Plant lectins as versatile tools to fight coronavirus outbreaks

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Abstract
The S protein forming the homotrimeric spikes of pathogenic beta-coronaviruses, such as MERS-CoV, SARS-CoV and SARS-CoV-2, is a highly glycosylated protein containing mainly N-glycans of the complex and high-mannose type, as well as O-glycans. Similarly, the host cell receptors DPP4 for MERS-CoV and ACE2 for SARS-CoV and SARS-CoV-2, also represent N- and O-glycosylated proteins. All these glycoproteins share common glycosylation patterns, suggesting that plant lectins with different carbohydrate-binding specificities could be used as carbohydrate-binding agents for the spikes and their receptors, to combat COVID19 pandemics. The binding of plant lectins to the spikes and their receptors could mask the non-glycosylated receptor binding domain of the virus and the corresponding region of the receptor, thus preventing a proper interaction of the spike proteins with their receptors. In this review, we analyze (1) the ability of plant lectins to interact with the N- and O-glycans present on the spike proteins and their receptors, (2) the in vitro and in vivo anti-COVID19 activity already reported for plant lectins and, (3) the possible ways for delivery of lectins to block the spikes and/or their receptors.

Keywords Beta-coronaviruses · MERS-CoV · SARS-CoV · SARS-CoV-2 · COVID-19 · Man-specific lectin · Con A · Galanthus nivalis agglutinin (GNA) · Pisum sativum lectin (PsA) · Lens culinaris lectin (LcA) · Aleuria aurantia lectin (AAL) · Morus nigra lectin (Morniga-G) · Sambucus nigra lectin (SNA-I).

Introduction
Pathogenic beta-coronaviruses like MERS-CoV, SARS-CoV and SARS-CoV-2, are enveloped viruses covered by spikes built from trimeric S proteins that allow virions to interact with specific receptors present on the surface of target cells to subsequently entry and infect the host cells [1–3]. Although these spikes are heavily glycosylated, their receptor binding domains (RBD) are almost free from glycosylation and can therefore interact with the corresponding surfaces from the host cell receptors [4] (Fig. 1). Similarly, the host cell receptor dipeptidyl peptidase-4 (DPP4) for MERS-CoV, and the angiotensin-converting enzyme 2 (ACE2) for SARS-CoV and SARS-CoV-2, are also glyco-sylated proteins exhibiting glycan free surfaces allowing the recognition of the RBDs from the pathogenic beta-corona-viruses [5, 6] (Fig. 1).

Since the onset of beta-coronavirus-related respiratory syndromes, the glycans covering the MERS-CoV, SARS-CoV and SARS-CoV-2 spikes, have been investigated in detail [7–10]. Complex-, high mannose- and hybrid-type N-glycans occupy the S proteins forming the spikes from MERS-CoV, SARS-CoV and SARS-CoV-2, but the proportions of these three types of N-glycans occurring at the 23 N-glycosylation sites of MERS-CoV and the 22 N-glycosylation sites of SARS-CoV and SARS-CoV-2 are very different (Fig. 3) [7]. In this respect, high-mannose type N-glycans are most abundant in spikes of MERS-CoV, whereas complex-type glycans are predominantly distributed on the spikes of SARS-CoV and SARS-CoV-2, respectively. High-mannose type glycans occurring in the S proteins of beta-coronaviruses essentially correspond to...
Man3-Man9 chains, with a predominance of Man8 oligosaccharides. Compared to this rather homogeneous composition in high-mannose N-glycans, complex glycans offer an extreme diversity including sialylated and fucosylated bi-, tri- and tetra-antennary glycans (Fig. 2). The core structure Man3GlcNAc2 of the complex glycans is often α1,6-fucosylated on the first GlcNAc linked to the Asn residue of the N-glycosylation site. According to these discrepancies in the N-glycan composition of their spikes, MERS-CoV, SARS-CoV and SARS-CoV-2 shall interact differently with lectins and, especially, with mannose-specific lectins. In addition to N-glycans, O-glycan have been identified on the spikes of SARS-CoV-2 and could be recognized by other plant lectins with a O-glycan-binding specificity [10, 11].

