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Review

Potential Roles of Modified Pectin Targeting Galectin-3 against Severe Acute Respiratory Syndrome Coronavirus-2

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Abstract: Modified pectin (MP) is a bioactive complex polysaccharide that is broken down into smaller fragments of units and used as an oral dietary supplement for cell proliferation. MP is safe and non-toxic with promising therapeutic properties with regard to targeting galectin-3 (GAL-3) toward the prevention and inhibition of viral infections through the modulation of the immune response and anti-inflammatory cytokine effects. This effect of MP as a GAL-3 antagonism, which has shown benefits in preclinical and clinical models, may be of relevance to the progression of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in coronavirus disease 2019 patients. The outbreak of emerging infectious diseases continues to pose a threat to human health. Further to the circulation of multiple variants of SARS-CoV-2, an effective and alternative therapeutic approach to combat it has become pertinent. The use of MP as a GAL-3 inhibitor could serve as an antiviral agent blocking against the SARS-CoV-2-binding spike protein. This review highlights the potential effects of MP in viral infections, its proposed role as a GAL-3 inhibitor, and the associated function concerning a SARS-CoV-2 infection.

Keywords: modified pectin; galectin-3; SARS-CoV-2; polysaccharide; COVID-19; inflammation; immune response

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged as a novel virus in December 2019 in Wuhan, Hubei Province, China, causing the global pandemic coronavirus disease 2019 (COVID-19) [1]. Up to 27 July 2021, a total of about 194 million cases and over 4 million deaths were reported around the world, making COVID-19 a major worldwide health risk [2]. The global public health community faced an imminent need to understand the pathogenesis of the novel coronavirus and produce an effective therapeutic approach to combat its emergence and re-emergence [3]. Several therapies including the antivirals remdesivir and chloroquine have been intensively researched. However, these come with mixed results, lacking a viable standard of treatment for COVID-19 patients [4,5]. Consequently, it has become imperative to identify alternative therapeutic medicines.

SARS-CoV-2 belongs to enveloped RNA viruses, subgenus betacoronavirus of the family coronaviridae [6–8]. SARS-CoV-2 is made up of four primary structural proteins: homotrimer spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein and nucleocapsid (N) protein as well as a few ancillary proteins [8]. In coronavirus, the spike proteins (with a distinctive "corona" crown-like shape on the virion surface) have two subunits, the S1 and S2 glycoproteins. S1 has an N-terminal domain (NTD) and a C-terminal domain (CTD), which facilitate the host adhesion binding to the receptor. S2 has a CTD responsible for the fusion of the viral and cellular membranes and the entrance into the cells by attracting angiotensin-converting enzyme 2 (ACE-2) [9,10].

The recent literature has indicated a COVID-19 treatment with a GAL-3-targeted therapy linking the spike proteins of coronaviruses, with human GAL-3 having a similar

protein structure [11–13]. This involves the use of the GAL-3 inhibitor as an antiviral agent blocking against the SARS-CoV-2-binding spike protein. However, there is still more to explore and understand about this promising GAL-3 target therapy route. Recently, attention has been paid to the potential involvement of pectin as a bioactive complex polysaccharide, which when broken down into smaller fragments is referred to as modified pectin (MP). The antagonistic activity of MP against GAL-3 has been of great interest in the majority of the preclinical and clinical reports in the prevention of and reduction in cancer [14–19] as well as fibrotic, renal injury and cardiovascular diseases [20–23] and inflammatory and immune functions [24–27].

The effects of MP are the subject of new and interesting research with evidence indicating that galactan-rich tiny molecular weight pectin fragments can bind to the carbohydrate recognition domain (CRD) on the pro-metastatic protein, GAL-3. This hinders GAL-3 from interacting with other proteins and peptides, limiting its capacity to stimulate cell adhesion, migration, angiogenesis, tumorigenesis and apoptosis [28–30]. This suggests that MP through the inhibition of GAL-3 could be used in a potentially safe and non-toxic method to prevent or reduce the viral adhesion and viral-associated inflammatory responses targeting a therapeutic approach [13,31]. Given the above, this review looks to highlight the potential effects of MP in viral infections, its proposed role as a GAL-3 inhibitor, and the associated function concerning SARS-CoV-2 infections.

