Review

β-Glucans, *Pneumocystis jirovecii* and Atherogenic Inflammation: From Pulmonary Immunity to Cardiovascular Risk

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Abstract

The interaction between *Pneumocystis jirovecii* and systemic inflammation has emerged as a potential modulator of cardiovascular risk. This review describes the potential of β-glucans to contribute to atherogenic inflammation. A narrative review was developed on the PubMed/MEDLINE, Scopus, Web of Science and Google Scholar databases. The inflammatory pathways induced by β-glucans from *P. jirovecii* contrast with the immunometabolic effects of dietary β-glucans. The relevance of serum (1→3)-β-D-glucans as a marker of systemic exposure was also described. *P. jirovecii* β-glucans activate Syk–CARD9–NFκB, MAPK and STAT3 signalling pathways. This signalling promotes proinflammatory monocyte/macrophage polarization and a systemic microenvironment of low-grade inflammation with proatherogenic potential. The serum persistence of (1→3)-β-D-glucan indicates prolonged exposure, even in the absence of overt clinical manifestations of colonisation. Conversely, dietary β-glucans have been observed to elicit regulatory effects facilitated by microbiota and metabolism. Using murine models and cell systems, a causal link has been established between fungal β-glucans and atherosclerosis. *P. jirovecii* β-glucans act as immunological mediators capable of amplifying pulmonary and systemic inflammation, constituting a possible modulator of cardiovascular risk. Distinguishing between fungal and dietary β-glucans is imperative for comprehending emerging mechanisms of vascular inflammation.

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1. Introduction

Systemic inflammation plays a pivotal role in understanding cardiovascular vulnerability and the progression of atherosclerosis, a chronic condition with a substantial global burden [1]. In this context, *Pneumocystis jirovecii* is a relevant factor due to the immunomodulatory properties of its β-glucans, structural components capable of activating pattern recognition receptors, such as Dectin-1 and EphA2, and inducing proinflammatory signaling cascades [2,3]. In general, fungal β-glucans are recognized as modulators of innate and adaptive immunity. These modulators have the ability to promote cytokine secretion and the activation of multiple immune pathways [4]. It has been demonstrated that persistent exposure to these polysaccharides, even in scenarios of subclinical colonization—as described in populations with chronic respiratory diseases or immunological vulnerability—could contribute to the sustained modulation of local inflammatory pathways and the configuration of an altered immune microenvironment [5]. This approach is relevant given the high prevalence of atherosclerosis and growing evidence that colonization by *P. jirovecii* is more prevalent than is clinically recognized, with varying prevalences reported in different vulnerable populations and in chronic respiratory diseases [5–7].

Despite the mounting interest in the immunomodulatory role—predominantly immunostimulatory—of *P. jirovecii* β-glucans, there are currently no epidemiological studies directly evaluating the incidence of major cardiovascular events in populations with a high prevalence of infection or colonization by this fungus. The extant evidence derives primarily from experimental and observational studies that describe the activation of inflammatory pathways induced by β-glucans and the biological changes associated with colonization in chronic respiratory diseases. These findings suggest a possible relationship that warrants further evaluation using population cohorts and prospective designs [1–7].

In order to contextualize these possible links, it is pertinent to review the biological and immunological characteristics of *P. jirovecii*. This human-specific opportunistic fungus exhibits a clinical spectrum that ranges from subclinical states to overt respiratory symptoms [8,9]. The life cycle of this organism comprises two morphotypes that exhibit divergent immunological implications. Cysts, the infective form, are characterized by a cell wall that is rich in branched β-glucans (β-1,3 and β-1,6). In contrast, trophic forms are devoid of these polysaccharides [10,11]. This distinction is salient because the β-glucans present in cysts, in contrast to the predominant surface glycoprotein, which does not stimulate dendritic cells, serve as the primary catalyst for immune recognition and the initiation of inflammatory pathways [10]. Trophic forms induce adaptive responses with minimal inflammatory activation. This promotes their persistence in subclinical settings [11]. Overall, the release of β-glucans from cysts during active infection represents a key mechanism of immune activation, associated with local inflammation and, in contexts of established disease, potentially linked to systemic manifestations [8,9].

These processes are of particular interest within the context of atherosclerosis, a chronic inflammatory disease characterized by the accumulation of lipids and immune cells within the arterial wall. The sustained activation of monocytes, macrophages, and endothelial cells constitutes a pivotal element in the initiation and progression of atherosclerotic lesions, as it promotes the amplification of local inflammatory responses [12]. In this context, low-grade systemic inflammation—as reflected in inflammatory indices derived from circulating cell populations—is recognized as a pathophysiological link between distal immune stimuli and vascular alterations, including endothelial dysfunction [13,14].