Mannose-specific lectins from higher plants have been used as valuable tools for targeting the complex glycans that cover enveloped viruses such as HIV-1, Herpes simplex virus, influenza and Ebola viruses [12]. Two-chain lectins from the Vicieae tribe like pea (Pisum sativum) lectin PsA and lentil (Lens culinaris) lectin LcA, are particularly interesting because they specifically recognize the α1,6-fucosylated trimannoside core Man3GlcNAc(Fuc)GlcNAc which frequently occurs in complex glycans from the beta-coronaviruses [13, 14]. This enhanced affinity of Vicieae lectins towards complex glycans having an α1,6-fucosylated Man3GlcNAc2 core, depends on the direct interaction of the lectin carbohydrate-binding site with the α1,6-linked Fuc residue, as shown from the study of the Lathyrus ochrus isolecitin II (LoL-II) complexed with a human lactotransferrin-derived peptide [15]. Accordingly, Man-specific lectins from the Vicieae can be used as glycan probes for targeting the complex glycans of MERS-CoV, SARS-CoV and SARS-CoV-2 viruses. Other Man-specific legume lectins, e.g. Con A from Jackbean (Canavalia ensiformis), differ from the Vicieae lectins because they primarily interact with the non-fucosylated Man3GlcNAc2 core of complex glycans.

High-mannose type glycans can be recognized by Man-specific lectins related to the snowdrop (Galanthus nivalis) lectin, the so-called GNA-like lectins from the storage organs, bulbs and rhizomes, of different monocot families, e.g. Amaryllidaceae, Liliaceae and Orchidaceae [16] (Fig. 2). These lectins readily recognize either linear or branched α1,2-, α1,3- and α1,6-linked mannosyl oligosaccharides, and thus represent nicely adapted lectin probes for targeting the high-mannose glycans that decorate the spike S-proteins of beta-coronaviruses. Although hybrid type glycans have been identified as usual glycan components of the beta-coronavirus spikes, they are quantitatively less important in most of the viruses [7]. In addition, the beta-coronavirus spikes also contain a few O-glycan chains, which often coincide with the S or T residues of N-glycosylation sites non occupied by complex, high-mannose or hybrid glycans [11]. Lectins belonging to the group of GalNAc/T/ Tn-specific lectins, e.g. amaranthin from Amaranthus caudatus, peanut (Arachis hypogaea) lectin and some Moraceae lectins, could specifically recognize these O-glycans [16].

Similar to the spike proteins, DPP4 for MERS-CoV, and ACE2 for SARS-CoV and SARS-CoV-2, also consist of glycosylated proteins except in the regions that specifically interact with the RBD of beta-coronaviruses (Fig. 1). The N-glycans decorating DPP4 [17] (Fig. 4), and ACE2 [18] (Fig. 5), essentially correspond to complex and high-mannose type glycans, with the exception of DPP4 which exhibits its highly fucosylated multimeric tandem repeats of Leα/Leβ epitopes [17] (Fig. 4). It is noteworthy that some N-glycans occurring on the spike glycoprotein of beta-coronavirus, also occur on their DPP4 and ACE2 receptors, especially some complex and high-mannose glycans. Accordingly, Man-specific lectins can also be used as glycan probes for the beta-coronavirus receptors.

The present review was aimed at reporting (i) the N-glycan similarities between the beta-coronavirus MERS-CoV, SARS-CoV and SARS-CoV-2 and their corresponding host cell receptors DPP4 and ACE2, (ii) the possible interaction of these glycans with Man-specific lectins and other lectins with different carbohydrate-binding specificities, and discuss on (iii) the possible biomedical applications of Man-specific lectins as relevant tools for fighting coronavirus outbreaks.

**Interaction of Man-specific lectins with the beta-coronavirus spike glycoproteins**

The carbohydrate-binding specificity of Man-specific lectins has been investigated in detail and, especially for the garden pea (Pisum sativum) lectin PsA, the snowdrop (Galanthus nivalis) lectin GNA, and the Jackbean (Canavalia ensiformis) lectin Con A. Results from glycan array experiments performed by the Consortium for Functional Glycomics (http://www.functionalglycomics.org) for PsA, GNA and Con A, yielded the best interaction with the high-mannose and some of the complex glycans that decorate the S protein of the MERS-CoV, SAR-CoV and SARS-CoV-2 spikes (Fig. 3). Detection of the spike high-mannose glycans, which occur in the range between Man3 and Man9 in beta-coronaviruses, could be easily performed using GNA as a glycan probe. Conversely, due to the extreme diversity of complex glycans in beta-coronaviruses, most of their tri- and tetra-antennary complex glycans were not assayed in the glycan array experiments. Taking into account that most of these complex glycans contain a α1,6-fucosylated Man3GlcNAc2 core additional interactions with PsA could...
occur. Similarly, hybrid glycans which have not been tested in the glycan array experiments, could interact with PsA and Con A. In addition, many branched complex glycans are sialylated on their terminal Gal residues and could be detected using Neu5Ac-specific lectins like SNA-I from the black elderberry (Morus nigra) as a glycan probe.