2. Galectin-3

GAL-3 is a chimeric carbohydrate-binding protein member of the galectin family. It is a galactose-binding protein that is expressed in numerous human cells including epithelial, endothelial, immunological and inflammatory cells as well as macrophages from the head, neck, thyroid, stomach, brain and alveolar cells in the lungs [32–35]. GAL-3 has a small molecular weight (30 kDa) and comprises three main terminals, namely, the -NH2 terminal domain (NTD), a collagen-like repeated tandem rich of the Gly-Pro-Ala-Try protein domain (CPD) and the carbohydrate recognition domain (CRD) containing -COOH terminals and the Asp-Trp-Gly-Arg (NWGR) anti-death motif (Figure 1) [29,36]. The GAL-3 CRD is connected to a long, flexible N-terminal domain with a specific affinity that binds to β-galactosides such as lactose and larger galacto-oligosaccharides. The N-terminal domain of GAL-3 is required for multimerization and is vulnerable to proteolysis by matrix metalloproteinases and may interact with other intracellular proteins. The interaction of GAL-3 with glycoconjugates containing N-acetyllactosamine is controlled by its C-terminal CRD [37].

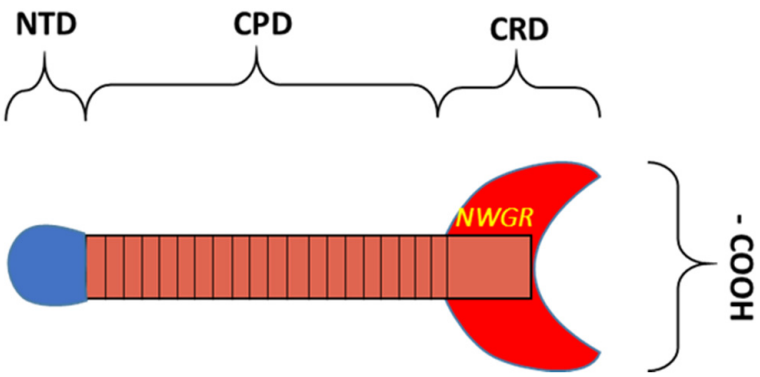

Figure 1. Structure of galectin-3 comprising the -NH2 terminal domain (NTD), the collagen-like protein domain (CPD), consisting of about 100 amino acids, and the carbohydrate recognition domain (CRD), consisting of the -COOH terminal and NWGR.

Recent studies have begun to shed more light on the significance of GAL-3 and its prominent role in viral infections. GAL-3 has been identified as a binding mediator in the entrance and attachment of the herpes simplex virus (HSV) in ocular infection [38].

However, it remains unclear whether this holds for the virus at other sites of entry during infection, including the mucosa [31]. During HSV infection, the expression of GAL-3 is increasingly high [39]. Similarly, HIV infection increases GAL-3 expression by activating Toll-like receptor 4 (TLR4)/NF-kB-dependent pathways [40]. GAL-3 is abundantly produced in many infected human T-lymphotropic virus type 1 (HTLV-1) T cells and causes the GAL-3 to be upregulated via HTLV-1 Tax binding to the GAL-3 promoter [41,42]. Endogenous GAL-3 works by interacting intracellularly with the HIV-1 protein Gag and the cellular ALG-2-interacting protein X (Alix), both of which are required for viral budding and replication when new infectious virions are produced [43]. GAL-3 was found to be upregulated in promoting HIV-1 replication in infected CD4 T cells [44].

The endogenous galactoside-binding GAL-3 is implicated in cell growth, as well as cell proliferation, adhesion, differentiation, migration, angiogenesis, mRNA splicing promoter, malignant transformation, and apoptosis [45]. These cellular processes are potential targets to inhibit viral genome replication. Coronaviruses have five primary open reading frames (ORFs) encoded in their genomes which include a 5′ frameshifted polyprotein and four 3′ structural proteins—S, E, M, and N proteins [46]. Potential ORFs implicated in viral genome replication in SARS-CoV-2 and related severe acute respiratory syndrome genomes were investigated using the computer program Gene prediction by Open reading Frame Identification utilizing X motifs [47]. The ORF8b encoded in the SARS-CoV genome promotes the synthesis of cellular DNA and viral replication, as well as the activation of the nucleotide oligomerization domain-like receptor protein 3 (NLRP3) inflammasome [48,49]. Similarly, the activation of the NLRP3 inflammasome by the endogenous GAL-3 increases the severity of avian influenza A H5N1 virus-induced lung inflammation. The lungs of infected mice produced more GAL-3 mRNA protein as a result of influenza virus A H5N1 infection [50]. ORF8b aggregates associated with the GAL-3 cause endoplasmic reticulum and lysosomal stress lead to the nuclear translocation of the transcription factor. The viral genomic RNA triggers TLR to activate the NLRP3 inflammasome [50]. Therefore, the genetic manipulation or inhibition of TLR4 may impede the activation of NLRP3 to reduce the ability of the influenza A virus replication [51] through ORF8b-associated GAL-3 inhibition. This implies that targeting the inhibition of GAL-3 may also affect viral RNA synthesis in the case of the SARS-CoV-2.