The intricate interplay between *P. jirovecii* β-glucans and inflammatory processes, coupled with the methodological heterogeneity of the extant evidence, warrants a narrative approach that aims to integrate pathophysiological, experimental, and clinical dimensions [12]. This review examines, in an integrative—though not exhaustive—manner, how these β-glucans, characterized by a

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predominantly immunostimulatory profile, could directly or indirectly contribute to atherosclerotic processes in vulnerable populations [10–12]. The analysis focuses on immunological and vascular mechanisms, without addressing therapeutic interventions or making quantitative comparisons. In this context, the proposed synthesis aims to provide a conceptual framework for interpreting plausible mechanisms, contextualizing emerging findings, and guiding both the interpretation of biomarkers and the design of future research in fungal immunology and vascular biology [12,14]. It is imperative to underscore that extant evidence is predominantly derived from experimental studies, preclinical models, and indirect clinical observations; consequently, the relationships discussed herein should be interpreted as biologically plausible associations rather than clinically established causal links [12–14].

2. Materials and Methods

A narrative review was conducted to integrate representative evidence on the potential associations between *Pneumocystis jirovecii* β-glucans and inflammatory processes implicated in atherogenesis. This review considered their interaction with pattern recognition receptors, including Dectin-1, various lectin-like receptors (CLRs), and EphA2, in macrophages, monocytes, and lung epithelium. This framework was developed to address the conceptual and exploratory nature of the objectives. It was intentionally non-exhaustive aligning with the recommendations of the International Committee of Medical Journal Editors (ICMJE) for narrative reviews with an integrative purpose [15].

The design of the review followed the principles of synthesis described by Baumeister and Leary [16], with the objective of conceptual construction and the development of explanatory frameworks in the absence of homogeneous evidence. In addition, elements of the methodological proposal by Green, Johnson, and Adams [17] were incorporated, emphasizing the clear delimitation of the topic, the explicit definition of the scope, and the progressive integration between literature review and analytical writing.

In accordance with these guidelines, the review team methodically focused the analysis on immunological, pulmonary, and vascular mechanisms associated with atherogenic inflammation, with the objective of preventing thematic dispersion and maintaining alignment with the central question of the manuscript.

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, using combinations of terms related to *P. jirovecii*, β-glucans (β 1,3 and β 1,6) and other cyst wall polysaccharides, pulmonary immunity, systemic inflammation, atherosclerosis, pattern recognition receptors (Dectin-1, CLRs, EphA2), microbiota, metabolism, and serum (1→3)-β D glucan. The following types of documents were included: original articles, specialized reviews, experimental studies, relevant clinical reports, and consensus documents published in English or Spanish.

The selection of sources was based on their conceptual relevance, methodological rigor, scientific validity, and contribution to the proposed pathophysiological framework. Although no explicit time limits were stipulated, priority was accorded to recent publications that reflected contemporary advances in the domains of fungal immunology, vascular biology, metabolism, microbiota, and atherogenic inflammation.

Information was extracted, compared, and organized through an iterative process that allowed for the refinement of findings and the evaluation of convergences and discrepancies between studies. During this process, the evidence was structured around three main analytical themes:

1. the role of *P. jirovecii* β-glucans as triggers of pulmonary and systemic inflammation.
2. the modulatory or cardioprotective effects of dietary or fungal β-glucans on microbiota, metabolism, inflammation, and atherosclerosis must be considered.
3. the presence and relevance of serum (1→3)-β D glucan as a marker of systemic exposure in the context of *P. jirovecii* must be acknowledged. Importantly, other types of glucans exist;

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however, this biomarker is the available and standardized tool for assessing systemic fungal exposure.

These three axes functioned as a conceptual framework for integrating the different levels of evidence and exploring possible pathophysiological relationships between antifungal immunity, vascular inflammation, and cardiovascular risk.

In accordance with this methodological approach, the manuscript was organized in stages. First, the structural and immunological characteristics of *P. jirovecii* β-glucans are analyzed and then contrasted with dietary β-glucans. In the following section, the primary inflammatory pathways that are activated by these polysaccharides in macrophages and lung epithelium will be delineated. Additionally, their potential contribution to a proatherogenic phenotype will be discussed. On this basis, the clinical implications related to the persistence of circulating β-glucans and their potential systemic impact are explored, and finally, experimental models that could allow the evaluation of causal relationships between exposure to *P. jirovecii* β-glucans and atherogenic inflammation are discussed.

Conflicts of interest were declared and managed following the guidelines of the World Association of Medical Editors (WAME), ensuring transparency and adherence to international ethical standards [18]. No external funding was received. Literature selection relied solely on academic search engines.

3. Results and Discussion

3.1. The Structural and Immunological Characteristics of Pneumocystis Jirovecii β-Glucans Are Examined and Contrasted with Those of Dietary β-Glucans

P. jirovecii β-glucans have a distinctive molecular architecture with a highly branched network of β-1,3 and β-1,6 bonds, together with a minimal presence of α-glucans and chitin, components that are more common in other environmental fungi and in polysaccharides of dietary origin [2]. This composition undergoes fluctuations throughout the microorganism's life cycle: cysts, which constitute the infective form, exhibit the highest proportion of these polysaccharides and function as the primary stimulus for immune activation, while trophic forms are nearly devoid of β-glucans and possess significantly diminished immunogenicity [2,10,11]. This structural and functional differentiation is essential to the recognition process by the innate immune system, particularly through its interaction with receptors such as Dectin-1 and EphA2. The activation of these receptors triggers proinflammatory signaling cascades and cytokine production [3,4].

