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REVIEW ARTICLE

Pentosan Polysulfate, An Anti-Viral Heparinoid, Prevents Severe Acute Respiratory Syndrome Corona Virus-2 Infection and Treats Symptoms of Long Coronavirus Disease

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ABSTRACT

This study highlights the roles of pentosan polysulfate as a decoy anti-viral prophylactic that prevents severe acute respiratory syndrome coronavirus-2 infection. PPS also has multifunctional cell and tissue protective properties relevant to the treatment of the symptoms produced by long COVID disease. PPS has heparan sulfate (HS)-like properties, a key functional component of the lung glycocalyx. The glycocalyx is also rich in hyaluronan which has important cell shielding and cell regulatory properties. A healthy glycocalyx prevents access of viral particles to cell surface heparan sulfate-proteoglycans (syndecan, glypican) which act as viral receptors. Pentosan polysulfate promotes hyaluronan synthesis by many cell types, ensuring cells are surrounded by a healthy protective glycocalyx. Hyaluronan, however, has a relatively short biological half-life and is susceptible to degradation by hyaluronidases that are upregulated by inflammatory cytokines in acute respiratory distress syndrome in COVID-19 disease. This results in the glycocalyx becoming degraded and endothelial cells dysfunctional in COVID-19 disease. Prevention of viral interaction with the host cell surface intercepted by pentosan polysulfate, a decoy viral binding prophylactic agent, blocks viral interaction with cell-surface heparan sulfate, preventing viral interactions with other cell surface receptors such as neuropilin-1 and angiotensin-converting enzyme 2. Co-operation between heparan sulfate, neuropilin-1 and angiotensin-converting enzyme 2 facilitates the infection of host cells with severe acute respiratory syndrome coronavirus 2, thus if the initial interaction with heparan sulfate is blocked this prevents the subsequent viral interactive stages. Pentosan polysulfate also has multifunctional cell and tissue protective properties, broad anti-oxidant and anti-inflammatory properties and inhibits cytokine production in acute respiratory disease syndrome. Pentosan polysulfate inhibits p38 mitogen-activated protein kinase and nuclear factor-κB activation, reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β and interleukin-6. Furthermore, pentosan polysulfate is processed by enzymes of the gut microbiome into prebiotic xylo-oligosaccharides that preserve gut health and combat gut dysbiosis seen in COVID-19 disease. Studies are thus warranted to fully assess pentosan polysulfate as an anti-severe acute respiratory syndrome coronavirus-2 prophylactic agent and its multifunctional cell and tissue protective properties. Furthermore, from a practical and economic point of view, treatment with pentosan polysulfate would offer substantial cost-benefit advantages over conventional vaccine and antibiotic treatments and could also be used in an adjunctive capacity with existing therapies, offering flexibility in its use.

Keywords: Pentosan polysulfate; SP54; Neuropilin-1; angiotensin-converting enzyme-2; Heparan sulfate; SARS-CoV-2; HIV; Herpes simplex; Dengue virus; Papillomavirus.

1. Introduction

The aim of this study was to highlight the roles of pentosan polysulfate (PPS), a semisynthetic heparinoid, as a decoy anti-viral prophylactic in the prevention of SARS-CoV-2 infection of host cells. The multifunctional cell and tissue protective properties of PPS are also described illustrating how PPS may be employed to treat the multi-parameter symptomatology that characterises long COVID disease (Figure 1).

1.1 COVID-19 IS A PANDEMIC VIRAL DISORDER OF GLOBAL IMPACT

COVID-19 is a pandemic disease that emerged in Wuhan, China in late 2019 with the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2), a single strand RNA virus that is 96.2% identical in genomic sequence to the bat CoV RaTG13 virus. SARS CoV-2 is highly transmissible through aerosols, droplets, fomite affected surfaces or direct skin contact[1]. Historically, SARS-CoV-2 has demonstrated an unprecedented infectious global profile and has undergone rapid evolutionary mutational changes as part of its natural life cycle into several variants which avoid immune detection. Some of these SARS-CoV-2 variants bind more efficiently and with greater rapidity to respiratory epithelial cells, rendering these viral forms significantly more infectious[2,3]. The Omicron variant is currently a dominant global variant, 99% of all variants circulating in the U.S. are mutations of Omicron, most commonly EG.5 (24% of all SARS CoV-2 strains) and FL 1.5.1 (14%) (https://covid.cdc.gov/covid-data-tracker/#variant-proportions)[4]. A distinctive feature of these Omicron variants is a change in their infective profiles displaying more effective infection of the nose and throat rather than the original Wuhan and Delta variants which primarily infected the lungs[5]. Respiratory distress is a prominent feature of SARS CoV-2 infections, but other organ systems can also be affected including the brain, liver, heart, and kidney[6-8]. Symptoms of SARS CoV-2 infection include fever, anosmia, ageusia, dry cough, fatigue, breathlessness, hair-loss and so-called brain-fogging with a decline in problem solving capability, cognition, ability to concentrate, negative neurological impact and an increase in long-term anxiety[9,10]. These symptoms can be mild, moderate or severe and a fatality rate of 1 in 100 is reported depending on the co-morbidities that patients display; these can significantly impact the severity of COVID-19. A global systematic review of 76 studies that examined a total of 17,860,001 patients across 14 countries showed that age >75 years, male sex, severe obesity, lymphopenia, and cancer increased the impact of SARS CoV-2 infection on health and well-being[11].

Viral recombination is a normal part of the viral life cycle but results in an extremely wide spread in epitope presentations and these continually undergo changes in structure. This makes it problematic to raise vaccines or antibodies to current infectious viral strains and these require continual updating putting enormous strain on viral treatment resources. In the present study we have shown how PPS can inhibit all viral classes by blocking the interaction of virion particles with cell surface HS and we propose that this has considerable merit as a preventative approach to treatment of potential infections by SARS CoV-2 but is also applicable to other viral classes. Furthermore, PPS is a pleotropic cell and tissue protective agent[12,13] as we have outlined in this review and is suitable for the treatment of many facets of the varied symptomatology encountered in COVID-19 infected tissues throughout the human body. This is a further strength of PPS as a therapeutic agent for viral conditions.

