

Physical Form Determines the Effects of β -glucan On the Gut-Brain Axis

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Abstract:

The gut has a fungal ecosystem whose cell walls are made of β -glucan, an immunostimulatory innate ligand. β -Glucan simultaneously acts as a fungal PAMP and a neuroprotective dietary fibre in two literatures which each carry extensive clinical and mechanistic rationale, but are largely decorrelated with one another. The present review incorporates them by analyzing 28 studies published between 2006 and 2026. The framework proposed here rests on three physical variables. Linkage geometry and physical state are interpreted directly by the pattern-recognition receptor Dectin-1: particulate or immobilized glucans cross-link the receptor and initiate signaling, whereas soluble forms bind without activating and act as competitive inhibitors. The third variable, anatomical compartment, is governed by epithelial barrier function, which determines whether the encounter occurs at all, and whether β -glucan arrives alone or translocated with endotoxin. Supporting this, branched fungal-type glucan is protective when taken orally, which linkage geometry alone cannot explain. The central unresolved question is the physicochemical nature of β -glucan present systemically after barrier compromise. Existing assays report only concentration, so whether translocated fragments retain the helical order required for Dectin-1 agonism is unknown. Resolving this will require characterizing the physical state of circulating β -glucan rather than its concentration alone, and comparing structurally defined glucans across a graded range of dysbiosis severity.

Key Word: β -glucan; Dectin-1; gut mycobiota; intestinal barrier; microglia; neuroinflammation

I. Introduction

Analysis of fungal DNA in mouse feces revealed that more than 100 identified fungal species from 50 genera, along with many unidentified species. Although the fungal community was diverse, most of the detected fungi belonged to only a few species. *Candida tropicalis* alone accounted for around 65% of all fungal sequences. Since only 1.5 % of the fungi originates from food, these fungi are considered residents of the gut. Similar fungi communities have also been found in several other mammals, including rats, rabbits, pigs, dogs, and humans. The binding of a dectin-1 probe to fungal components further showed that these fungi can be seen by the immune system (1). β -glucans are polysaccharides made up of D-glucose units linked by β -glycosidic bonds. They are found in fungi and yeast, including mushrooms, as well as in some bacteria, seaweeds, and cereals such as oats and barley (2). Based on their structure, β -glucans can be classified into two main groups: fungal and yeast β -(1,3;1,6) glucans, and cereal β -(1,3;1,4) glucans. They vary in their type of linkage, which may include β (1,3), β (1,4), and β (1,6) bonds, and can be either branched or unbranched. Their molecular weight also differs depending on the source, ranging from approximately 10^2 to 10^6 Da, with higher molecular weight β -glucans generally showing greater viscosity (2).

An interesting contradiction exists in the current literature. On one hand, Dectin-1 is a well-established receptor involved in CNS disorders, and changes in its expression have been linked to neuroinflammatory processes in both Alzheimer's and Parkinson's disease (3). On the other hand, β -glucan supplementation has been shown to prevent cognitive impairment and reduce microglial activation in the hippocampus of diet-induced obese mice (4). Surprisingly, these two areas of research rarely reference each other, and studies often fail to report the physical state of the β -glucan used, making this apparent contradiction difficult to interpret.

This review argues that the effects of β -glucans are shaped by three key variables: their molecular structure, physical state, and their interaction with the gut environment. Dectin-1 acting as the primary reader of the first two factors and the gut barrier regulating the third. The following sections examine each variable and their relevance to neuroinflammation and brain health.

II. Methodology

This review has been conducted in accordance with the procedures of a structured narrative review. It does not adhere to PRISMA. Literature was searched in PubMed, Scopus, Web of Science, and Google Scholar. Searches were from 2006 to 2026. Key words included β -glucan, Dectin-1, CLEC7A, microglial, neuroinflammation, *Candida*, gut barrier, Short Chain Fatty Acids (SCFA). Studies comprised in this review were primary, English-translated, *in vitro* or *in vivo* studies comprising of mouse or human models. Review articles

were included to provide background. Each article was assessed for research methods. A total of 26 articles were assessed. Findings from the primary studies comprising this review are presented in this report.

