. Wei S et al (2021) A composite hydrogel with co-delivery of antimicrobial peptides and platelet-rich plasma to enhance healing of infected wounds in diabetes. *Acta Biomater* 124:205–218
79. Żyła E (2021) Anti-inflammatory activity of oat beta-glucans in a Crohn's disease model: time-and molar mass-dependent effects. *Int J Mol Sci* 22(9):4485
80. Amaral AR et al (2024) Translating human and animal model studies to dogs' and cats' veterinary care: beta-glucans application for skin disease, osteoarthritis, and inflammatory bowel disease management. *Microorganisms* 12(6):1071
81. Xu Z et al (2022) A novel hydrogel with glucose-responsive hyperglycemia regulation and antioxidant activity for enhanced diabetic wound repair. *Nano Res* 15(6):5305–5315
82. Ahmad F (2024) B-glucan signalling stimulates NOX-2 dependent autophagy and LC-3 associated autophagy (LAP) pathway. *Int J Biol Macromol*. <https://doi.org/10.1016/j.ijbiomac.2024.136520>
83. Castro E et al (2021) β -1, 3/1, 6-glucans and immunity: state of the Art and future directions. *Mol Nutr Food Res* 65(1):1901071
84. Waleed A-A et al (2020) The potential improvements of naked barley pretreatments on GABA, β -glucan, and antioxidant properties. *LWT* 130:109698
85. Anis N et al (2024) Optimization of ultrasonic-assisted extraction of soluble dietary fiber (β -glucan) from different barley varieties and study of its characterization and functional attributes. *Food Sci Nutr* 12(10):8394–8407
86. Yadav R et al (2023) Pigmented Barley: Phytochemical Composition, β -Glucan Content, and Applications
87. Baloch H et al (2024) Moringa leaf extract enhances the growth and yield characteristics of buckwheat genotypes by modulating the biochemical and physiological activities. *Asian J Agric Biology* 2024(04).
88. Caferoglu Z et al (2022) Effects of whole-grain barley and oat β -glucans on postprandial glycemia and appetite: a randomized controlled crossover trial. *Food Funct* 13(19):10225–10234
89. Vasiliev A et al (2025) Whole wheat bread with grape seed powder. *J Glob Innov Agric Sci* :467–473
90. Lante A, Canazza E (2023) Insight on extraction and preservation of biological activity of cereal β -D-glucans. *Appl Sci* 13(19):11080
91. Fitriyah AT et al (2025) Analysis of Sago contribution as staple food alternatives to household food security. *J Glob Innov Agric Sci* :1059–1067
92. Hejazi MA, Panahi B (2025) Evaluation of physio-morphological characteristics associated with drought tolerance in drought tolerant and sensitive barley cultivars. *Asian J Agric Biol* 4:2024233
93. Kellogg JA et al (2025) High β -glucan whole grain barley reduces postprandial glycemic response in healthy adults—Part one of a randomized controlled trial. *Nutrients* 17(3):430
94. Nurhayati A, Madjid R (2025) Innovations in agricultural E-Commerce: analyzing purchase decisions and the role of consumer credibility. *J Glob Innov Agric Sci* :607–616
95. Li Y et al (2021) Creating Amylose-Free barley cultivars with high. Soluble Sugar Content By Genome Editing
96. Vendidandala NR (2021) Gallocatechin–silver nanoparticle impregnated cotton gauze patches enhance wound healing in diabetic rats by suppressing oxidative stress and inflammation via modulating the Nrf2/HO-1 and TLR4/NF- κ B pathways. *Life Sci* 286:120019
97. Fuse Y et al (2020) Effect of high β -glucan barley on postprandial blood glucose and insulin levels in type 2 diabetic patients. *Clin Nutr Res* 9(1):43–51
98. Zhang Y (2023) Recent advances of cereal β -glucan on immunity with gut microbiota regulation functions and its intelligent gelling application. *Crit Rev Food Sci Nutr* 63(19):3895–3911
99. Nagarjuna Reddy V et al (2022) Gallocatechin-silver nanoparticles embedded in cotton gauze patches accelerated wound healing in diabetic rats by promoting proliferation and inhibiting apoptosis through the Wnt/ β -catenin signaling pathway. *PLoS ONE* 17(6):e0268505
100. Alhadede AA-KA, Al-Khafagi QDE (2025) Effect of ionic strength on the dissolution and precipitation of carbonate minerals and the nature of ionic species from some calcareous soil. *J Glob Innov Agric Sci* :699–705
101. Sivieri K et al (2022) Insights on β -glucan as a prebiotic coadjutant in the treatment of diabetes mellitus: a review. *Food Hydrocolloids for Health* 2:100056

102. Hasddin H, Ulyasniati U (2025) Sustainable agriculture: the role of biostimulants in enhancing crop growth and resilience. *J Glob Innov Agric Sci* :561–573
103. Telle-Hansen VH (2022) A three-day intervention with granola containing cereal beta-glucan improves glycemic response and changes the gut microbiota in healthy individuals: a crossover study. *Front Nutr* 9:796362
104. Aoe S et al (2020) Low molecular weight barley β -glucan affects glucose and lipid metabolism by prebiotic effects. *Nutrients* 13(1):130
105. Mio K et al (2022) Arabinoxylan as well as β -glucan in barley promotes GLP-1 secretion by increasing short-chain fatty acids production. *Biochem Biophys Rep* 32:101343
106. Damayanti R et al (2025) Machine learning based Estimation of chlorophyll and flavonoid content in bitter leaf using color and GLCM texture features. *J Glob Innov Agric Sci* :1011–1019
107. Zurbau A et al (2021) The effect of oat β -glucan on postprandial blood glucose and insulin responses: a systematic review and meta-analysis. *Eur J Clin Nutr* 75(11):1540–1554
108. Marcobal AM et al (2024) Highly soluble β -glucan fiber modulates mechanisms of blood glucose regulation and intestinal permeability. *Nutrients* 16(14):2240
109. Musa-Veloso K (2021) A systematic review and meta-analysis of randomized controlled trials on the effects of oats and oat processing on postprandial blood glucose and insulin responses. *J Nutr* 151(2):341–351
110. Sule S, Hidayat K (2025) Linking farmer knowledge and learning to agricultural sustainability: A study of Apple farmers in Indonesia. *J Glob Innov Agric Sci* :1021–1029

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.