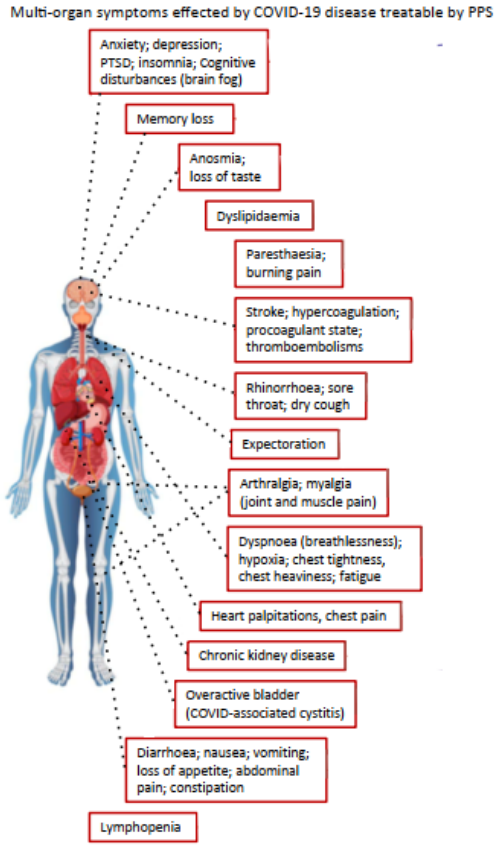

Figure 1. The multifunctional properties of pentosan polysulfate. Multi-organ systems affected by COVID-19 treatable with pentosan polysulfate.

1.2 PENTOSAN POLYSULFATE, A PROPHYALACTIC ANTI-VIRAL PLEOTROPIC CELL AND TISSUE PROTECTIVE AGENT

Pentosan polysulfate is a semi-synthetic sulfated xylan biomimetic heparinoid that has been categorized as a disease modifying anti-arthritic drug (DMOAD). It has a smaller molecular weight than heparan sulfate (HS) or heparin but has a higher charge density and has many properties that mimic HS found on cell surfaces and in extracellular matrix heparan sulfate proteoglycans (HSPGs) (Figure 2). This provides PPS with a multifunctional cell and tissue protective profile that is discussed more fully later in this review[12,13].

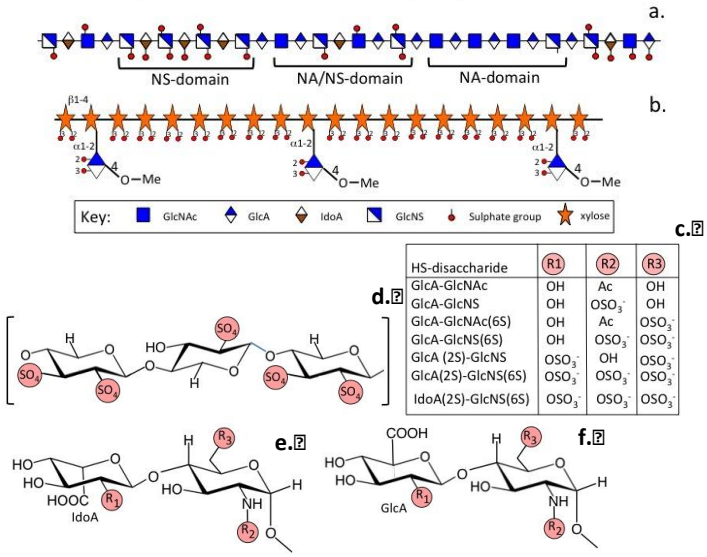

Figure 2. Sulfation patterns of heparan sulfate and pentosan polysulfate. Structural organization of a putative HS chain (a) and pentosan polysulfate (PPS) with its 4-*O*-methyl-glucuronic acid monosaccharide side chain α1-2 linked to every tenth xylose residue (b), disaccharides HS is assembled from (c), saccharide structure of PPS (d), and two examples of HS disaccharides (e, f). Heparan sulfate contains three substitution sites in the D-glucuronic acid 1-4 linked N-acetyl glucosamine repeat disaccharide, marked R1, R2, R3 on HS can be occupied by combinations of hydroxyl, acetyl, and sulfate groups.

2. The impact of Coronaviruses on human health and well-being

Coronaviruses (CoVs) are enveloped viruses of the *Nidovirales* order, *Coronaviridae* family[14]. Bats, dogs, cats and humans can all be infected with these viruses[14]. Seven species of CoVs have so far been identified, four of these produce relatively mild symptoms of the common cold[15] but severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and SARS-CoV-2 have a higher impact and can be life-threatening diseases[16]. The SARS-CoV pandemic of 2002–2003 resulted in 774 deaths and 8098 cases of infection distributed over 26 countries [17]. Middle East respiratory syndrome coronavirus (MERS-CoV) emerged ten years later as the sixth coronavirus and resulted in infections across 27 countries in the Middle East, Asia, North Africa and Europe which resulted in 2040 infections and 712 deaths. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh coronavirus (CoV) which has recently emerged resulting in a global health pandemic. Severe acute respiratory syndrome coronavirus 2 is closely related to Severe acute respiratory syndrome coronavirus (SARS-CoV) but has a far more infectious profile and thus has a significantly greater impact on global human health. As of 19th Sept 2024 704 million confirmed cases of SARS-CoV-2 infection in 223 countries and territories, 7 million deaths and 675 million cases of recovery from infection have been reported by Worldometer [https://www.worldometers.info/coronavirus/ accessed on 19-9-2024][18]

2.1 PREVENTION OF VIRAL INFECTION OF HOST CELLS BY PENTOSAN POLYSULFATE

To infect human cells, viruses must pass a dense layer of carbohydrate (glycocalyx) attached to the cell surface. Several viruses, including Herpes, HIV and other coronaviruses, bind to HS during this infection phase. HS and ACE2 are necessary for SARS-CoV-2 infection and Nrp-1 has additional roles to play as a co-receptor in this infective process[19-24]. Molecular modeling, atomic force measurements and X-ray crystallography have shown that SARS-CoV-2 HS binds the Spike S1 receptor binding domain (RBD). Infection can be prevented by enzymatic removal of HS from the cell surface, demonstrating the importance of HS in the initial viral attachment phase. Exogenous heparin, LMW heparin and PPS block coronavirus infections in lab-grown cells by binding to the isolated SARS-CoV-2 viral particles dispersed in biological fluids and this prevents them from entering and infecting host cells. A GAG-binding site in the N-terminal domain (NTD) of Spike protein in residues 241–246[25] binds HS. Prophylactic administration of HS oligosaccharides also bind to this site and prevent productive associations between Spike protein and ACE2 showing how PPS blocks SARS CoV-2 infection[25]. Molecular dynamic simulations of the Spike trimer interaction with HS dodecasaccharides (and PPS) indicate that when attached to this HS binding site these GAG components span the RRAR (CendR) furin cleavage site interfering with Spike protein interactions with cell surface receptors essential for SARS-CoV-2 infection[26]. Use of heparin in-vitro can block this infective process in epithelial cells[27]. Polysulfates block SARS-CoV-2 uptake into cells showing electrostatic interactions are important in this process[28] explaining why PPS inhibits SARS-CoV-2 infection of host cells. Biochemical, biophysical, and genetic studies show HS induces an open conformation in S protein required for binding to ACE2[29], a high degree of coordination between host cell HS and S protein asparagine-linked glycans enables ACE2 binding and host cell infection[29]. Prophylactic use of PPS disrupts this interaction with cell surface HS and prevents host cell infection. SARS-CoV-2 Spike protein is proteolytically processed by transmembrane protease, serine 2 (TMPRSS2) and furin produced by host cells to prime the S1 domain for binding to ACE 2[21,24,30-35]. Transmembrane protease, serine 2 (TMPRSS2), a respiratory and gastrointestinal membrane anchored protease, plays a crucial role in the activation of SARS-CoV-2 spike protein. Endogenous serine protease inhibitory proteins in