The plasma levels of GAL-3 protein were higher in viral infections associated with inflammatory cell infiltration. In hepatitis B infection, the level of GAL-3 may be a useful predictor of chronicity by stimulating CD98 interaction with macrophages to promote the production of certain cytokines and chemokines [52]. The interaction of endogenous GAL-3 with NLRP3 amplifies the impact of H5N1 infection by modulating the production of macrophage IL-1 [50]. In addition, the binding of GAL-3 to influenza virus A promotes pneumococcal adherence to the cell surface [53]. All these indicate that GAL-3 may also have an important role in the primary and secondary airway infections in COVID-19 patients. Although, it is still unclear what causes the increase in GAL-3 in the majority of viral infections. It was suggested that viral gene expression may be driving GAL-3 expression in part [41,54]. This multi-functional protein is synthesized in the cytoplasm as a cytosolic protein but can be expressed in the nucleus when transported to the multiple subcellular localization of the cell nucleus, or secreted into the extracellular matrix (ECM) (outside of the cell) [35,55]. GAL-3 regulates cell homeostasis both intracellularly and extracellularly [56]. At the extracellular surface, GAL-3 can bind glycoconjugates as an aggregate of cells coming together to form cell–matrix interactions [57].

3. Modified Pectin

Pectin is a naturally occurring polysaccharide found in the cell wall of plants such as fruits and vegetables. It is mainly extracted from the citrus peel due to its high concentration in the skin and core parts of the fruit [58]. Pectin is known to be a complex water-soluble polysaccharide composed majorly of: (i) predominant 1,4-linked α-D-galacturonic acid of the Rhamnogalacturonan-I (RG-I) region, (ii) a part of the methoxylated-esterified

carboxyl group structure of the Homogalacturonan (HG) region, which makes it an acidic polysaccharide, and (iii) the Rhamnogalacturonan-II (RG-II) [29]. The RG-I region has more flexibility which is so important because galactan, arabinan, and arabinogalactan side chains are located on the RG-I and attached to the rhamnose residue [59,60]. The rhamnose backbone residue is covered in two forms of arabinogalactans: the linear β-(1-4)-D-galactan and the branched β-(1-3,6)-D-galactan. The β-(1-4)-D-galactan is most likely a structural weapon with an affinity for binding to the CRD [29].

When MP is originally derived from the citrus fruit, it is then referred to as modified citrus pectin (MCP). MCP is a smaller size uniform fragment of about 10–20 kDa obtained through the effect of pH modification by alkaline (sodium hydroxide) and/or acid treatment or by enzymatic breakdown [61]. Ordinarily, the degree of esterification in industrial pectin is as high as 70%; it has been defined in MP to be <10% by the removal of methoxyl group from the high methoxyl pectin to form low methoxyl pectin. This modification causes the β-elimination cleavage from the HG backbone, thereby releasing oligomers of polygalacturonic acid. The RG-I region can be further split into galactan and arabinogalactan with fewer arabinose substitutes as the treatment cleaves linkages between the neutral sugars and eventually modifies the RG-I (Figure 2) [62,63]. This modification produces unique bioactivity in MCP which creates a chance for the carboxyl group on the galactan to interact more with GAL-3 and increases the bioavailability of the free galactans that bind to the GAL-3 [63].

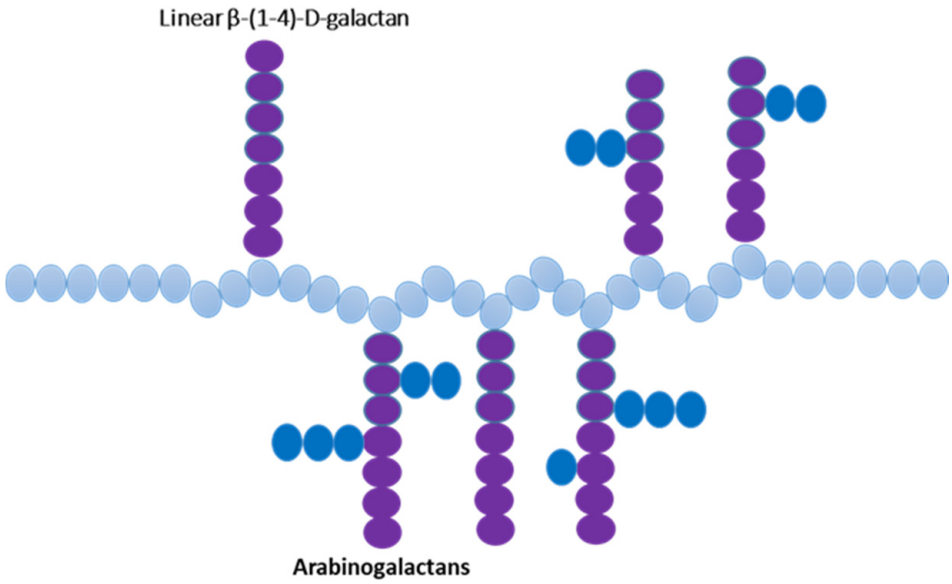

Figure 2. Schematic diagram of modified pectin RG-I consisting of the linear β-(1-4)-D-galactan and the arabinogalactans residues after the enzymatic treatment cleaves the sugars linkage in pectin [29].