From an immunological perspective, the high degree of branching and exposure of β-1,3/β-1,6 motifs characteristic of the cyst wall of *P. jirovecii* favor efficient interaction with pattern recognition receptors, including Dectin-1, other lectin-like receptors (CLRs), and the tyrosine kinase receptor EphA2. The concerted activation of these systems induces signaling pathways involving NF-κB, MAPK, and routes related to cytokine and chemokine expression. These inflammatory responses can extend beyond the pulmonary compartment and exert effects on the vascular endothelium and circulating monocytes [2,3]. In this context, *P. jirovecii* β-glucans act as immune modulators, exhibiting a predominantly proinflammatory profile. These β-glucans are capable of sustaining the activation of monocytes, macrophages, and pulmonary epithelial cells, a finding that is consistent with the observations made for other fungal β-glucans [2,4].

Dietary β-glucans, derived from cereals, yeasts, or edible fungi, generally have simpler structures, with a reduced degree of branching and variable proportions of β-1,3 and β-1,4 bonds. Moreover, these polysaccharides are frequently linked to other cell wall components, such as α-glucans, proteins, or polysaccharide-protein complexes, which modulate their bioavailability and interaction with immune receptors. Consequently, their immunological recognition is often integrated into immunometabolic regulation circuits, which are predominantly associated with the gut-microbiota axis [4,19].

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These structural differences result in markedly different functional profiles. While dietary β-glucans are predominantly associated with immunomodulatory, metabolic, and potentially cardioprotective effects—mediated in part by microbial fermentation, the generation of metabolites with anti-inflammatory activity, and the modulation of innate immunity—β-glucans from *P. jirovecii* configure a signaling pattern characterized by more pronounced inflammatory activation, with the ability to amplify both local and systemic responses [2–4,19].

This finding underscores the notion that the biological impact of β-glucans is not solely determined by their chemical composition, but rather by a complex interplay between molecular structure, exposure context, and predominant biological compartment [4,19].

Overall, the high affinity for receptors associated with proinflammatory signaling, the complex β-1,3/β-1,6 branching, and the relative absence of structural components with a buffering effect give *P. jirovecii* β-glucans a particularly efficient profile for inducing amplified immune responses [2]. This phenomenon stands in contrast to the effects of dietary β-glucans, which have been traditionally associated with regulatory and potentially cardioprotective effects that are mediated by microbiota and modulation of innate immunity [4,19]. This functional differentiation provides a framework for understanding fungal β-glucans. Their exposure could contribute to systemic inflammatory processes and vascular dysfunction [2–4,19].

3.2. Inflammatory Pathways That Are Activated by Pneumocystis jirovecii β-Glucans and Their Contribution to a Proatherogenic Phenotype

P. jirovecii β-glucans, characterized by a highly branched architecture with β-1,3 and β-1,6 linkages, have been shown to possess a high capacity to activate pattern recognition receptors in macrophages and pulmonary epithelial cells [2,3]. This activation triggers multiple inflammatory pathways, which, although initially oriented towards antifungal defense, can acquire systemic projection and promote processes involved in atherogenesis [2–4].

In macrophages, interaction with Dectin-1 constitutes a central axis of recognition. Binding to the extracellular domain of this receptor induces phosphorylation of its ITAM-like motif. This leads to the recruitment of Syk with subsequent activation of the CARD9–BCL10–MALT1 complex. This cascade ultimately leads to the activation of NF-κB and MAPK, which in turn promote the expression of IL-6, TNF-α, IL-1β, and various chemokines, including CCL2, CCL3, and CXCL8. These mediators both amplify the local inflammatory response and promote monocyte mobilization and their polarization toward proinflammatory profiles, a process closely linked to the early stages of atherosclerotic development [20–22].

Conversely, *P. jirovecii* β-glucans have been observed to interact with other lectin-like receptors (CLRs), modulating additional pathways that converge on NF-κB activation and proinflammatory cytokine production. The coordinated participation of these recognition systems amplifies the initial response and contributes to the configuration of a pulmonary microenvironment characterized by cell recruitment, increased oxidative stress, and the release of mediators with potential systemic repercussions [2–4,20–22].

In the lung epithelium, β-glucans have been shown to activate EphA2, a tyrosine kinase receptor involved in the recognition of fungal components. This activation triggers intracellular signaling pathways such as NF-κB [3]. This axis has been demonstrated to promote the production of IL-6, CXCL8, and other mediators that facilitate functional communication between the epithelium and immune cells, thereby contributing to the maintenance of a persistent inflammatory state [2–4,22]. This epithelial-immune circuit is especially relevant in prolonged colonization scenarios, where repeated stimulation can lead to low-grade chronic inflammatory signaling with potential systemic consequences [1–4,22].