In agreement with these predicted N-glycan-lectin interactions, a few binding experiments have been performed with Man-specific lectins as glycan probes for beta-coronaviruses. Thus, glycans from SARS-CoV spikes have been successfully probed by a panel of lectins including GNA and other Man-specific GNA-related lectins [20, 21]. The Man-specific lectin FRIL from the legume Lablab (Dolichos) purpureus also recognized the complex glycans covering the SARS-CoV-2 spikes [22]. The lentil (Lens culinaris) lectin LcA, a two-chain Vicieae lectin closely related to pea lectin PsA, and two other Man-specific lectins, succinyl-Con A and snowdrop lectin GNA, interacted with MERS-CoV, SARS-CoV and SARS-CoV-2 pseudoviruses, and LcA developed a broad antiviral activity against SARS-CoV-2 variants [23]. Griffithsin, the red algal Man-specific lectin from Griffithsia sp., was identified as a potent inhibitor of MERS-CoV infection [24], and was shown to specifically interact with SARS-CoV [25] and SARS-CoV-2 [26] spikes, and display an inhibition effect on viral entry [25]. Griffithsin was also shown to block the entry of SARS-CoV-2 and its Delta and Omicron variants in Vero E6 cell lines [27], and preliminary data from experiments performed using microbeads conjugated with S proteins from the Wuhan (wild type) and Delta strains of SARS-CoV-2, showed interaction with FITC-labelled lectins including the Man-specific lectins PsA from pea, LcA from lentil, GNA from snowdrop and Con A from Jack bean (Simplicien, M. et al., unpublished). Very recently, another GNA-like lectin NTL-125 from daffodil (Narcissus tazetta) was documented as a Man-specific lectin that binded to the SARS-CoV-2 spikes in pseudo-virus neutralization assays and thus, prevented the attachment of the virus to its ACE2 receptor [28].

**Interaction of lectins with different specificities with the beta-coronavirus spike glycoproteins**

In addition, due to the extreme diversity of glycan composition of the beta-coronavirus spikes, lectins with other specificities different from the Man-specificity, were also shown to interact with glycans of SARS-CoV and SARS-CoV-2 spikes, respectively. A list of 33 lectins, including lectins with different carbohydrate-binding specificities, e.g., Gal-specific lectin Morniga-G and GalNAc/T/Tn-specific lectin Morniga-G from Morus nigra, GalNAc-specific lectin ML
Interaction of plant lectins with host cell receptors DPP4 and ACE2

Receptors for MERS-CoV (DPP4) and SARS-CoV/SARS-CoV-2 (ACE2) also consist of glycosylated proteins containing glycan free regions that interact with the RBD from the viruses. The N-glycans occurring at the surface of DPP4 have been identified as high-mannose glycans and hybrid glycans, respectively, similar to those found in the beta-coronavirus spikes (Fig. 4) [17]. Accordingly, these N-glycans should be recognized by PsA, GNA and Con A. In addition, DPP4 contain highly fucosylated multimeric tandem repeats of Leα/Leβ glycotopes that should be specifically recognized by Fuc-specific lectins such as the Aleuria aurantia lectin AAL (Fig. 4) [17]. A more detailed study of N-glycans occurring on ACE2 has been performed, and revealed a high number of biantennary complex glycans, and a few high-mannose glycans (Fig. 5) [18, 19]. Some of these glycans are similar to those occurring in SARS-CoV and SARS-CoV-2 spikes and therefore, could be easily recognized by PsA, GNA, and Con A. In addition, DPP4 contain highly fucosylated multimeric tandem repeats of Leα/Leβ glycotopes that should be specifically recognized by Fuc-specific lectins such as the Aleuria aurantia lectin AAL (Fig. 4) [17]. A more detailed study of N-glycans occurring on ACE2 has been performed, and revealed a high number of biantennary complex glycans, and a few high-mannose glycans (Fig. 5) [18, 19]. Some of these glycans are similar to those occurring in SARS-CoV and SARS-CoV-2 spikes and therefore, could be easily recognized by PsA, GNA, and Con A since most of them contain the fucosylated or non-fucosylated Man₃GlcNAc₂ core interacting with PsA and Con A, and the Man₅ and Man₆ motif interacting with GNA.