MCP is rich in β-galactose, potentially safe, and non-toxic. It is used as a dietary supplement to promote cell growth. Recent research has linked the effects of the oral consumption of MCP to its specific molecular interaction with the GAL-3. Studies have shown the health benefits of MP, highlighting the roles of targeting the inhibition of GAL-3 in immune response, inflammation, macrophages, cytokines, cardiovascular, renal injury, fibrosis, and cognitive impairment [28]. Most of these studies have given considerable focus to the effect of MCP with significant preclinical and clinical trials in vivo and in vitro. This has demonstrated reliable outcomes to justify the health benefit and acceptable safety profile of the MCP. Although, to date, there is little or no information on the role of MP targeting viral infections, particularly toward GAL-3 inhibition. However, it is plausible to extrapolate the potential role of pectin and its impact on COVID-19 infection.

4. Potential Role of Modified Pectin Binding Galectin-3 in SARS-CoV-2 Infections

Studies have shown the potential role of industrial pectin in exploring its antiviral activity (Table 1). In most MCP research, GAL-3 plays several prominent roles which influence its bioactivity by inducing extracellular functions such as the interaction between cells and inflammation. The relevance of the effect of MP through GAL-3 antagonism to the progression of SARS-CoV-2 in COVID-19 patients can be extrapolated from the perspective of (i) MP and GAL-3 binding as a mediator for viral adhesion in the virus infection mechanism through the viral spike protein, given that the N-terminal domain of SARS-CoV-2 evolves from a galectin origin, (ii) MP and GAL-3 response to inflammation and macrophage driving the cytokine storm in severe SARS-CoV-2 cases.

Table 1. Antiviral effect of pectin on various viral infections.

Disease Indication	Model of Study	Virus	Outcome of Study	References
COVID-19	Molecular docking	SARS-CoV-2	Citrus pectin binding to the protein receptor inhibits the replication of the SARS-CoV-2.	[64]
COVID-19	Molecular docking	SARS-CoV-2	Citrus specific binding to the ACE-2 inhibits the replication of SARS-CoV-2.	[65]
Mosaic disease	Plant	Tobacco Mosaic Virus	MP mediated virus-induced gene generates short interfering silencing of viral RNA and spread.	[66,67]
Mosaic disease	Plant	Tobacco Mosaic Virus	Pectin methylesterase suppresses the transport of viral protein in antisense plants.	[68]
Genital Herpes	In vitro	Herpes Simplex Virus Type 1 and Poliovirus	Pectin inhibits viral replication by binding to the glycoprotein and carboxyl groups on the cell membrane.	[69]
Hepatitis	In vitro	Hepatitis B Virus	Pectin (SLP-4) inhibits the secretion of surface and envelope antigens of HBV in HepG2 cells through pectin polysaccharide and HBV protein interaction.	[70]
Influenza	Mouse	Influenza A Virus	MCP induces Th1 T-helper immune response.	[71,72]
Genital Herpes	In vitro	Herpes Simplex Virus Type 2	Pectin polysaccharide shows an anti-HSV-2 activity.	[73]

Abbreviations: COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, ACE-2; Angiotensin-converting enzyme 2, MP: Modified pectin, MCP: Modified citrus pectin.

4.1. Modified Pectin and Galectin-3 Binding against a Viral Adhesion

GAL-3 has been identified as a binding mediator that aids viral attachment. In SARS-CoV-2 infection, the glycosylation of the outer membrane spike glycoprotein causes the interaction of the viral protein with the cell receptors and adhesion factors, including ACE-2. It was hypothesized that the unique N- and O-linked glycosylation sites of the S1-NTD spike glycoprotein in SARS-CoV-2 may interact with immunoregulatory factors [74]. This suggests that GAL-3 plays an important role in SARS-CoV-2 host interaction [13]. NTD and CTD domains can function as receptor-binding domains (RBDs). The S1-NTDs are in charge of sugar-binding, recognizing both N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc) sugar receptors [75–77] and the S1-CTDs detect ACE-2 protein receptor [78,79]. It is noteworthy that a recent study reveals a dual interaction of S1-NTD binding to the sugar co-receptor, Neu5Ac [75] and the ACE-2 receptor in SARS-CoV-2

infection. The negatively charged -COOH terminal of the 9-O-acetyl-Neu5Ac is positioned for interaction with available sugar or protein molecules [80,81].