tissues may have a protective role to play in the prevention of this protease mediated remodeling of SARS CoV-2 Spike protein required to facilitate its interaction with ACE2. Small drug inhibitors (Camostat, Nafamostat, and Bromhexine) have been re-purposed from anti-tumor applications to inhibit TMPRSS2 mediated SARS-CoV-2 S protein priming[36]. Entry of SARS-CoV-2 into host cells via the receptor binding domain (RBD) of S protein after the S1 and S2 subunits dissociate from each other by the action of TMPRSS2 allow conformational rearrangement and prime it for interaction with the host cell[37-39]. Furin, a type 1 membrane protease, also cleaves between S1 and S2 in SARS-CoV-2 S protein to facilitate binding to ACE2 and viral membrane fusion with the host cell plasma membrane, effecting internalisation of SARS-CoV-2[36]. Transmembrane protease, serine 2 is part of a mucous secretory network highly upregulated in inflammation by interleukin-13. Interleukin-13 (IL13) and viral infection also mediate effects on ACE2 expression in the airway epithelium with interferon mediated responses to respiratory viruses highly upregulating ACE2 expression[40]. Moreover, some viruses synthesize their own TMPRSS2[41] and this also has roles in viral activation[42,43]. While ACE2 is considered to be the primary host receptor in SARS-CoV-2 and SARS-CoV infections these related viruses have vastly different infection rates, suggesting the involvement of factors in addition to ACE2 that promote SARS-CoV-2 infection. Severe acute respiratory syndrome coronavirus-1 (SARS CoV-1) and SARS CoV-2 both bind to the ACE-2 receptor on host cells, however the latter is considerably more infectious, utilising multiple factors to achieve this higher infection rate (Table 1). Severe acute respiratory syndrome coronavirus-2 is particularly good at infecting cells, in the upper respiratory tract, and deeper in the lungs[44]. Neuropilin-1 (NRP-1) is another host cell co-receptor that SARS-CoV-2 also uses for cellular attachment[35]. Furin generates a C-end rule motif (CendR) in the SARS-CoV-2 spike protein and this interacts with a CendR receptor in Nrp-1 promoting the internalisation of CoV-2 viral particles by endocytosis[37-39,45] (Table I). The greater infective efficiency of the Omicron CoV-2 variant suggests it utilises these additional cell surface motifs to infect host cells. Cell surface HS is used by many viruses as a docking module in host cell infection (Table 2). Heparan sulfate proteoglycans (HSPGs) are endocytic receptors that viruses use for cell entry[46-48]. NRP-1 is also an endocytic receptor[49]. Herpes simplex, hepatitis, papilloma, flaviviruses and respiratory syncytial virus all utilize multiple cell surface receptors as part of their internalization strategy to infect host cells[50-53].Viruses do not bind to the non-sulfated HA component of the glycocalyx, and this acts as a barrier to viral penetration[54-58]. It has been proposed that COVID-19 is an endothelial disease[59] brought on by the cytokine storm of ARDS that produces destructive changes in the endothelial cell glycocalyx[60,61]. Significantly, binding of viral particles to PPS in biological fluids prevents them from interacting with the HS chains of syndecan (SDC) or glypican (GPC) to gain access to the Nrp-1 or ACE2 receptors on host cells. As shown in Table II, many human and animal viruses utilize cell surface HS as a docking module to facilitate infection of host cells.

Table I ACE2, cell surface HSPGs and Nrp-1 interact with SARS CoV-2 Spike protein facilitating viral entry to host cells.

Receptor	Physiological properties	Evidence for roles as a SARS CoV-2 receptor	Ref
HS	Cell-ECM signaling Cell adhesion Cell growth factor and cytokine interactions	Direct interaction of HS with S glycoprotein in ECM, GAG microarray, co-precipitation experiments. Enzymatic removal of HS or HS knockdown results in reduced SARS CoV-2 infection levels.	62-64
ACE2	Regulation of blood pressure	Cryo EM images/ X ray crystallography demonstrate ACE2 bound to S RBD. ACE2 over-expression in cells results in enhanced CoV-2 infection. Human ACE2 over-expression in mice results in enhanced CoV-2 infection. Inhibition of SARS CoV-2 infection is evident in ACE2 knockout cells	65-70
Nrp-1	Regulation of neural network development and angiogenesis in tissue development	Demonstration of binding of Nrp-1 to Furin generated C-end rule (CendR) motif in Spike protein. Overexpression of Nrp-1 in cells results in enhanced SARS CoV-2 infection. Nrp-1 KO results in a reduced SARS CoV-2 infection	37,39,71,72

Viruses utilize cell surface syndecan and glypican HS-proteoglycan as docking structures as part of the infective process of prospective host (Table II). These proteoglycans have a ubiquitous cellular distribution.

Table II Cell surface HS Proteoglycans that act as viral receptors

HSPG receptor	Viruses	Ref
Syndecan-1	Hepatitis C virus	73
Syndecan-2	Hepatitis B virus, Dengue virus strain DEN2 16681	74,75
Syndecan-3	HIV-1	76
Syndecan-4	Adeno-Associated Virus 9, Porcine reproductive and respiratory syndrome virus	77,78
Glypican-5	Hepatitis B and D viruses	79
Syndecans and glypicans	Porcine hemagglutinating encephalomyelitis virus, Papilloma viruses.	80-82
Syndecan	SARS-CoV-2	83
Syndecans	HIV-1	84-86