It is noteworthy that the beta-coronavirus receptors DPP4 and ACE2 share some high-mannose glycans, complex glycans and hybrid glycans, in common with the corresponding beta-coronaviruses MERS-CoV, SARS-CoV and SARS-CoV-2, that predicts a similar reactivity of the viruses and their host cell receptors towards Man-specific
Discussion

Although the N-glycan repertoire of the beta-coronaviruses varies from one virus to another, MERS-CoV, SARS-CoV and SARS-CoV-2 share common complex glycans and high-mannose structures, that could be recognized by Man-specific lectins from the Vicieae tribe (PsA), GNA-like lectins (GNA), and legume lectins (Con A). This promiscuity in the glycan composition of beta-coronaviruses is not surprising because, regardless of the virus, both N- and O-glycosylation processes of virus envelope are orchestrated by a complex set of glycosyl transferases that belong to the host cells. This is also the reason for which beta-coronaviruses and their receptor counterparts, DPP4 and ACE2, share common glycan structures. According to this glycan promiscuity, lectins like PsA, GNA and Con A. However, conversely to the beta-coronavirus spikes, only few lectin-binding experiments were performed using the receptors DPP4 and ACE2 as possible targets for Man-specific lectins. Recent experiments performed with microbeads conjugated with glycosylated ACE2 receptors, showed binding with FITC-labelled Man-specific lectins PsA from pea, LcA from lentil, GNA from snowdrop and Con A from Jack bean. Similarly, FITC-labelled Morniga-G and SNA-I, interacted with microbeads conjugated with ACE2, suggesting that the cell receptor for SARS-CoV and SARS-CoV-2 also contains O-glycans and sialylated N- or O-glycans (Simplicien, M. et al., unpublished).
from plants and fungi can interact with both the heavy glycosylated spikes from coronaviruses and their similarly glycosylated host cell receptors. In this respect, the binding affinity ($K_D$) of lectins for complex glycans, which is usually in the range of 1–10 mM [31], comparable to affinities measured for polyclonal antibodies, seems sufficient to promote an interaction with the glycans from the viruses and their receptors. Furthermore this lectin binding can outcompete the interaction of the viral RBDs with their host cell receptors. Along this line, the Man-specific tetrameric lectins like Con A, which possess four carbohydrate-binding domains (CBDs), should display an enhanced avidity for the glycans from coronaviruses and their DPP4 and ACE2 receptors, compared to Man-specific dimeric lectins like PsA or LcA, which only contain two CBDs.

Initially considered as displaying a protective function for the beta-coronaviruses [32], the glycan shield covering the spikes of MERS-CoV, SARS-CoV and SARS-CoV-2, plays in fact a complex and still incompletely understood role in multiple diverse processes such as the recognition of the virions by their host cell receptors, the infectivity of the viruses, and the possible escape from the surveillance by the immune system of the infected host. In addition, subtle changes in the glycosylation status of ACE2 were shown to impact the interaction with the SARS-CoV-2 spikes [19]. In this respect, sialylation of complex $N$-glycans favoured the binding of the spike to ACE2 whereas desialylation of $N$-glycans had a negative effect on the interaction. The $O$-glycosylation also plays a role in the interaction between the SARS-CoV-2 spike and ACE2 [33]. Depending on their degree of sialylation, the elongated $O$-glycan chain associated to S494 of the SARS-CoV-2 RBD creates new polar contacts with the surrounding amino acid residues of the interacting ACE2 surface, that stabilizes the RBD-ACE2 interface. Moreover, clusters of sialic acid residues occurring on the surface of host cells have been proposed to play the role of an additional co-receptor for the attachment of the SARS-CoV-2 RBD [34]. In fact, blocking of $N$- and $O$-glycosylation processes in both the SARS-CoV-2 and ACE2, revealed that glycosylation has little impact on the SARS-CoV-2/ACE2 interaction but plays a major role in regulating the viral entry of SARS-CoV-2 into the host cells [35].