SARS-CoV-2 may be able to recognize Neu5Ac co-receptors besides the ACE-2 by acquiring the GTNGTKR motif on the S1-NTD [82]. In extreme cases of SARS-CoV-2, a new type of sialic acid-linked ganglioside-binding domain was discovered at the S protein's N-terminal domain [82]. It is therefore noteworthy that SARS-CoV-2 binds to Neu5Ac, GAL-3, GTNGTKR motif, and sialic acids-linked ganglioside could contribute to the greater infectivity of the virus compared to the SARS-CoV [75,82,83]. Similarly, the abundance of Neu5Ac and GAL-3 receptors in the human body particularly at the nasopharynx and oral mucosa has been noted compared to the ACE-2 receptors [83]. This could contribute to the high transmissibility and infectivity of SARS-CoV-2, particularly at viral entry points [32,34].

Recent studies have reported a high degree of similarity in the NTD receptor-binding domain of different coronaviruses, as well as similarity in the structural alignment of the S1-NTD and GAL-3 of SARS-CoV-2 [82]. This indicates that both Neu5Ac and GAL-3 receptors may have similar -COOH terminal domains. The terminal galactose in the neutral sugar side chain of the polysaccharide enables MP to bind specifically to GAL-3 CRD [84]. GAL-3 CRD has an affinity for β-galactosides and MP is a sugar molecule with an abundance of β-galactose [85]. This enables MP to antagonize the GAL-3 β-galactoside protein by binding tightly to it and modulate its bioactivity [86]. It is reasonable to assume that the β-1,4-galactan of the neutral sugar chain in MP has the potential affinity to bind specifically to the -COOH terminal of the Neu5Ac and/or GAL-3 receptors. This inhibits the attachment of the S1-NTD of SARS-CoV-2 to the host cell (Figure 3). Although, a detailed investigation of the mechanisms involving GAL-3 binding and/or inhibition by MP will provide a means of testing this molecular hypothesis and identifying the particular pectin-derived components responsible for the effects.

The knowledge of antiviral compounds containing sugar or sugar analogs that may be used to prevent coronavirus from attaching to its sugar co-receptor [78] has led to unraveling the antiviral potential of pectin and related flavonoids. A study has shown that plants can protect themselves against virus infection by silencing virus-induced genes stimulated by pectin methylesterase [87]. This suggests that pectin methylesterase may contain compounds that mediate the prevention of viral infection in their host. A pectin polysaccharide from a plant named '*Portulaca oleracea*' containing galacturonic acid, galactose, and glucose with small amounts of arabinose and rhamnose showed significant inhibition against herpes simplex virus type 2 (HSV-2) with a selectivity index of more than 20 [73]. Similarly, pectin has high inhibitory effects of 179 $\mu g/mL^{-1}$ and 58 $\mu g/mL^{-1}$ against herpes simplex virus type 1 (HSV-1) and the poliovirus, respectively in Hep-2 cells [69]. This further suggests that the interaction of pectin with the cation amino acids glycoprotein-binding site in HSV-1 and the anion sulfated/carboxyl group heparin-sulfate chains of the cell membrane impedes viral initiation and replication at the initial early stage [69,88].

The S glycoprotein on the NTD is the major antigen on the viral surface that neutralizing antibodies can attack during an infection, hence preventing viral entry [89,90]. It is pertinent to mention that the attachment of SARS-CoV-2 to the cell surface for replication through viral spike protein has multiple potential therapeutic targets. Although the relationship between GAL-3 and SARS-CoV-2 is also mixed, it is still unclear if it is pro- and/or anti-SARS-CoV-2. Furthermore, investigating the possibility of having similarities in the molecular structure of S1-NTD and MP could decipher the potential of a direct binding affinity of the sugar galactan to the CRD of SARS-CoV-2. This will provide an understanding of the interaction of N- and O-linked glycosylation sites of the spike glycoprotein with the carboxyl group on the MP galactan CRD in SARS-CoV-2 infection.

