Mini Review

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Bioactive β -Glucans, Adjuvants in SARS-CoV-2 Antiviral Therapy

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ABSTRACT

Abbreviations: SARS: Severe Acute Respiratory Syndrome; PRS: Pattern Recognition Receptors; CR3: Complement Receptor; SRs: Scavenger Receptors; DCs: Dendritic Cells; CTLs: Cytotoxic T Lymphocytes; CRS: Cytokine Release Syndrome; ANE: Acute Necrotizing Encephalopathy

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In the context of the outbreak crisis, a particular interest in finding solutions for treatment and prophylaxis of Severe Acute Respiratory Syndrome (SARS-CoV-2) exist. As long as treatment for COVID-19 is supportive we must turn our attention to the natural defense mechanism of the body, in this case, the immune system. The fighting ability of the immune system against coronaviruses can be attributed to some antiviral agents, type I interferon, high doses of vitamin C and other immunomodulators that can support the immune function [1-3]. Other therapies such as immunoglobulins from convalescent plasma can suppress viremia and might be used from the early stage of infection without any serious adverse effect [4]. Special emphasis is placed on β -glucans, in this case the group of a diverse class of long polymers of β -D-glucose consisting with a backbone of β -1-3 glucopyranosyl units and β -1-6 linked side chains such as those found in yeast and fungi who can modulate both innate and adaptive immune functions [5]. With over 20000 studies yeast glucan is considered to exert the highest biological effect related to immunomodulation [6] by binding to the Pattern Recognition Receptors (PRRs) involving: Complement Receptor (CR3), Scavenger Receptors (SRs), lactosylceramide (LacCer) and to the dectin-1 receptors [7] depending on the type and route of administration and among other natural agents used in immunotherapy, glucans might improve clinical outcomes in patients with COVID-19.

Apart from infectivity and mortality, no doubt that this β -coronavirus shares similarities with seasonal influenza [8] and has a 79.5% sequence homology with SARS-CoV [9]. So a broad-spectrum of antivirals previously used against SARS and MERS appears to be effective by blocking the COVID-19 infection [8]. Medication such as: ribavirin, ritonavir+lopinavir, arbidol, IFN-α , IFN-β and IFN-γ with the potent immunomodulation are in the first-line treatment for this new coronavirus [10]. Mechanistic models on how glucans stimulate innate and adaptive immune responses highlight future directions of large-scale systems immunology [11]. Thus β –glucans can work on the path by reducing the influenza virus. A study performed by supplementation on mice with a mix of glucans during 14 days period shows an increase in antibody response to influenza infection [12]. Unlike the control group fed with phosphate-buffered saline, those with glucan appears to have a significant reduction of the virus titer in the lungs from day three after infection and in the thymus and heart after five days [12]. In another clinical trial in a swine influenza model, pigs infected with the H1N1 virus and pre-administered with –glucan from *Saccharomyces cerevisiae* had shown elevated levels of interferon γ in bronchoalveolar lavage fluid after seven days post-infection and for nitric oxide after five days, resulting in a reduction of lung lesion score and viral replication, a treatment that has been proved to exert a strong antiviral effect [13].

The major glucan receptor dectin-1, an archetypical non-TLR pattern-recognition receptor expressed predominantly by myeloid cells, can trigger its intracellular signaling and mediate a variety of cellular responses, such as cytokine production [14] and has the ability to produce increased levels of type I IFNs which are shown to play a key role in antiviral defense. For instance, during RNA virus infection with coronaviruses, an external supply of type I IFNs have a protective effect on the macrophages and Dendritic Cells (DCs) which in that context are unable to enhance IFN α levels because of particular viral proteins, showing that IFN system is essential in viremia control [15,16]. Particularly to yeast glucan, type I IFN is produced by DCs in accordance with the dectin-1 activation in an autocrine manner and independent of toll-like receptors which are demonstrated by analyzing the activation of the main transcriptional activators required to assembly the type I interferon [17]. All of these pathways are crucial for the protection against any viral infections by limiting the spread of the virus within the host as well as on SARS-CoV2 from an early stage of infection, making interferon a safe and easy to upscale treatment. Well documented articles about the role of type I interferon in COVID-19 disease can be found in an antiviral research article about interferon treatment as reported by Sallard and colleagues (2020) [18] and how –glucans are recognized by the innate immune system via dectin-1 signaling pathway see Goodridge and coworkers (2009) [11].