Structural Determinants of Dectin-1 Recognition and Activation

Dectin-1 is a pattern recognition receptor encoded by the *CLEC7A* gene and belongs to the family of type II transmembrane C-type lectin receptors. Unlike receptors of the adaptive immune system, it is germline encoded and recognizes conserved molecular patterns (3). Its structure consists of an extracellular carbohydrate recognition domain (CRD), followed by a stalk region, a single transmembrane domain, and a short cytoplasmic tail of about 40 amino acids that contains a hemITAM motif (3). Eight isoforms of Dectin-1 have been identified, named A to H. Isoform A is the full-length form, whereas isoform B lacks the stalk region, a difference that may influence receptor function (3). Although Dectin-1 belongs to the C-type lectin family, it lacks the amino acid residues normally required for calcium binding, making its ligand recognition calcium-independent (3,5). Dectin-1 is mainly expressed on myeloid cells and is also present on microglia in the CNS, where expression increases during immune activation and injury (3).

Studies using oligosaccharide microarrays containing 187 sequence-defined probes showed that Dectin-1 binds exclusively to β -(1,3)-linked glucose oligomers (5). Detectable binding required a minimum chain length of around 10 or 11 glucose units. When clustered 11 to 13-mer oligomers were displayed on liposomes, they mimicked larger β -glucans and were able to compete with zymosan for receptor binding and TNF- α production (5). However, Dectin-1 does not respond equally to all β -(1,3)-glucans. Binding affinities range from 2.6 mM to 2.2 pM, with factors such as chain length and β -(1,6) branching strongly affecting receptor affinity (6). Even a single glucose side branch can enhance binding. Based on these findings, it can be inferred that cereal β -(1,3;1,4)-glucans may interact weakly with Dectin-1 because their β -(1,3) sequences are frequently interrupted by β -(1,4) linkages, reducing long continuous regions available for recognition.

Binding alone is not enough to activate Dectin-1. Soluble β -glucans of different molecular weights were able to bind the receptor and block anti-Dectin-1 antibodies, yet they failed to induce reactive oxygen species production, TNF- α release, IL-6 production, or Syk activation (7). In contrast, particulate whole-glucan molecules triggered all of these responses. Simply increasing polymer size did not restore signaling. Interestingly, the same soluble glucans produced strong Dectin-1-dependent responses when immobilized on cell culture plates or attached to latex beads larger than 0.5 μ m (7). This suggests that Dectin-1 requires an immobilized and multivalent ligand presentation rather than particulate material itself.

The underlying mechanism involves the formation of a phagocytic synapse. During contact with a glucan-containing particle, Dectin-1 receptors cluster at the interaction site while the phosphatases CD45 and CD148 are physically excluded from that area (7). Experimental disruption of this organization reduced TNF- α production by approximately 45%. Structurally, Dectin-1 contains a hemITAM with only one YXXL motif, whereas conventional ITAM receptors contain two. Because Syk kinase requires two phosphotyrosines for stable recruitment, signaling depends on receptor clustering rather than activation of a single receptor molecule (7,8). As a result, soluble β -glucans often behave as competitive antagonists, explaining why compounds such as laminarin have long been used to block β -glucan receptors (7).

The biological activity of β -glucans is also influenced by their three-dimensional structure. Depending on molecular weight and source, β -glucans can exist as random coils, structured conformations, or insoluble fibers. Medium- and high-molecular-weight fungal glucans tend to be highly structured, whereas lower-molecular-weight glucans are less organized (9). Although glucans with different structures showed similar binding affinity for Dectin-1, their ability to trigger signaling varied considerably. When a stimulatory glucan was denatured using DMSO, calcium signaling was lost, while partial restoration occurred after renaturation through dialysis (9). These findings suggest that glucan structure influences its ability to activate the receptor without necessarily altering binding affinity. The receptor clusters formed were relatively small, measuring less than 15 nm, and their formation increased with greater glucan exposure on fungal surfaces (9).