An additional component of this response corresponds to the activation of pathways dependent on lactosylceramide, a glycosphingolipid that acts as a signaling platform in the cell membrane. The interaction of β-glucans with these pathways has been shown to promote the activation of NADPH oxidase and the generation of reactive oxygen species, contributing to the establishment of a state of

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oxidative stress and the amplification of proinflammatory pathways [2–4,20–22]. This mechanism, described in fungal recognition models, enhances endothelial dysfunction. It also promotes monocyte activation, two central processes in atherogenic progression [1–4,20–22].

The convergent activation of Dectin-1/CARD9, CLRs, EphA2, and lactosylceramide pathways leads to a sustained inflammatory response. This response is characterized by the production of IL-6, TNF-α, and multiple chemokines, along with other cytokines with modulatory functions, such as IL-10 or IL-23. The participation of these latter cytokines may adjust the intensity and profile of the response rather than simply amplifying it [2–4,20–22]. These mediators both sustain the antifungal response and promote a proatherogenic phenotype. The promotion of a proatherogenic phenotype is achieved through the following mechanisms: endothelial activation, inflammatory recruitment and polarization of monocytes/macrophages, and increased oxidative stress. Consequently, the induction of signaling by β-glucan in the pulmonary compartment may have some effects beyond this organ, thereby contributing to systemic processes associated with vascular inflammation and the development of atherosclerosis [1–4,20–22].

3.3. The Effects of β-Glucans on Cardiovascular Risk, with a Particular Focus on the Contrast Between Dietary Effects and Systemic Fungal Exposure

β-glucans have been the subject of extensive research as a potential modulator of cardiovascular risk. However, the specific effects of these compounds are contingent upon their origin, molecular architecture, and the biological context of exposure. Dietary β-glucans, derived from cereals, yeasts, or edible fungi, generally have simpler structures and a composition that favors predominantly regulatory immune interactions rather than intense inflammatory responses [4,19]. Consequently, their cardiometabolic impact is linked to modulation of the gut microbiota and regulation of lipid metabolism. They also attenuate systemic inflammation, mechanisms that converge in an overall cardioprotective profile [13,14,19].

In the gastrointestinal microbiota, dietary β-glucans act as fermentable substrates. They promote the growth of short-chain fatty acid-producing bacteria, including *Faecalibacterium*, *Roseburia*, and *Bifidobacterium*. These metabolites, particularly butyrate and propionate, exert anti-inflammatory effects. They reinforce intestinal barrier integrity and modulate metabolic pathways involved in lipid and carbohydrate homeostasis [4,19]. These changes are associated with reductions in LDL-C and triglycerides, improved insulin sensitivity, and decreased circulating inflammatory markers, as well as slower progression of atherosclerotic lesions in experimental models [14,19].

Conversely, circulating fungal β-glucans, especially the highly branched β-1,3/β-1,6 derivatives of *P. jirovecii*, have high affinity for proinflammatory receptors. These include Dectin-1, CLRs, and EphA2 thereby facilitating their recognition by the innate immune system [2–4]. Upon entering the circulation, these polysaccharides activate the Syk–CARD9–NF-κB axis, thereby promoting the production of proinflammatory cytokines, such as IL-6, TNF-α, and IL-1β, as well as various chemokines, and stimulating the activation of circulating monocytes [20–22]. This response, initially aimed at antifungal defense, may persist systemically, promoting a proatherogenic phenotype characterized by sustained inflammation and vascular activation [2–4,14,20–22].

Furthermore, fungal β-glucans contribute to endothelial dysfunction by activating lactosylceramide-dependent pathways. This leads to reactive oxygen species generation which, in turn, has been demonstrated to promote the expression of endothelial adhesion molecules, monocyte recruitment, and the progression of atherosclerotic lesions [2–4,20–22]. In contrast to dietary β-glucans, which modulate the inflammatory response into a regulatory profile, circulating fungal β-glucans have been observed to amplify systemic inflammation and oxidative stress. These phenomena are two processes closely linked to vascular vulnerability [1–4,20–22].

From an integrative perspective, this functional divergence highlights that β-glucans are not a homogeneous biological entity. Rather, they are a group of molecules whose immunometabolic activity depends on structure, exposure route, and biological compartment [2–4,19–22]. In this sense, while intestinal exposure to dietary β-glucans has been associated with protective metabolic and anti-

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inflammatory signals, systemic exposure to fungal β-glucans in invasive infections or persistent colonization scenarios may promote low-grade chronic inflammation, endothelial dysfunction, and a molecular environment conducive to atherogenesis [2–4,14,19,22]. This distinction is especially important when interpreting inflammatory biomarkers and exploring emerging mechanisms of vascular inflammation associated with subclinical infections [2–4,14,22].