2.2 CELL SURFACE GLYCOSAMINOGLYCANS AND VIRAL INFECTION OF HOST CELLS.

2.2.1 Anionic anti-viral compounds

Anionic polysulfate GAGs have inhibitory effects on host cell infection with multiple viruses including SARS-CoV-2[87] and AIDS; PPS has been proposed as a drug for the prevention of infection with AIDS and SARS-CoV-2[88]. It has been proposed that these compounds should be administered as aerosols inhaled into lung tissues to increase their potency[89]. Administration of sulfated hyaluronan derivatives delivered by aerosol prolong the survival of K18 ACE2 mice infected with a lethal dose of SARS-CoV-2[90]. PPS (SP 54), a low molecular weight sulfated polysaccharide is one of the most

active *in vitro* inhibitors of retrovirus-specific reverse transcriptase[90] and is a selective anti-HIV and anti-SARS-CoV-2 agent *in vitro*[91,92]. Polysulfated polyxylan (HOE/BAY 946) completely inhibited syncytium formation induced by HIV infection of T-lymphocytes as well as viral replication and inhibited HIV reverse transcriptase. Furthermore, a drastic decrease in the release of viral particles in HIV infected U937 pro-monocytic cells was also elicited by HOE/BAY 946[93], this increases membrane hydrophobicity of human lymphocytes and specifically suppresses HIV-protein synthesis[94], and also inhibits HIV replication in human monocytes/macrophages[95]. The pharmaco-kinetics of intravenous HOE/BAY 946 has been examined in HIV patients[96]. Sulfated polysaccharides have also been shown to inhibit lymphocyte-to-epithelial transmission by HIV-1[97]. Chemically oversulfated galactosaminoglycan sulfates inhibit the enveloped viruses HIV-1, HSV-1 and HCMV[98]. Chondroitin polysulfate displays anti-HIV-1 activity *in vitro*[99]. A synthetic polysulfonated naphthalene polymer (PRO 2000) binds to HIV-1 gp120 glycoprotein and interferes with viral binding to $CD4^+$ T cells but also interacts with CD4 and CXCR4, a G-protein coupled chemokine receptor that can induce expression of selective chemokines with potential anti-viral activity[100,101], it also inhibits infection of host cells with HIV and SARS-CoV-2[100]. Pentosan polysulfate also ameliorates the symptoms of human T lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) which is characterized by lower extremity motor dysfunction[102].

2.3 SEVERE ACUTE RESPIRATORY SYNDROME VIRUS-2 VARIANTS

A highly virulent Delta SARS-CoV-2 variant (B 1.617.2) emerged in India in 2020 becoming the dominant global strain. On 24 November 2021, a further highly infectious SARS-CoV-2 variant (B.1.1.529/BA.1) was reported, this has also had a significant global impact displacing the delta variant as the dominant SARS Cov-2 strain[103]. The World Health Organization Technical Advisory Group on SARS-CoV-2 Viral Evolution designated this emergent CoV variant as B.1.1.529, the fifth Coronavirus variant and named it Omicron[104]. Several Omicron variants have emerged since then with the BA-4 and BA-5 variants becoming firmly established. Vaccines raised to the original Wuhan strain of SARS CoV-2 offer incomplete coverage of these variants and multiple COVID-19 re-infections two or three times have been reported. This emphasizes the need to develop alternative preventative strategies to prevent COVID-19 infections rather than vaccines or antibodies that treat the symptoms. It is not known to what extent all of the symptoms of long COVID disease are treatable or whether full recovery is possible, however besides acting as a viral anti-infective agent, PPS also treats COVID-19 disease symptomatology[105].

The BA-4 and BA-5 Omicron variants are the most infectious forms of SARS-CoV-2 and are of major concern; their greater infectivity is related to 32 mutations in their S protein compared to the original Wuhan CoV-2 strain, 15 of these mutations specifically affect the CoV-2 RBD of S protein[106] (Figure 2). The high infective rate of the Omicron variants suggest these utilise a more effective range of cell surface binding motifs in addition to the ACE2 receptor and Nrp-1. A further Omicron sub-variant, a so-called second generation sub-variant, BA.2.75 has emerged in India, unofficially named Centaurus[107-110] and has been detected in Germany, The Netherlands, Japan, UK, US, Australia and New Zealand.

Two mutations in the BA.2.75 variant (G446S and R493Q) allow it to escape immune detection and to bind more strongly to the ACE2 receptor, it is predicted that this increases its infectivity. Prior COVID-19 immunizations may limit the infectiousness of this new sub-variant however it is not known how effective pre-existing antibody preparations will be against this new Omicron variant.

2.4 MUTATIONS IN S1 SPIKE GLYCOPROTEIN IN SEVERE ACUTE RESPIRATORY SYNDROME VIRUS -2 VARIANTS.

Examination of amino acid sequences in the S1 glycoprotein of SARS-CoV-2 variants demonstrates

significant substitutions of native SARS-CoV-2 sequence which partly explains the waning effectiveness of vaccines and therapeutic antibodies in the treatment of COVID-19 disease and the evasion of immune detection of these variant forms of SARS-CoV-2. Of the viral strains of SARS-CoV-2 so far identified, the Omicron strain has the highest number of S1 RBD substitutions (Figure 3).

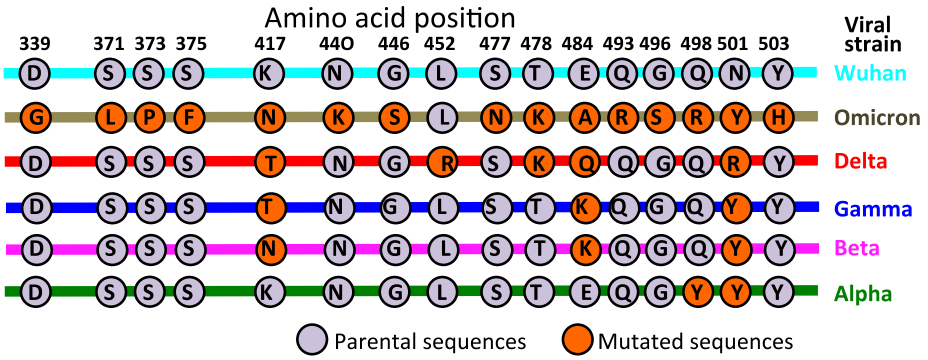

Figure 3. Point mutations in the receptor binding domain of spike protein in coronavirus variants. Amino acid sequences in the receptor binding domain of the SARS CoV-2 Spike protein in the original Wuhan strain and the mutations in its variant forms. Figure from[111].