The progression of the disease can often be correlated with exhaustion of cytotoxic lymphocytes and in the case of patients with COVID-19 who shows severe lung inflammation, the immune response of natural killer cells (NK) and for Cytotoxic T Lymphocytes (CTLs) is largely aggravated by the NKG2A expression (a major NK inhibitory receptor) [9].The reduction in NKG2A expression after antiviral therapy in convalescent patients occurred concomitantly with an increase in the number of depleted cytotoxic cells. Beta glucans with the ability to maturate dendritic cells through the PI3K/AKT pathway makes the cytotoxic lymphocyte response to be improved by increasing the IL-12 levels (cytokine necessary for CTLs responses), IFN- and IL-2 [19]. The study used particulate β –glucan from *S.cerevisiae* with a backbone of long β –1,3 glucose units interconnected by 3-6% units of β –1,6 glucose side chains which are capable to induce maturation of dendritic cells. The use of anti-inflammatory medication is also documented and the need for this therapy is due to the fact that patients with severe forms of infection suffer a rapid deterioration after 1-2 weeks of onset and the initiation of anti-inflammatory treatment can have promising results [20]. In-depth studies using neural networks to speed up finding a treatment for COVID-19 had identified a set of anticancer drugs that have the potential to inhibit viral infection, one of these, baricitinib with fewer side effects is working by interfering with the inflammatory processes within the immune system which cause symptoms of rheumatoid arthritis [21]. Further, such combinations between ritonavir/lopinavir the direct-acting antivirals, and baricitinib could reduce these atypical inflammatory responses and infectivity [22]. Beta glucans also exert anti-inflammatory and anticancer effect by promoting the Th1 responses through the IL-12 production (which is a strong stimulator of IFN-γ) and such interactions augment the production of chemokines by maturating the DCs [23,24]. Also, compared to other cocktails of cytokines used to maturate DCs, particulate yeast glucan activate a considerable number of human dendritic cells and could be a promising component for vaccines [19].

Severe forms of SARS-CoV-2 can induce Cytokine Release Syndrome (CRS) in some patient [25] which can cause systemic symptoms and even death. Recently, this "cytokine storm" associated with SARS-CoV-2 could overcome blood-brain-barrier and determine neurological consequences such as Acute Necrotizing Encephalopathy (ANE) reported by Poyiadji et al. [26] in a female with SARS, recognized through the CT and MRI images [26]. Studies involving soluble -glucan in mice reported different cytokine responses by enhancing the INF-γ by the T cell activation and might "suppresses the magnitude of lymphocyte TNF- production" [27,28]. Second, the synthesis of IL-1Ra a specific inhibitor of pro-inflammatory cytokine and IL-10 is also attributed to particulate β -glucans [29]. In addition, this suppression effect due to the administration in small doses of -glucan on TNF- and two other cytokines (IL-1 β and IL-6) is effective in the treatment of inflammatory lung injury related to sepsis [30]. After the A/H5N1 influenza virus Vetvicka et al. [12] concluded that there are no significant differences in IL-1β levels on glucan treated mice compared to PBS but the INF-γ increased considerably [12]. Of course, it is important to note that even the cytokine response on IL-1 β production and Th1/Th2 balance varies greatly on β –glucan size, origin, conformation and molecular mass [31-33], thus the particle size is essential in cytokine production and small particles led to a reduction in inflammatory gene transcription compared to large particles [31].

Among other nutraceuticals such as glucosamine which activate the mitochondrial antiviral-signaling protein (a key mediator of type I IFN), spirulina (with the potential to enhance type I IFN in RNA virus infections) [34] or N-acetylcysteine (which promote glutathione production and protects against influenza), brewer's yeast β-glucan might prevent and control RNA viruses including coronavirus infections [35]. Indeed, not all yeast glucans act the same because of the growth conditions and this might be also a key factor in the immunomodulation process. Besides the strain, brewery yeast β-glucan has a different pattern than those found in baker's yeast and it seems to be well tolerated [36]. Nor such combinations between yeast glucan, vitamin C and resveratrol are neglected so a significant synergistic effect exists in order to boost the antibody production [37]. Even orally administered -glucans has increased efficiency in the immune system [36] and a mixture of various β-glucans leads to a reduction of mortality in influenza virus infection (up to 60% after 14 days) [12]. Taking together,

the idea of using -glucans in SARS-CoV-2 is due to the fact that this bioactive compound exerts a great antiviral activity and previous studies clearly demonstrate its effectiveness in viral infections at the stage of viral entry, thus, it is necessary to perform further clinical trials and find the best combination which is suitable in the treatment of COVID-19.

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