Some natural bioactive compounds and flavonoids such as hesperidin and hesperetin which are related to citrus pectin have demonstrated the potency of the antiviral effect. Hesperidin in citrus peel contains a very interesting molecule with potential antiviral activity against SARS-CoV-2 [91]. Studies reported that the inhibitory activities of hesperidin

against SARS-CoV-2 are through its binding affinity to the protease domain, the ACE-2 receptor-binding domain, and the spike glycoprotein receptor-binding domain [64,92,93]. Hesperetin binds to the receptor domain by inhibiting the attachment of SARS-CoV-2 to the ACE-2 receptor [65]. Further study revealed that citrus hesperidin and hesperetin have the highest binding affinity to the SARS-CoV-2 receptors spike glycoprotein (S1-NTD), protease, and ACE-2 by showing the lowest dock scoring, which indicates a high inhibitory potential against the viral infection and replication [64].

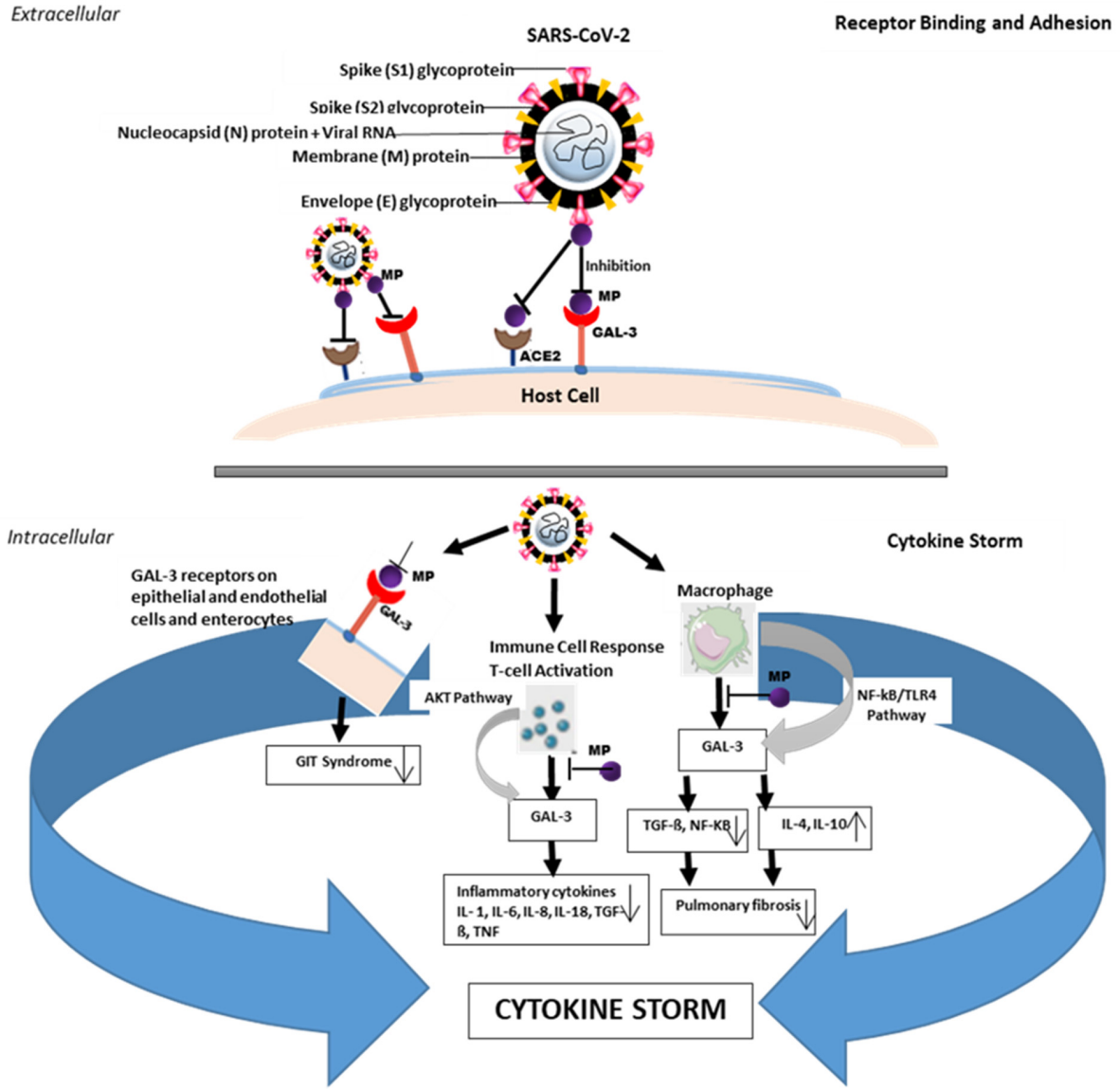

Figure 3. Effect of modified pectin (MP) associated with galectin-3 (GAL-3) during severe SARS-CoV-2 infection. Receptor binding and adhesion: MP binds to the GAL-3 receptor to inhibit SARS-CoV-2 attachment and adhesion to the host cell surface. During severe SARS-CoV-2 infection, the activation of T cell immune response through AKT and NF-KB/TLR4 pathways induces the release of GAL-3 and increase inflammatory cytokines such as interleukins (IL-1, IL-6, IL-8, IL-18) in circulating macrophages and monocytes, resulting in a feedback loop that may contribute to the development of the cytokine storm. This elevates the levels of TGF-ß and NF-KB, leading to pulmonary fibrosis. MP binds GAL-3 at the initiation and/or activation of the immune response stage, epithelial membranes, endothelial, and enterocytes to inhibit cytokine feedback and also prevents gastrointestinal tract (GIT) syndrome. GAL-3 inhibition by MP prevents or reduces the release and/or levels of the inflammatory cytokines which contributes to preventing pulmonary fibrosis.

4.2. Modified Pectin and Galectin-3 Response to the Cytokine Storm Effect

According to studies, cytokine inhibition is one of the best therapeutic methods for COVID-19 depending on the stage of infection in the patient. It was further suggested that therapies aimed at reducing hyper inflammation and lung damage should be administered at the severe (pneumonia) stage [94,95]. Based on the human immune response against SARS-CoV-2 infection, changes in T lymphocytes subsets (lymphopenia) accompanied by the cytokine storm syndrome contribute to the progression of the disease and poor prognosis. During this period, lymphopenia is commonly observed with an increase in IL-6 and other inflammatory cytokines (pneumonia phase). Acute lung injury, high initial viral titers, and macrophage/neutrophil build-up in the lungs are all symptoms of severe SARS-CoV-2 infection, as well as a high level of pro-inflammatory cytokines such as the interleukins IL-1, -6, -8, -18 and monocyte chemotactic protein-3 in the blood [96].