3.4. The Serum Persistence of (1→3)-β-D-Glucan in Pneumocystis jirovecii, Encompassing Its Progression from Chronic Colonization to Systemic Inflammation and Vascular Dysfunction

Serum (1→3)-β-D-glucan is a widely used biomarker for diagnosing invasive fungal infections, including *P. jirovecii* pneumonia. However, beyond its diagnostic value, the magnitude and, in particular, the persistence of its positivity could reflect a state of immunologically active exposure to fungal β-glucans with possible systemic consequences. This consideration is especially important in scenarios of chronic or subclinical colonization by *P. jirovecii*, in which the absence of overt clinical manifestations does not preclude the existence of persistent low-grade inflammatory stimulation [2,6,21].

Montes Cano et al. demonstrated that colonization by *P. jirovecii* can exhibit dynamic patterns. These include cycles of acquisition, loss, and accelerated recolonization by different genotypes, even in individuals without overt clinical disease [23]. These cycles may cause fluctuations in β-glucan release into the pulmonary compartment. This can result in persistent or intermittent serum positivity. This, in fact, reinforces the hypothesis of sustained antigenic exposure with the capacity to modulate systemic inflammation [2,6,21,23].

Several studies have documented that patients with *P. jirovecii* pneumonia, as well as colonized individuals—particularly the elderly, individuals with chronic obstructive pulmonary disease, pulmonary fibrosis, or mild immunosuppression—may have serum concentrations of (1→3)-β-D-glucan that are elevated and sustained even after clinical resolution of the respiratory episode [2,6]. This finding suggests that β-glucans may translocate from the pulmonary compartment to the systemic circulation. This process could be sustained over time, either due to persistence of the microorganism, slow replacement of cell wall components, or alterations in the alveolar-capillary barrier associated with chronic inflammation [2,6,21,23].

Pathophysiologically, circulating β-glucans are not merely passive markers of exposure, but rather active immunological stimulus capable of interacting with pattern recognition receptors expressed on immune and vascular cells, including Dectin-1, various CLRs, and EphA2 [2–4,20–22]. Sustained activation of these signaling axes can drive a chronic proinflammatory state, characterized by the production of cytokines such as IL-6, TNF-α, and IL-1β, as well as the release of chemokines that promote the recruitment and activation of circulating monocytes [2–4,20–23].

This state of low-grade systemic inflammation is highly relevant to vascular biology. Chronic exposure of the endothelium to inflammatory mediators derived from β-glucan-induced activation may be associated with endothelial dysfunction, increased expression of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin, and alterations in the bioavailability of nitric oxide [2,14,21]. These alterations promote the adhesion and transmigration of monocytes to the arterial intima, a pivotal event in the initial phases of atherogenesis [2,14,21,23].

It has been proposed that circulating β-glucans may influence platelet activation and coagulation, either directly or indirectly through systemic inflammation and oxidative stress. In this context, the activation of the endothelium and myeloid cells may promote a procoagulant environment, characterized, among other changes, by an increase in tissue factor expression [2,14,21,23].

3.5. Experimental Models to Explore a Potential Causal Link Between Pneumocystis jirovecii β-Glucans and Atherosclerosis

The establishment of a causal relationship between systemic exposure to *P. jirovecii* β-glucans and the progression of atherosclerosis necessitates the development of experimental models that

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coherently integrate immunological, vascular, and metabolic components. Given that *P. jirovecii* is a strictly human fungus that cannot be cultured by conventional methods, available approaches must focus on the controlled administration of purified β-glucans or on models that reproduce their key immunobiological effects [2–4,20–25].

Nevertheless, this constraint does not preclude the utilization of complementary methodologies. The utilization of models employing *Pneumocystis carinii* in rats and *P. murina* in mice, which are extensively employed in preclinical research, facilitates the analysis of responses elicited by the entire microorganism. These models provide a comparative framework for examining the contribution of β-glucans to pulmonary and systemic inflammation. In this context, several reviews emphasize that β-glucans, as abundant components of the *Pneumocystis* cell wall, interact with multiple receptors of the innate immune system and activate proinflammatory signaling networks that cannot be reproduced using axenic cultures of *P. jirovecii* [2–4,20–24]. Conversely, the integration of animal models with elevated physiological intricacy, such as porcine models of atherosclerosis, has the potential to enable the assessment of vascular and metabolic ramifications within a cardiovascular system that more closely resembles that of humans. This development offers a way for the exploration of the association between exposure to fungal β-glucans and atherosclerotic progression with enhanced precision [23–25].

3.6. Murine Models of Atherosclerosis

Genetically modified murine models, particularly ApoE$^{-/-}$ and LDLR$^{-/-}$ mice, have been extensively validated as platforms for studying atherogenesis and the interaction between systemic inflammation and vascular biology [25]. In this context, the repeated administration of *P. jirovecii* β-glucans—either via intratracheal or systemic routes—would facilitate the evaluation of their impact on the burden and composition of atherosclerotic plaques, immune cell infiltration, and the expression of inflammatory and oxidative stress markers in the arterial wall [2,20–25,27].

Similarly, in studies necessitating exposure to the complete microorganism, infection models with *P. murina* or *P. carinii* can be utilized. These models facilitate complementary exploration of the contribution of the *Pneumocystis*-induced inflammatory response to vascular dysfunction and the progression of atherosclerosis, integrating both β-glucan-mediated signaling and the participation of other components of the fungal wall [2–4,20–25,27].