Although β -glucans are currently the only carbohydrate ligand class assigned to Dectin-1, they are not its only ligands. For example, A β 42 has also been shown to bind directly to Dectin-1, promoting receptor dimerization and activation of Syk and NF- κ B signaling pathways (10). Together, these findings suggest that the response to β -glucans depends not only on their chemical structure but also on their physical form and location, an idea explored further in the following sections.

The Fungal Route: From Gut Overgrowth To Systemic B-Glucan

The evidence from animal studies suggests that Dectin-1 plays an important role in controlling intestinal fungi. Mice lacking Dectin-1 (*Clec7a*^{-/-}) developed more severe DSS-induced colitis, showing greater weight loss, increased mucosal erosion, crypt destruction, and higher levels of TNF- α , IFN- γ , and IL-17 compared with wild-type animals (1). Importantly, transferring fecal microflora from knockout mice into wild-type mice did not transfer disease susceptibility, indicating that the phenotype was linked to host genotype rather than the starting microbial community (1). During colitis, *Candida* and *Trichosporon* expanded while non-pathogenic *Saccharomyces* declined, and fungi infiltrated inflamed tissue in knockout mice but remained confined to the intestinal lumen in wild-type animals. Treatment with fluconazole reduced disease severity specifically in knockout mice (1). Supporting the relevance of these findings to humans, a two-marker *CLEC7A* haplotype has been associated with medically refractory ulcerative colitis and a shorter time to colectomy. In a separate colitis model, *C. albicans* became the dominant fungal species, and its cell-wall β -glucan influenced disease severity in a concentration-dependent manner (11).

Several mouse studies have shown that intestinal fungal expansion can worsen gut barrier dysfunction. Oral administration of *C. albicans* increased dysbiosis and gut permeability in obese mice subjected to cecal ligation and puncture sepsis, as well as in bilateral nephrectomy and 5/6 nephrectomy models (12–14). Increased leakage was detected using FITC-dextran, while one study also confirmed barrier disruption through altered tight-junction staining in intestinal tissue (13). Though, none of these studies examined neuroinflammation directly which limits how far the proposed pathway can be extended.

In each of the mouse models described above, circulating levels of serum (1 $\rightarrow$ 3)- β -D-glucan and endotoxin increased and were detected using the Fungitell assay (12–14). Similar measurements are used clinically, where serum β -D-glucan serves as a marker of microbial translocation alongside biomarkers such as I-FABP, zonulin, REG3 α , LPS, and sCD14 (15). However, these assays only measure the amount of circulating β -glucan. They provide no information about its structural conformation or physical state. As a result, nothing in the current literature establishes what form the circulating material actually takes.

Evidence suggests that β -glucan may act differently when combined with bacterial products. Whole-glucan particles alone did not activate macrophages, but glucan combined with LPS produced much stronger inflammatory responses than LPS alone, including increased cytokine production and enhanced expression of NF- κ B, Malt-1, and Syk (13). Interestingly, glucan alone increased macrophage ATP production through upregulation of mitochondrial and glycolytic pathway genes. This did not induce cell activation and this is described as pre-conditioning effect on cellular energy status by the authors. Similar interactions were observed in renal and hepatic cell models, where LPS plus β -glucan increased IL-6, TNF- α , Dectin-1, and TLR-4 expression and promoted fibrotic responses that were later observed in the kidney, liver, and heart (14). This pattern of gut fungi contributing to disease in distant organs has also been described in chronic liver disease (16). A key difference that emerges here is that a leaking gut delivers β -glucan together with LPS, whereas the dietary route does not.