Patients with severe COVID-19 have significantly higher levels of GAL-3, tumor necrosis factor (TNF), IL-1, and IL-6 than those with moderate disease [97,98]. Furthermore, GAL-3 regulates and possibly causes a dysregulated pattern of these pro-inflammatory cytokine expressions during infection through the AKT signaling pathways [53]. Consequently, the inhibition of GAL-3 greatly reduces the level of these cytokines, which suggests that it could be useful in lowering the inflammatory consequences of COVID-19 [97,99]. Secreted GAL-3 produced by macrophages during injury promotes the upregulation and elevated level of TGF-ß receptors, leading to pulmonary fibrosis (fibroblast activation), observed to be one of the major complications of SARS-CoV-2 infection [100,101]. The inhibition of GAL-3 has been shown to reduce adenovirus-induced lung fibrosis [102]. Thus, it is worthwhile to investigate MP as a potential treatment through its GAL-3 inhibition for pulmonary fibrotic-related diseases including severe cases in COVID-19.

The unique anti-inflammatory bioactivity of MP in humans being connected to the sugar β-galactose-inhibiting cell signaling protein, GAL-3, is responsible for tumor cell proliferation and metastasis [29]. This stimulates or modulates intestinal homeostasis and also plays a role in immunological modulation [103]. Although GAL-3 inhibits the inflammatory response of the intestinal system via the GALT, which modulates macrophage signaling recruitment [104], it can as well bind to cell surface receptors to create a clustering effect [57]. Consequently, a higher concentration of GAL-3 at this binding site activates T cells with a possible evasion of the immune surveillance system. The initiation of MP binding to GAL-3 in addition to the possible Neu5Ac interaction linked to the ganglioside domain on the epithelial cell surface may inhibit the extracellular matrix interactions.

The RNA of SARS-CoV-2 has been presented in the gastrointestinal tracts and stool samples of COVID-19 patients [105–107]. This implies that SARS-CoV-2 can infiltrate enterocytes and serve as a virus reservoir [107]. It is noteworthy that a rising number of SARS-CoV-2 patients have reported the possible indication of gastrointestinal symptoms including diarrhea (2.0–10.1%), nausea and vomiting (1.0–3.6%), and abdominal pain in COVID-19 patients [108,109]. Most of these patients infected with SARS-CoV-2 have mild gastrointestinal symptoms and a good prognosis after the infection indicates that the immune function is a strong defense against this virus. The SARS-CoV-2 binds to the ACE-2 receptors which are highly expressed on alveolar cells of the lungs, upper esophagus, and stratified epithelial cells, as well as other cells such as absorptive enterocytes from the ileum and colon, myocardial cells, and kidney proximal tubule cells [110]. This explains why, in some cases, COVID-19 patients not only experience respiratory problems but also disorders of the heart, kidneys, and digestive tract [111].