In this regard, robust activation of the NLRP3 inflammasome and NETosis-associated pathways has been described in mice infected with *P. murina*, with the generation of intense pulmonary inflammatory responses and local microvascular alterations [28]. In accordance with this observation, murine models of chronic respiratory diseases have demonstrated that *Pneumocystis* infection exacerbates perivascular inflammation and immune cell infiltration around the vessels. This finding suggests a possible convergence with mechanisms involved in endothelial dysfunction and chronic vascular disease progression [23–25,27,28].

3.7. Cell Cultures and In vitro Vascular Models

In vitro models provide a complementary approach to elucidating mechanisms at higher molecular resolution. Human endothelial cell cultures exposed to *P. jirovecii* β-glucans allow for the evaluation of changes in endothelial activation, reactive oxygen species production, adhesion molecule expression, and alterations in barrier function [2–4,20–22,24,26]. The integration of co-culture systems with monocytes or macrophages facilitates the analysis of cellular interactions pertinent to the initial phases of atherosclerotic injury. This approach integrates CLR- and CARD9-mediated signaling pathways, as well as additional inflammatory mechanisms previously described in *Pneumocystis* infection models. These mechanisms include NLRP3 inflammasome activation and NETosis processes, which have the potential to amplify oxidative stress and endothelial dysfunction [26–28].

Conversely, the utilization of three-dimensional endothelial models or microfluidic systems that replicate laminar flow and shear stress conditions could yield more physiologically accurate data

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concerning the way exposure to β-glucans influences the endothelial response within an environment analogous to the in vivo vascular environment [2–4,20–22,24,26].

3.8. Integration with Immunometabolic and Omic Profiles

A contemporary experimental approach necessitates the integration of the analysis of transcriptomic, epigenetic, and metabolic profiles in response to exposure to *P. jirovecii* β-glucans, ideally combined with integrative analysis and computational modeling strategies. The characterization of the plasticity of monocytes and macrophages towards proinflammatory or proatherogenic phenotypes, as well as the identification of molecular signatures associated with vascular inflammation, could reinforce the biological plausibility of the proposed link and facilitate the construction of predictive models that capture complex interactions between immunometabolic pathways and disease progression. In this context, the combination of animal models, omic analyses, and measurement of circulating biomarkers—including cytokines, chemokines, and markers of endothelial activation—would allow parallels to be drawn with clinical observations and advance toward a more robust translational integration [20,24,27,28].

3.9. Methodological Limitations and Considerations

Notwithstanding their value, these models are subject to inherent limitations. The extrapolation of findings from murine models to human subjects necessitates caution, particularly within the context of antifungal immunity. Furthermore, the structural heterogeneity of β-glucans, in conjunction with variations in dosage, route of administration, and duration of exposure, can exert a substantial influence on experimental outcomes. In this regard, the standardization of *P. jirovecii* β-glucan preparations and the detailed characterization of their structure emerge as critical requirements for the reproducibility and proper interpretation of studies [2,24,27,28].

3.10. Experimental Synthesis and Translational Projection

The use of murine models of atherosclerosis, vascular cell systems, and integrated omics approaches is a coordinated effort that provides a robust experimental framework for testing the hypothesis that *P. jirovecii* β-glucans act not only as markers of fungal exposure but also as active modulators of vascular inflammation and atherosclerotic progression. These approaches signify a crucial advancement from observational associations and biological plausibility toward a more causal comprehension of the intersection between antifungal immunity and cardiovascular risk [20,24,27,28].

This approach is particularly relevant in populations with persistent or repeated exposure to *P. jirovecii*, such as older adults and patients with chronic obstructive pulmonary disease, pulmonary fibrosis, or mild immunosuppression, in whom subclinical colonization and low-grade inflammation could acquire greater systemic relevance [23,24,27–29].

3.11. The Pathophysiological and Clinical Implications of Pneumocystis jirovecii β-Glucans in Atherogenic Inflammation

An integrative review of the extant literature was conducted, and the evidence supports a pathophysiological model in which *P. jirovecii* β-glucans function not only as markers of fungal exposure but also as active mediators of systemic inflammation with potential vascular repercussions. In contrast to dietary β-glucans, whose immunometabolic effects are frequently linked to modulatory and potentially cardioprotective profiles, *P. jirovecii* β-glucans possess structural characteristics that promote sustained activation of proinflammatory pathways, particularly in scenarios of persistent colonization or active infection [2,24,27,28].

From a pathophysiological perspective, the activation of receptors such as Dectin-1, other C-type lectins (CLRs), and EphA2 constitutes a central axis in the transduction of signals induced by highly branched β-glucans. The interplay between Syk-CARD9-NF-κB-dependent signaling, the activation

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of MAPK, STAT3, and oxidative stress-related pathways, has been demonstrated to promote the production of key cytokines and chemokines, including IL-6, TNF-α, IL-1β, and CXC chemokine ligand 8 (CXCL8). This process has been shown to modulate both pulmonary innate immunity and the systemic inflammatory response. The prolonged presence of these signals has the potential to induce alterations in the plasticity of monocytes and macrophages, leading to a proinflammatory phenotype. This process is intricately associated with the progression of atherosclerotic lesions [2,24,27,28].