Table III. A.Viruses that gain access to cells through interaction with cell surface HS and B. antiviral sulfated polysaccharides that block such viral interactions

Virus	Docking module	Ref
Viruses that utilize HS or related GAGs for infection of host cells **A**		
Adeno-associated virus 2	HS	112-114
Adeno associated virus serotype 3B		
Akabane and Schmallenberg Viruses.	HS	115
Chikungunya Virus Strains	Sulfated GAGs	116
Coxsackievirus B3 variant , Coxsackievirus A16, B4	N- and 6-O-sulfated HS	117-119
Dengue Viruses	HS	120-122
Duck Tembus virus	HS	123
Ebola virus	HS	124
Echovirus 5	HS	125
Enterovirus A71	HS	118,126,127
Filovirus	HS	128
Henipavirus	HS	129
Hepatitis B virus	HSPG	130
Hepatitis delta virus	HSPG	131
Hepatitis C	HS, HS-proteoglycans	132,133
Human herpes virus 8	HS	134
Herpes simplex virus type 1	HS	135
Human meta pneumo virus	HS	136
Herpes simplex virus type 1	Syndecan-1	137,138
HIV	HS	139-141
Human, monkey, rodent Foamy virus	HS	142,143
Human papillomavirus 16 virus	HS	144
Human respiratory syncytial virus	HS	145
Human meta pneumovirus	HS	146
Human Parechovirus	HS	117
Japanese encephalitis virus	HS	147

Virus	Docking module	Ref
Merkel cell polyomavirus	HS, sialylated glycans	148
Murine leukemia virus	HS	149
Murine herpes virus 68	HS	150
Moloney Murine leukemia virus	HS	140
Porcine epidemic diarrhea virus	HS	151
Pseudorabies virus	HS	152
Rabies virus	HS	153
Respiratory syncytial virus G	Heparin	154,155
SARS CoV-2	HS, HSPGs	21,24,28,33,64,156
Swine vesicular disease virus	HS	157
Sindbis virus	HS	158
Swine fever virus	HS	159
Vaccinia virus	HS	160
Zika virus	HS	161
Inhibition of viral attachment to host cells using sulfated polysaccharides **B**		
Virus	**Blocking polysaccharide**	**Ref**
African swine fever virus	PPS and Sulfated polysaccharides	162
Herpes simplex, Cytomegalovirus, Vesicular stomatis virus, Sindbis virus HIV	PPS and Sulfated polysaccharides	163,164
T cell leukemis virus type-1	PPS	165
Chikungunya virus	PPS	166
Ross river virus	PPS	166,167
SARS-CoV-2	PPS, Polysulfates, heparin, enoxaparin	24,28,64,156,168

3. Anti-inflammatory and tissue protective properties of pentosan polysulfate

Pentosan polysulfate has anti-inflammatory properties in knee OA, reducing joint swelling and pain[169] and has reno-protective effects in kidney injury, nephrectomy and diabetic nephropathy[170]. Pentosan polysulfate is also effective against arthritogenic alphaviruses such as Ross River virus (RRV) and chikungunya virus (CHIKV) which cause cartilage destruction, crippling pain and joint inflammation[166]. Pentosan polysulfate increases production of the anti-inflammatory cytokine IL-10 and reduces production of proinflammatory cytokines, modulates growth factor signaling and lymphocyte activation and reduces inflammatory infiltrates in joint fluids in chikungunya infected mice[171]. Pentosan polysulfate has systemic and local anti-inflammatory activity in post-acute pulmonary inflammation in an influenza virus A induced pulmonary inflammation model[172]. The beneficial effects of PPS are due to a combination of its anti-viral and anti-inflammatory properties[173]. Pentosan polysulfate also supports tissue repair processes in the degenerate IVD[13], representing part of its pleotropic tissue and cell protective properties[105].

3.1 THE HYPERCOAGULATIVE STATE OF COVID-19 IMPAIRS PLATELET FUNCTION AND TISSUE REPAIR RESPONSES, WEAKENING NORMAL LUNG FUNCTION

Corona virus-2 infected patients that develop a severe pro-inflammatory state are also frequently associated with a procoagulant endothelial phenotype[174] that produces an elevation in fibrinogen and D-dimer/fibrin(ogen) degradation products associated with systemic hypercoagulability[175]. Fibrinogen D-dimer levels positively correlate with mortality rates in COVID-19 patients and lead to arterial thrombotic events including stroke, ischemia and microvascular thrombotic events in the pulmonary vascular beds[176]. Heparan sulfate is a critical regulator of the

immunoreceptor tyrosine-based inhibition motif (ITIM) receptor G6b-B-R that regulates platelet production and activation[177]. Binding of G6b-B-R to the HS side chains of perlecan and multivalent heparin inhibits platelet and megakaryocyte function by inducing downstream signaling via the protein tyrosine phosphatases Shp1 and Shp2. SARS-CoV-2 initiates programmed cell death in platelets[178] thus G6b-B-R has important roles to play maintaining platelet levels in wound healing responses[179]. Perlecans interaction with G6b and G6b-R regulates fibrotic changes in tissues produced by excessive levels of platelet activation [180]. Perlecan HS also regulates cell adhesion, proliferation and growth factor signaling in tissue repair responses in tissue homeostasis and optimal tissue function, features mimicked by PPS[180,181].

3.2 A DYNAMIC BALANCE BETWEEN THE FIBRINOLYTIC AND COAGULATION SYSTEMS IS CRITICAL TO NORMAL LUNG FUNCTION AND HOMEOSTASIS.

The fibrinolytic and coagulation system are inter-connected however in COVID-19 can be overwhelmed by a hypercoagulative state that prevails. Plasmin is a major clot dissolving fibrinolytic enzyme produced with elevated levels of tissue plasminogen activator (tPA) which in turn is regulated by plasminogen activator inhibitors-1 and -2 (PAI-1, PAI-2). Autopsies of COVID-19 fatalities shows thrombosis, micro-angiopathy, haemorrage and alveolar damage. The dyslipidemia displayed by COVID-19 patients results in abnormally high levels of low density lipoproteins (LDLs) and low levels of high density lipoproteins (HDLs) in serum.