In our previous studies, we reported the initiation of MCP and adhesion of probiotic bacteria to specific receptors on the epithelial cell surface of the colon to inhibit the extracellular matrix interactions of GAL-3 [17]. We further showed that MCP alginate supplemented with a probiotic, *Lactobacillus acidophilus ATCC 4356*, significantly increases fecal lactobacilli and improves the integrity of intestinal microbiota [25,112]. As a result, the synthesized extracellular macromolecules also contribute to modulating the immune response [113,114]. During the adhesion of microbiomes at the site, MCP modifies their

functionality and physiological properties in the gut which causes the reduction and prevention of GIT syndromes. The gut microbiome has a significant influence on systemic and distant immune responses at the mucosal sites such as the lungs [115,116]. Certain probiotic strains help prevent bacterial and viral infections such as gastroenteritis, sepsis, and respiratory tract infections. The administration of certain strains of Bifidobacterium and Lactobacilli aided the clearance of the influenza virus from the respiratory tract with minimal inflammatory damage to the lung tissue [116]. This is influenced by the ability of the probiotic strains to modulate a systematic balance between pro-inflammatory and anti-inflammatory immunoregulatory cytokines. In a randomized control trial study conducted on upper respiratory tract-infected middle-aged patients, a probiotic with *Lactobacillus plantarum DR7* reduces plasma IFN-γ and TNF-α pro-inflammatory cytokines, as well as stimulates the increases in IL-4 and IL-10 anti-inflammatory cytokines [117].

Further evidence has shown the influence of MCP on immunomodulatory activities for the regulation of inflammatory cytokines. MCP upregulates the level of IL-4, an anti-inflammatory cytokine in the spleen of treated BALB/c mice [24]. The stimulation of this cytokine might be of particular relevance to COVID-19 patients in preventing complications of acute respiratory distress syndrome. MCP inhibits MAP kinase activation, increases the expression level of downstream target Bim (a pro-apoptotic protein), and induces the cleavage of Caspase-3 in PC3 and Caspase-1.1 [118]. Its ability modulates the immune response, T helper cells, pro-inflammatory cytokines (IL-17, IFN-γ, and TNF-α levels), and anti-inflammatory cytokines (IL-4 and IL-10) [24]. MCP induces the Th1 T-helper immune response in murine influenza vaccination and allergic asthma models [71,72]. This selectively stimulates T cytotoxic and NK cell responses, as attributed to the presence of a low degree of methyl esterification in MCP [27]. Pectin polysaccharides from natural plants cell walls may modulate immunity against SARS-CoV-2 through the release of cytokines such as TNF-α and IL-6, anti-inflammatory activity, and the increased phagocytosis of macrophages. Additionally, they may achieve this through the production of nitrous oxide, reactive oxygen species formation, and activation of signaling pathways including Toll-like 4, type A hijacker receptor, NF-κB, and glucan receptor [119,120].

5. Conclusions and Future Directions

With the understanding that there is a global health emergency to curb the high mortality and morbidity caused by COVID-19, the repositioning of drugs and alternative therapies may be a new option for the treatment of SARS-CoV-2 infection. Evidence has shown emerging MP as one of the most promising and naturally occurring anti-GAL-3 substances. A novel approach using a GAL-3 inhibitor highlights a potential therapeutic target against SARS-CoV-2 infection. MP has shown the potential of the GAL-3 inhibitor in disease progression and new benefits of this bioactive compound will continuously be unraveled. The bioactive effect of MP against GAL-3 is a promising treatment target against SARS-CoV-2 infection. However, it is important to mention that this would be a new area of research that will help understand that MPs are likely to interfere with the initial attachment of viral particles to the surface epithelium of the respiratory tract.

Despite evidence from numerous studies that MP inhibits various steps in cell–cell interactions, fibrotic, renal injury, and cardiovascular diseases by interacting with GAL-3, the details of the underlying mechanisms are still largely unknown. Although pectin-derived galactan binds specifically to GAL-3, the precise structural characteristics responsible for the optimal binding to GAL-3 causing pro-inflammatory mechanisms associated with immune modulation remain unknown. As variants of SARS-CoV-2 are evolving, the virus may switch in binding sites to new receptors, from the firstly known ACE-2 to newly discovered ones as in the case of GAL-3. This implies that virus inhibitors at the attachment and entry stage are key to mitigating SARS-CoV-2 replication in the host cell; hence, the quick development of these inhibitors should suffice. Despite a few uncertainties, there is a good level of tolerance with regard to the safety and non-toxic acceptance of MP oral consumption, with evidence that dietary and citrus pectin polysaccharide RGI fragments

have a positive effect and good prognosis on some viral infections in vitro. Its potential to benefit COVID-19 patients by regulating the immune response system is a possibility yet to be determined; hence, both in vitro and in vivo studies should be explored.

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