No study identified in this review measured β -glucan directly within brain tissue, and any CNS involvement remains inferred rather than demonstrated. Several possible routes have been proposed. One possibility is transport by circulating monocytes. Another is passage through regions where systemic inflammation increases paracellular permeability. A third possibility is endothelial transcytosis across the blood-brain barrier. At present, none of these mechanisms has been tested for translocated fungal β -glucans. This creates an important uncertainty because material released from a remodeling fungal cell wall is likely to be small and soluble, and Section 3 showed that soluble β -glucans can bind Dectin-1 without triggering signaling.

Although translocated fungal β -glucan has not been tested in the CNS, microglial Dectin-1 is clearly capable of driving inflammatory responses. A β 42 binds directly to Dectin-1, and this causes homodimerization of the receptor and activating downstream Syk and NF- κ B signaling to induce inflammatory factor expression. In A β 42 infused mice, dectin-1 knockout reduced microglial activation, inflammatory responses and synaptic as well as cognitive deficits. (10). Similarly, in an LPS-induced Parkinson's disease model, Dectin-1 expression increased in microglia, and inhibition with laminarin reduced dopaminergic injury, improved behaviour, and shifted microglia toward a less inflammatory phenotype (17). Therefore, the weakest link remains the step from circulation into brain parenchyma.

The Dietary Route: Fermentation, Short-Chain Fatty Acids and Barrier Maintenance

Humans cannot break down β -glucan with their own enzymes, so it remains in the intestinal lumen where microbial enzymes take over. These include β -(1,3)-glucanases that cut internal bonds to release oligosaccharides, β -(1,3)-glucosidases that release glucose from the non-reducing ends, and β -(1,6)-glucanase of the GH30 family that works on the branches (2). As these glucans are large and viscous (2), they stay mostly confined to the lumen rather than being absorbed directly, and in the colon they undergo fermentation that produces short-chain fatty acids such as acetate, propionate, and butyrate.

The importance of the microbiota in this process was shown clearly in a study where barley β -glucan was fed to high-fat diet mice for twelve weeks at either high (2%) or low (0.6%) levels, under both conventional and germ-free conditions (18). In conventional mice, supplementation reduced weight gain and fat mass, increased secretion of PYY and GLP-1, lowered food intake, improved insulin sensitivity, and raised SCFA levels, especially butyrate (18). Yet every one of these benefits disappeared completely in germ-free mice (18), making it clear that the effects depend on the microbiota rather than the molecule itself. A separate comparison of 5% barley β -glucan against 5% cellulose went further, since only β -glucan increased PYY and GLP-1 and reduced food intake, showing that the outcome was not simply due to bulk fibre (18).

Beyond metabolic changes, β -glucan also influences the colonic barrier. Long-term supplementation increased mucus thickness, raised tight junction proteins such as occludin and zonula occludens-1, and reduced bacterial endotoxin leakage across the barrier (4). The microbiota shifted as well, with changes in Bacteroidetes and its lower taxa being especially striking (4). Short-term supplementation for just seven days produced strong microbiota changes before any cognitive improvement appeared, which the authors interpreted as evidence of causal direction (4). Mushroom β -glucan showed similar protective effects, increasing colonic mucus and occludin, lowering plasma LPS, and preventing proinflammatory macrophage accumulation in the colon (19).

The link from the gut to the brain goes through microglia. Germ-free mice display broad microglial defects, including altered cell proportions, immature features, and impaired innate immune responses. Removing the microbiota in normal mice reproduced these defects, while recolonisation with a complex microbiota partly restored normal features (20). SCFAs were identified as the mediators, and genetic evidence confirmed this: mice lacking FFAR2, the SCFA receptor, showed the same microglial defects as germ-free animals (20). Cognitive outcomes across several studies strengthen the case: β -glucan prevented cognitive impairment with reduced hippocampal microglial activation and lower TNF- α , IL-1 β , and IL-6 (4); it prevented recognition memory impairment with improved synaptic ultrastructure and restored BDNF (19) maternal supplementation raised butyrate in dams and pups and improved offspring spatial memory at eight weeks (21); and in APP/PS1 mice, it reduced amyloid plaque deposition and microglial activation (22).