3.3 LUNG HEPARAN SULFATE PROTEOGLYCANS AND THEIR CELL REGULATORY PROPERTIES

Cell surface HSPGs in the lung are growth factor coreceptors binding these through HS and core protein interactions[182]. Instructive interactions with growth factors, morphogens, chemokines and ECM components, regulate cell adhesion, proliferation, migration, and differentiation, regulating pathophysiological processes in tissue development and repair, inflammation, infection, and tumor development[182,183]. HS-proteoglycans in the lung have instructive roles critical to regulation of tissue development, organ structure, and the control of resident cell populations[184-188]. Pikachurin, agrin, perlecan are HSPG components of the lung interactome with essential roles in lung development, homeostasis and function and roles in tissue fibrosis in lung disease[179,189]. Fragmentation of lung ECM components due to endogenous protease activity or by proteases produced by an influx of inflammatory cells in lung disease leads to the release of bioactive protein fragments (matricryptins, matrikines) which can regulate cell metabolism. Matrikines have been identified with tissue repair properties[190,191]. While ACE2 is the primary receptor for SARS CoV-2 entry other cell surface and ECM proteins may also bind to the SARS CoV-2 spike RBD such as perlecan LG3 and may potentially enhance RBD-ACE2 interactions representing a potential therapeutic target[192]. Proteoglycans embedded in the vascular endothelial glycocalyx, regulate the activity of cytokines and inflammatory responses but are proteolytically cleaved in inflammatory diseases and modulate pathological inflammatory responses. Soluble forms of SDC-1, SDC-3 and BGN are anti-inflammatory, suppress proinflammatory cytokine expression and leukocyte migration, and induce autophagy of proinflammatory M1 macrophages. However, soluble versikine, SDC-2, mimecan and DCN are proinflammatory increasing inflammatory cytokine synthesis and leukocyte migration. This contrasts with SDC-4 and perlecan which have anti-inflammatory properties[193] promoting tissue repair[194]. Glypicans also regulate Hh and Wnt signaling in systemic inflammation. Collectively, vascular endothelial glycocalyx-derived SDC-1-4 ectodomains, BGN, versikine, mimecan, perlecan, GPC and DCN are thus of therapeutic potential in the regulation of cytokine and leukocyte responses in lung inflammatory diseases[195]. Pentosan polysulfate down regulates the secretion of a range of inflammatory cytokines and has potent anti-oxidant

activity. Both of these properties exert protective properties on cells and preserves tissue function[105].

4. Depolymerisation of HA in COVID-19 disease.

4.1 CELL MIGRATION-INDUCING AND HYALURONAN-BINDING PROTEIN (CEMIP, KIAA1199) IS A DEAFNESS GENE LINKED WITH DEPOLYMERISATION OF HYALURONAN

KIAA1199 knockdown abolishes HA degradation by human skin fibroblasts, cellular transfection of KIAA1199 cDNA confers an ability to catabolize HA in an endo-β-N-acetylglucosaminidase-dependent manner[196]. The enhanced degradation of HA that occurs in synovial fibroblasts in OA[197] and RA correlates with elevated KIAA1199 expression and can be abrogated by knockdown of KIAA1199[198].

Depolymerisation of HA in long COVID-19 disease is associated with loss of hearing. Auditory neuropathy (deafness) is caused by disruption of nerve impulses travelling from the inner ear to the brain. Viral infection with mumps, measles, meningitis, SARS-CoV-2 and cytomegalovirus can all result in hearing loss. COVID-19 does not cause a sudden hearing loss but irreversible hearing loss and tinnitus can develop as a complication of SARS-CoV-2 infection[199]. KIAA1199, a deafness gene of unknown function, plays a central role in HA binding and depolymerization independently of CD44 and HYAL-1 and HYAL-2[196]. Pentosan polysulfate stimulates HA production in a number of cell types[200] and also inhibits hyaluronidase[201] helping to maintain a healthy glycocalyx.

4.2 ROLES FOR ENDOTHELIAL CELLS AND HYALURONAN IN TISSUE MORPHOGENESIS AND EXTRACELLULAR MATRIX REPAIR

Hyaluronan promotes proliferation and migration of many cell types, and has important roles in tissue morphogenesis, wound healing, inflammation, angiogenesis, and tissue repair processes[202]. Endothelial cells are responsive to HA oligosaccharides which stimulate proliferation, migration, new vessel formation and tissue repair responses[203-206]. Pulmonary stromal fibroblasts and myofibroblasts synthesise HA contributing to the deposition of HA in the endothelial glycocalyx[207], COVID-19 has been proposed to be an endothelial cell dysfunction disease. Angiotensin converting enzyme is highly expressed by endothelial cells, ACE2 has critical roles that impact on the progression of COVID-19 disease[208-211].

5. A summation of the pleotropic cell and tissue protective properties of Pentosan polysulfate

Supplementary Figure 1 summarises the major changes that have been documented in COVID-19 and studies which have utilized PPS to treat the multiple symptoms which arise from viral infection[105,212]. Besides having the ability to prevent attachment of a large range of viruses to host cells which occur through cell surface HS interactions (Table II, Table III) PPS also has many cell and tissue protective properties. These include application in the treatment of cystitis and painful bowel disease[213-219], as a tissue protective enzyme inhibitor[220-223], promotion of cartilage and IVD repair[224-227], healing of OA cartilage and the degenerate IVD[221,223,228,229]. PPS has been used in bioscaffolds in tissue engineering applications[230-232]. PPS regulates Complement activation[233,234], coagulation/fibrinolysis[235-238], thrombocytopenia[239,240] and induces HA production by many cell types[200,241]. Pentosan polysulfate inhibits NGF production by osteocytes which reduces bone pain in OA/RA[242] and promotes lipid removal from subchondral blood vessels engorged with lipid in OA/RA reducing pain in these conditions[243]. Regulation of cytokine and inflammatory mediator production by PPS in ARDS reduces inflammation in tissues. PPS also has anti-viral activity[162,166,167] and is an anti-tumor agent in a number of cancers[244].

5.1 PENTOSAN POLYSULFATE AND THE GUT MICROBIOME

The gut microbiome is disturbed in COVID-19 disease, with alterations in cell populations and imbalance in beneficial symbionts and opportunistic pathogens[245,246]. Xylan is the second most

abundant plant carbohydrate biomass found in nature. Accumulated evidence shows that xylans interact with gut microbiota in a beneficial way[247]. Humans cannot digest xylans but they act as bulking material aiding in the throughput of digested food items through the gut. The gut microbiome produce a number of xylanolytic enzymes that allow the gut microbiome to utilize xylans as a nutrient source, the generated xylo-oligosaccharides have pre-biotic properties that aid in gut homeostasis[248] countering the gut dysbiosis that occurs in COVID-19 disease[249]. Endoxylanases produced by the gut microbiota generate xylo-oligosaccharides (xylo-oligos)[250,251] promoting beneficial symbiont microbes such as *Bifidobacterium* and *Lactobacillus* populations in the human gut improving mucosal health and immune function[252] and inhibit colonization of the gut by pro-inflammatory bacteria such as *Salmonella sp*. This improves gut barrier properties, and plasma lipid levels attenuating pro-inflammatory effects of a high fat diet and decreases blood LPS levels and the damaging effects of IL-1β and IL-13.