In this context, the lung emerges as a strategic immune node from which inflammatory signals can be amplified and disseminated systemically. In vulnerable populations, such as older adults, individuals with chronic lung disease, or those with mild immunosuppression, subclinical colonization by *P. jirovecii* has the potential to generate chronic low-grade inflammatory stimulation. This stimulation can be sufficient to sustain systemic inflammation, oxidative stress, and endothelial activation in the absence of obvious infectious manifestations [23,24,28,29]. This scenario is particularly salient in the context of atherosclerosis, a chronic inflammatory disease in which persistent endothelial activation, monocyte recruitment, and vascular dysfunction play a pivotal role [1,23,24,28].

Within the interpretative framework outlined, serum positivity for (1→3)-β-D-glucan assumes a more intricate dimension. Beyond its diagnostic utility in invasive fungal infections, the magnitude and duration of its elevation could reflect immunologically relevant exposure to circulating β-glucans, with the capacity to modulate vascular biology [5,24]. The potential correlation between prolonged levels of β-D-glucan, endothelial activation, coagulation alterations, and atherosclerotic plaque progression gives rise to clinical inquiries that exceed the scope of infectious diseases and extend into the domain of cardiovascular medicine [5,24,27,28].

The comparison with dietary β-glucans underscores the significance of origin and structural properties in determining biological effects. While β-glucans from cereals and edible fungi interact have a weaker interaction with the immune system and exert beneficial effects mediated, in part, by the gut microbiota and metabolic modulation, β-glucans from *P. jirovecii* lack structural elements that limit their immune recognition and show a high affinity for proinflammatory receptors. This functional divergence underscores the need to avoid simplistic interpretations that equate all β-glucans as biologically equivalent entities [2,24,27,28].

From an experimental perspective, murine models of atherosclerosis, in vitro endothelial systems, and integrated omics approaches offer tools to move from observational associations to pathophysiological inferences. The ability to analyze specific pathways, such as those dependent on Dectin-1/CARD9 or lactosylceramide, will facilitate the identification of critical signaling nodes susceptible to intervention and elucidate the extent to which exposure to fungal β-glucans directly contributes to vascular inflammation [20,24,27,28].

However, it must be acknowledged that this review is subject to inherent limitations, primarily due to its narrative nature and the heterogeneity of the available studies. A significant proportion of the extant evidence derives from experimental models or observational studies with limited sample sizes; consequently, extrapolation to human populations should be done with caution. Additionally, the standardized quantification of *P. jirovecii* β-glucans and the distinction between transient and persistent exposure remain significant methodological challenges [2,24,27,29].

To date, clinical evidence does not allow for definitive conclusions regarding a potential causal relationship between exposure to *P. jirovecii* β-glucans and the occurrence of cardiovascular events. However, the available experimental models provide a sufficient framework for the controlled evaluation of this hypothesis [24,27–29].

Concurrently, numerous studies have documented a high prevalence of *P. jirovecii* colonization in various populations, including individuals with HIV, patients with COPD, infants, and notably, the general population. The near ubiquity of the detection of *Pneumocystis* in the lungs of infants who died of sudden death syndrome suggests that subclinical exposure is a widespread phenomenon and potentially relevant from a pathophysiological point of view [23,24,29,30].

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The coexistence of frequent fungal colonization and atherosclerotic disease of high prevalence does not, in itself, imply a causal relationship. However, it does establish a biologically plausible scenario that justifies systematic investigation. In this regard, prospective studies assessing the presence of *P. jirovecii* or its immunoactive components in patients with atherosclerosis, together with longitudinal monitoring of colonization, would constitute a reasonable methodological approach to explore this potential immunobiological interaction [23,24,29,30].

In fact, with advances in antiretroviral therapy, most deaths in people with HIV are now attributable to noncommunicable illnesses, especially cardiovascular disease. Recently, a review discussed the epidemiology and clinical features of cardiovascular disease, with a focus on coronary heart disease, in the setting of HIV infection, which includes a substantially increased risk of myocardial infarction even when the HIV infection is well controlled [31]. In this context, *P. jirovecii* remains one of the most important pathogens in people living with HIV [5]. Based on the hypothesis presented in this document, it would be worthwhile to conduct studies on atherosclerosis in people living with HIV in whom colonization by *P. jirovecii* is significant.

4. Perspectives

Current evidence suggests that *Pneumocystis jirovecii* β glucans may represent an underrecognized contributor within the inflammatory continuum linking pulmonary immunity to vascular pathology. Yet, their clinical significance remains insufficiently defined. Several lines of investigation emerge as essential to advance this field.