Perhaps the strongest single argument comes from natural controls. In one experiment, three structurally distinct β -glucans, namely, mushroom β -(1,3)/(1,6), curdlan β -(1,3), and oat bran β -(1,3)/(1,4), were fed to the same mouse cohort for fifteen weeks (23). All three improved temporal order recognition memory, raised BDNF and PSD95 in the prefrontal cortex, reduced microglial numbers in the prefrontal cortex and hippocampus, and increased CD206-positive cells and IL-10 while lowering IL-6 and TNF- α in the colon (23). Yet only oat bran altered the gut microbiota and mucus, and only mushroom glucan increased post-synaptic thickness (23). Yeast-derived β -glucan, another fungal-type glucan, also improved cognition and reduced amyloid and neuroinflammation in APP/PS1 mice (22). Taken together, these findings show that branched fungal-type β -glucan taken orally can be protective. If linkage geometry alone determined the outcome, such results would not be possible, meaning that compartment regulates the action of geometry, and that is a central claim of this review. At the same time, only oat bran changed the microbiota, so the mechanisms behind mushroom and curdlan remain unresolved, and the three should not be presented as acting through a single pathway (23).

III. Discussion

Bringing the two literatures together is straightforward when they are understood as following the same basic rule. Linkage determines whether Dectin-1 can bind, presentation determines whether this binding leads to signalling, and compartment determines whether the meeting occurs at all. Thus, the two literatures are not really in conflict; they are simply describing different molecules in different places. The rule still holds when tested against challenging cases. Branching is not the main factor: whole glucan particles and the soluble fractions prepared from them by acid hydrolysis carry the same β -(1,6) branching, yet only the particles activate the receptor, while the soluble form binds and blocks it (7). Moreover, although curdlan is unbranched, it activated

when particulate (23,24). Laminarin is branched, but it is soluble and prevented activation (17). Thus, branching alters the strength of binding (6) but presentation determines whether the receptor will fire.

The body compartment also matters. Oral fungal glucan was protective (19,22,23). Mushroom and curdlan β -glucans were effective, even though only oat bran changed the microbiota (23). This suggests that some oral glucan may have reached immune cells directly. Therefore, the simple rule that "compartment decides" is too limited. Barrier failure provides a large dose together with LPS (13,14), while the diet provides a gradual dose without LPS. So, it is not just location, but also timing and what comes with it. In the brain, Dectin-1 is not entirely harmful. Particulate glucan has demonstrably helped optic nerve regeneration, and curdlan worked through Dectin-1 (24). Lentinan promoted remyelination, while laminarin blocked it (22). Modulation of Dectin-1 has also been reported to produce antidepressant effects (3). Thus, in the brain, it can help repair as well as cause damage.

Even the downstream pathway is not fixed. Curdlan activated ERK1/2 and CREB but did not activate NF- κ B p65 (24). Therefore, Dectin-1 does not always drive NF- κ B inflammation. Curdlan also caused retinal folding and detachment, and in knockouts both the benefit and the damage disappeared (24). This shows that the good and bad effects are linked. Another layer is TLR4. Particulate glucan activated Dectin-1 and TLR4 together, resulting in stronger NF- κ B activation, and soluble glucan worked with isoform A but not B, because B lacks the stalk (25). Blocking TLR4 in dendritic cells raised IL-23, IL-4, IL-6 and TNF- α , indicating that TLR4 acts as a brake rather than a co-activator (25). The same pattern was observed in macrophages (26). However, in a LPS-driven Parkinson's model, Dectin-1 and TLR4 acted together to drive damage (17), and glucan particles alone barely activated macrophages while LPS combined with glucan produced a more pronounced response (13). The role of TLR4 therefore appears to depend on whether LPS is present, which is precisely what separates a leaking gut from a healthy one.

The framework predicts that neuroinflammation develops only when glucan arrives in a clustering-competent form. However, the glucan shed from a fungal wall is small and soluble, and once soluble it binds without activating (7). There are four possible ways out, all untested. Fragments might retain their helical order (9). Re-aggregation could occur in serum. Immobilization on an endothelial surface or carrier cell could allow it to signal. Or LPS could provide the second hit that glucan alone cannot (13). None of these possibilities have been thoroughly tested.