6. Multi-organ involvement in Severe acute respiratory syndrome coronavirus 2 infection

SARS-CoV-2 is implicated in the clinical pathology of multiple organs and organ systems (Figure 4). Severe acute respiratory syndrome coronavirus 2 canonical mediators, ACE2, and TMPRSS2 are assisted by other coronavirus-associated receptors and factors, including basigin (BSG/CD147), dipeptidyl peptidase-4 (DPP4/CD26), cathepsin B/L, furin, interferon-induced transmembrane protein (IFTM1-3) and Nrp-1. The localization of these SARS-CoV-2 receptors, proteases, and genes involved in coding proteins that drive viral pathogenesis predisposes to SARS-CoV-2 infection in a number of tissues[253], COVID-19 infection thus involves the hACE2 receptor and its co-receptors Nrp-1 and DPP4/CD26 which engage with the SARS CoV-2 spike protein[254]. In-silico development of a bispecific antibody against SARS CoV-2 spike glycoprotein and DPP4 receptors (Regdanvimab and Begelomab) has been shown to block the D614G mutated spike glycoprotein of SARS-CoV-2 variants and host DPP4 receptor, respectively. This demonstrates the co-involvement of SARS CoV-2 S protein, hACE2 and DPP4/CD26 in the infective process in multi-organ viral infection[254,255].

6.1 HEMOLYSIS IN COVID 19 INFECTED LUNG TISSUES

Hemolysis is a common feature of COVID-19 infected tissues[256], fibrotic changes in tissues also occurs resulting in a reduction in tissue elastic properties and lung function[257]. Pro-coagulant activity also results in thrombus formations in tissues impairing their functional properties[258,259]. This leads to further detrimental effects on these tissues with free heme release resulting in oxidative stress, local generation of oxygen free radicals and mitochondrial and ER distress, leukocyte recruitment, vascular permeabilization, platelet and Complement activation, thrombosis, and fibrosis leading to impaired lung function. Platelets initiate blood clotting, severely affected COVID-19 patients display a high incidence of hypercoagulation in the lungs and brain. Plasma fibrinogen levels are also elevated with advancing age, high cholesterol, being female, menopause, obesity, smoking, inactivity and stress. Most of these features are putative risk factors for COVID-19[260,261]. Heparin treatment of COVID-19 patients displaying enhanced coagulation levels results in an improved prognosis however heparin will only prevent thrombus formation and will not dissolve existing fibrin clots, thus is palliative and not curative. Prevention of SARS-CoV-2 infection of host cells by PPS represents a more effective treatment strategy and has the added advantage of minimizing inflammatory cytokine production and exacerbation of inflammatory conditions in tissues[262]. Heme is a prosthetic group with functional roles in a wide variety of heme proteins such as hemoglobin and the cytochromes. Release of free heme in injured lung tissues promotes

adhesion molecule expression, leukocyte recruitment, vascular permeabilization, platelet activation, complement activation and thrombosis. Heme, however, can be degraded by the anti-inflammatory enzyme heme oxygenase (HO-1) generating biliverdin/bilirubin, iron/ferritin and carbon monoxide[263]. Free heme promotes lung inflammation in critically ill COVID-19 patients. Heme oxygenase -1 has anti-oxidative and anti-inflammatory properties and may represent a specific means of targeting hemolysis therapeutically in COVID-19 disease[264].

6.2 COVID AND COGNITIVE DECLINE

COVID-19 infected patients frequently exhibit neurological symptoms of anosmia and fatigue and long-term neurological deficits post-infection such as cognitive decline and brain-fogging [168,265,266]. Positron emission tomography (PET) and SPECT (Single-photon emission computed tomography) molecular imaging techniques have been used to shed light on how COVID-19 affects human brain structure[267]. Human brain structure is affected by long COVID-19 disease even after recovery of respiratory function and has been referred to as Post COVID Syndrome[268,269]. It is not known how long such neurological deficits will persist in cases of severe SARS CoV-2 infection following recovery of respiratory function[270] however reports of a reduction in IQ and altered immune regulation in young children effected by even very mild COVID-19 respiratory disease are particularly concerning[271,272]. Long-term CNS neuro-inflammation following COVID-19 infection in children may deleteriously affect brain development[273]. Disturbing reports are emerging of learning difficulties and a decline in the educational status of 9 year olds affected by COVID-19, an effect which may be exacerbated in individuals who also display underlying neurological deficits[274-276].

6.2.1 The impact of COVID-19 on patients suffering from neurological deficits

The COVID-19 pandemic has disproportionately impacted patients suffering from AD and dementia who have a reduced capacity to understand and comply with pandemic health care restrictions and may represent a spreader risk for COVID-19[277]. Present day AD/dementia patient numbers of 47 million are projected to triple by 2050 and this will be further compounded by the impact of the COVID-19 pandemic. It is thus predicted that neurological disorders will likely make a greater impact on general health even in patients who have only been impacted by mild symptoms of COVID-19. Cognitive deficits have been reported in patients after recovery from COVID-19 respiratory disease. An inability to concentrate and a fogging of thought processes, impaired concentration and problem-solving capability coupled with feelings of long-term anxiety and insecurity have all been reported[278-282]. Anecdotal reports of COVID-19 infection resulting in a reduction in IQ in children is particularly alarming. COVID-19 disease is often referred to as a mild disorder in children based on its relative impact on respiratory function however little regard is made of the potential long-term effects of COVID-19 disease on brain function. Long-term fatigue with COVID also impacts on the development of neuropsychiatric disorders[283].

7. Conclusions

Use of PPS as a prophylactic that intercepts SARS Cov-2 virion particles in the glycocalyx prevents their binding to cell surface HS in all viral strains and is not impeded by point mutations arising from recombination as part of the natural viral life-cycle. SARS-CoV-2 possesses 24 spike glycoproteins per virion particle which have central roles in binding to cell surface ACE2 facilitating viral entry into host cells. This occurs through the RBD of spike protein however this is buried within the S1 domain which is exposed by a conformational change upon interaction with cell surface HS. PPS prevents such HS interactions occurring and viral infection and warrant further investigation. PPS is effective against all classes of viruses and its anti-viral properties are not diminished by viral mutations. The emergence of a further bat coronavirus, HKU5-CoV-2 related to SARS CoV2[284,285] and of a mink

respiratory coronavirus (MRCoV)[286] related to MERS and SARS CoV2 indicates that due diligence is essential. PPS would be expected to be an effective blocking agent for these new CoV strains, however vaccines or antibodies have yet to be developed. It may thus be a prime time to adopt PPS in preventative anti-viral strategies.