A primary priority is the distinction between transient and persistent exposure. The sustained presence of circulating (1→3)-β D glucan, even in the absence of overt clinical manifestations, raises the possibility of chronic immunological stimulation with systemic repercussions [5,24]. Developing standardized methods capable of quantifying *P. jirovecii* specific β glucans—and differentiating them from other fungal sources—will be crucial for establishing causal inferences [24,27,29].

Equally important is the refinement of mechanistic understanding. Highly branched β glucans from *P. jirovecii* activate a network of proinflammatory pathways, including Dectin 1/CARD9 dependent signaling, MAPK and STAT3 activation, and oxidative stress–related cascades [24,27,28]. Dissecting these circuits through murine models of atherosclerosis, endothelial cell systems, and integrated omics approaches will help identify critical signaling nodes amenable to therapeutic modulation and clarify whether fungal β glucans directly contribute to vascular inflammation [20,24,27,28].

From an epidemiological standpoint, the high prevalence of subclinical colonization in vulnerable populations—older adults, individuals with chronic lung disease, those with mild immunosuppression, and people living with HIV—raises clinically relevant questions [23,24,29,30]. In these groups, the coexistence of frequent colonization and elevated cardiovascular risk creates a biologically plausible scenario that warrants prospective evaluation. Notably, in people living with HIV, where cardiovascular disease has become a leading cause of morbidity and mortality despite virological control, the potential contribution of *P. jirovecii* colonization deserves systematic investigation [5,31].

The comparison with dietary β glucans further underscores the need to abandon generalized assumptions of biological equivalence. Structural features that determine receptor affinity and immunological potency differ markedly between fungal and dietary β glucans, and elucidating these distinctions may open new avenues for selective immunomodulation [24,27,28].

Collectively, these perspectives outline an emerging research landscape at the intersection of pulmonary immunology, vascular biology, and medical mycology. Clarifying the role of *P. jirovecii* β glucans in systemic inflammation and cardiovascular risk has the potential not only to refine current models of atherogenesis but also to reveal novel diagnostic and therapeutic opportunities for high risk populations.

5. Conclusions

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The β-glucans of *P. jirovecii* may be conceptualized as active mediators of systemic inflammation with potential relevance for vascular biology and atherogenesis. Their highly branched architecture—dominated by β-1,3/β-1,6 motifs—and their interaction with proinflammatory receptors such as Dectin-1, various CLRs, and EphA2 promote sustained activation of monocytes, macrophages, and endothelial cells. This fosters an immunoinflammatory environment with pro-atherogenic characteristics, in contrast to the modulatory profiles described for dietary β-glucans.

The persistence of (1→3)-β-D-glucan in serum suggests subclinical or chronic exposure to fungal polysaccharides, potentially associated with low-grade inflammation, oxidative stress, platelet activation, and endothelial dysfunction—processes that converge in the progression of atherosclerotic lesions. Although most of the available evidence derives from experimental models and observational studies, the body of data establishes a coherent conceptual framework linking pulmonary antifungal immunity with mechanisms of systemic vascular inflammation.

The epidemiological coincidence between the high prevalence of *P. jirovecii* colonization and the global burden of atherosclerosis does not establish a causal relationship. However, it defines a biologically plausible scenario that justifies systematic evaluation. In this context, translational and longitudinal studies that discriminate between transient and persistent exposure, validate biomarkers, and explore specific pathophysiological pathways will be essential to more precisely delineate the clinical impact of *P. jirovecii* β-glucans on cardiovascular risk.

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Abbreviations

The following abbreviations are used in this manuscript:

Receptors and Recognition Molecules
CLRsC type lectin receptors
Dectin 1 C type lectin receptor Dectin 1
EphA2 Ephrin type A receptor 2
TLR2 / TLR4Toll like receptors 2 and 4
Signaling Pathways and Intracellular Complexes
CARD9Caspase recruitment domain containing protein 9
BCL10B cell lymphoma/leukemia 10
MALT1 Mucosa associated lymphoid tissue lymphoma translocation protein 1
ITAM like Immunoreceptor tyrosine-based activation motif like
Syk Spleen tyrosine kinase

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MAPK Mitogen activated protein kinase
NF κBNuclear factor kappa light chain enhancer of activated B cells
STAT3 Signal transducer and activator of transcription 3
NLRP3 NOD like receptor family pyrin domain containing 3
Cytokines, Chemokines, and Inflammatory Mediators
IL 1β Interleukin-1 Beta
IL 6 Interleukin 6
TNF α Tumor Necrosis Factor Alpha
CXCL8 C X C motif chemokine ligand 8
CCL2 / CCL3C C motif chemokine ligands 2 and 3
IL 10 Interleukin 10
IL 23 Interleukin 23
Endothelial Adhesion Molecules
VCAM 1Vascular cell adhesion molecule 1
ICAM 1 Intercellular adhesion molecule 1
Animal Models and Experimental Genetics
ApoE$^{-/-}$Apolipoprotein E knockout mouse
LDLR$^{-/-}$Low density lipoprotein receptor knockout mouse

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