Distinguishing between them requires a single measurement that none of the studies reviewed here has made, which is the conformation of β -glucan after translocation. Although the existing assays monitor concentration, it is not known whether the fragments circulating in the blood retain the helical structure necessary for Dectin-1 agonism. The whole pathogenic pathway hinges on this one specific, measurable physical quantity.

In addition to this main gap, there are still several important uncertainties. Since no study has directly measured *Candida*-derived β -glucan acting on the brain parenchyma, the claims regarding the central nervous system can only be inferred from systemic inflammation. Moreover, there is no *in vivo* microglial dose-response study that compares particulate and soluble glucan at doses that are precisely matched. Hu et al. (2022) had already compared three different glucan classes within a healthy group, so any new comparison between β -(1,3;1,4) and β -(1,3;1,6) glucans must specifically include a gradient of dysbiosis severity. Dectin-1 activation also leads to opposite results in different central nervous system models, causing damage in the Alzheimer's and Parkinson's phenotypes (10,17) but promoting repair in cases of optic nerve injury and demyelination (22,24). Future functional assessments therefore have to clearly specify both the disease state and the time points of the experiment. Timing occurs in two distinct senses here; the first is when the intervention is delivered relative to the insult since β -glucan delivered 48 hours after optic nerve injury worked as well as immediate administration (24). The second is when the outcome is measured since microbiota changes appear within seven days while cognitive benefit requires fifteen weeks (4,19). Lastly, the connection between the gut microbiota and the brain is still only correlational and so causality has not been established in the context of neurodevelopment (16).

Addressing these uncertainties requires a change in what is measured rather than new technology. Studies that characterize circulating β -glucan by size and conformation, rather than by concentration alone, would establish whether translocated material is capable of engaging Dectin-1 at all. Comparisons between structurally defined β -(1,3;1,4) and β -(1,3;1,6) glucans would also need to be made across a graded range of dysbiosis severity rather than at a single point, and would ideally include a solubilized preparation of the same glucan used in particulate form, since this holds the molecule constant while varying only its physical state.

Several limitations apply. The evidence synthesized here is derived from rodent models and the only human data available are associative: CLEC7A haplotype linked to refractory ulcerative colitis (1) and serum β -glucan used as a biomarker of microbial translocation (15). None of them establishes causation. The translocation evidence is further constrained by the models in which it was generated as gut leakage and elevated serum β -glucan were demonstrated in sepsis and renal failure (12–14). None of them is a model of neuroinflammation so extension to a neural context remains inference. The dietary evidence carries the converse limitation by being drawn almost entirely from high-fat diet and transgenic models with no study examining dietary β -glucan against fungal overgrowth. Therefore, the two routes have never been compared in the same animal. This review is a structured narrative synthesis and not a systemic review and it did not follow PRISMA. So, the relevant studies may have been missed. Ultimately, the measurement recommended above is not technically trivial as circulating β -glucan occurs at picogram concentrations while the chromatographic methods used to characterize glucan conformation have been applied to purified preparations at far higher ones.

IV. Conclusion

Ultimately, the biological outcomes are dictated by their geometrical linkage, physical state, and anatomical compartment with Dectin-1 as their molecular reader, and the gut barrier as the gate. Considering β -glucan as categorically beneficial or detrimental to the brain is a wrong dichotomy, because they have been considered under one umbrella term, but their separable features have been historically treated as an inseparable whole. The literature demonstrates currently an asymmetrical state of affairs wherein the neuroprotective dietary case rests on several rodent studies including a germ-free causal control, while the pathogenic paradigm stops at the blood-brain barrier. Therefore, the field has debated whether β -glucan helps or hurts the central nervous system without measuring the spatial and structural variables that determine the outcome, leaving the mechanistic question of what it does exactly unexplored.

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