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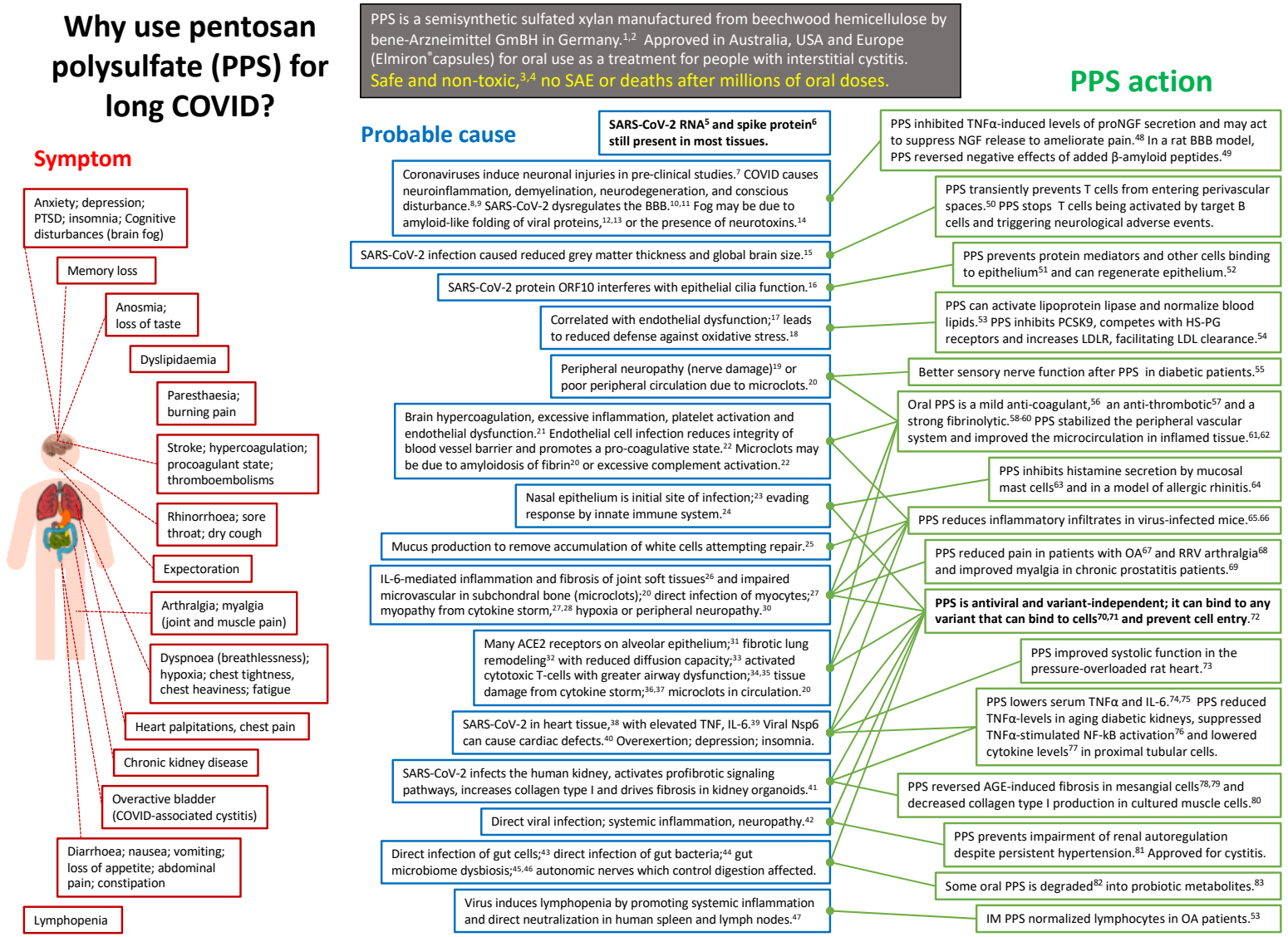
Author contributions

JM and MMS shared in conception of the study and shared in the writing and editing of this manuscript. JM and MMS both shared in the preparation of the figures. Both authors accepted the final version of the manuscript.

Supplemental Figure



Supplementary Figure 1. Illustration of how the multifunctional properties of pentosan polysulfate (PPS) can be used to treat COVID-19 infected tissues.

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Abbreviations used:

ACE2 Angiotensin-converting enzyme 2
ADAMTS A Disintegrin and Metalloproteinase with Thrombospondin motifs
AD Alzheimer's disease
ADHD Attention deficit hyperactivity disorder
ARDS Acute respiratory distress syndrome
AT Antithrombin
BSG/CD147 Basigin
BGN Biglycan
BMP Bone morphogenetic protein
CendR C-end Rule protein motif, interacts with NRP-1
CoV Coronavirus
COVID Coronavirus disease 2019
CoV RaTG13 Bat coronavirus RaTG13
CVI Chronic venous insufficiency
CSF Cerebrospinal fluid
DPP4/CD26 Dipeptidyl peptidase-4
DCN Decorin
DMOAD Disease modifying anti-arthritic drug
DVT Deep vein thrombosis
ECM Extracellular matrix protein
ERK1/2 Extracellular signal-regulated kinase 1 and 2
GPC Glypican
HS Heparan sulfate
HSPG Heparan sulfate proteoglycan
HUVEC Human umbilical vein endothelial cells
IAV Influenza A virus
IFTM1-3 Interferon-induced transmembrane protein
IL Interleukin
iNOS Inducible nitric oxide synthase
IQ Intelligence quotient
ITI Inter--trypsin inhibitor
ITIM Immunoreceptor tyrosine-based inhibitory motif
KIAA1199 *CEMIP (cell migration inducing protein)* deafness gene
LDL Low density lipoprotein
LMW-HA Low molecular weight hyaluronan
MAPK Mitogen-activated protein kinase
MERS Middle East respiratory syndrome
MSCs Mesenchymal stromal stem cells
NDST-2 *N*-Deacetylase/*N*-Sulfotransferase-2
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
NGF Nerve growth factor
NMJ Neuromuscular junction
NRP-1 Neuropilin-1
NTD N-terminal domain (of Spike protein)

OA, RA Osteoarthritis, Rheumatoid arthritis
OCD Obsessive compulsive disorder
PAI-1, 2 Plasminogen activator inhibitor-1, 2
PCSK9 Proprotein convertase subtilisin/kexin type 9
PET Positron emission tomography
PPS Pentosan polysulfate
RBD Receptor binding domain (of Spike protein)
ROS Reactive Oxygen species
SARS CoV-2 *Severe acute respiratory syndrome coronavirus-2*
S Spike protein of SARS CoV-2
SDC Syndecan
SPECT Single-photon emission computed tomography
TAZ Transcriptional co-activator with PDZ binding motif
TLR4 Toll-like receptor-4
TMPRSS2 Transmembrane protease, serine 2
TNF Tumor necrosis factor alpha
tPA Tissue plasminogen activator
TRAF-6 Tumor necrosis factor receptor associated factor 6
TS Tourette Syndrome
TSG-6 Tumor necrosis factor-inducible gene 6 protein
YAP Yes associated protein