The binding of plant lectins and especially, Man-specific lectins from the Vicieae (PsA, LcA), to the $N$-glycans located at the top of the $S$ protein forming the SARS-CoV-2 spike, should create some steric hindrance in the close vicinity of the RBD region, susceptible to prevent the correct interaction of the spike with the ACE2 receptor. Especially, $N$-glycan chains of the complex $N$-glycan type, carried by asparagine residues N165 and N343 located at the top of the spike, should serve as specific targets for this masking effect towards the RBD (Fig. 6). Other $N$-glycan chains exposed on the surface of the upper S1 part of the spike protein, could serve as targets for plant lectins but the masking effect resulting from their fixation should be less pronounced because of the large distance from the RBD-ACE2 interface. Similarly, the recognition of the glycan chains surrounding the RBD-binding region of ACE2 by plant lectins, should result in some steric hindrance capable to prevent ACE2 receptor from being properly recognized by the SARS-CoV-2 spikes (Fig. 1G,H). Accordingly, interaction of plant lectins with both RBD and ACE2, should interfere with the attachment and subsequent entry of SARS-CoV-2 into the host cells. Due to the dimeric or tetrameric organization of plant lectins, some carbohydrate-binding sites of the lectins previously bound to the SARS-CoV-2 spikes could remain unliganded and thus, could recognize the glycans exposed on the surface of the ACE2 receptors.
Despite the benefits plant lectins can offer to fight COVID-19, they have some disadvantages that could limit their use as virus blockers in vivo. Plant lectins have been identified for a long time, as bioactive compounds with mitogenic, immunomodulatory, allergenic and cytotoxic properties (see [36, 37] for these unwanted properties of plant lectins). The effects of plant lectins have been particularly studied on cancer cells, for which different lectins have been used as specific binders for diagnostic or therapeutic purposes [37–39]. In this regard, many lectins have been identified as molecules susceptible to stimulate various signaling pathways and trigger apoptotic and/or necrotic responses in the target cells [38, 39]. Healthy cells can also suffer from apoptotic/necrotic side-effects upon lectin recognition [36]. In this respect, lectins with four CRDs (Con A, Morniga G), compared to lectins with two CRDs (PsA, to favor the RBD-ACE2 interaction. In fact, the impact of this indirect RBD-ACE2 recognition should be extremely limited because lectins might as well target many other glycans exposed to the surface of host cells. In agreement with such a masking effect, lectins with different specificities were reported to act as a blocking agent for the attachment and the entry of pathogenic beta-coronaviruses into the host cells, under in vitro and in vivo conditions [22–30]. Interestingly, the inhibitory effects of plant lectins could result from their binding to either the virus spikes or their host cell receptors or both, due to common N-glycans shared by the virus spikes and ACE2. Moreover, lectins with different specificities could participate in this inhibition because of the diversity of glycan structures observed on the surface of the spikes and ACE2.
column[46]. Another ex vivo application has been proposed on the web (Pittsburgh University, 2020), in the form of a nasal spray of recombinant griffithsin to prevent COVID-19 infection in immune-compromised people. Spraying lectin solutions on facial masks or air conditioning filters, could enhance their capacity to protect susceptible people from a COVID-19 infection. Recently, another way for introducing lectins has been proposed in the form of the ProjectGRFT (2021) aiming at producing a transgenic rice expressing griffithsin, the red algal anti-COVID Man-specific lectin (http://app.jogl.io/project/582/ProjectGRFT).

However, even if successful, it is not certain that such an approach using genetically modified plants (GMPs) for combating COVID-19 will receive the approval of populations, who remain broadly unfavorable to the introduction of GMPs in food products. At the present time, however, the number of patents deposited with the aim of using plant or algal lectins to combat COVID-19 still remains limited[47].

Bioinformatics

The atomic coordinates of spikes from MERS-CoV (PDB code 5W9H) [2], SARS-CoV (PDB code 6ACD) [5], and SARS-CoV-2 (6VXX) [3], all in the closed conformation, together with the atomic coordinates of DPP4 (PDB code 4L72) [4], and ACE2 dimer (PDB code 7L7F) [6], were taken from the RCSB Protein DataBank [48]. The molecular surface of the glycopolypeptide was calculated and displayed with Chimera [49] and Chimera-X [50]. Assuming that putative N-glycosylation sites NXT/S of envelope glycoproteins are actually glycosylated, N-glycans

**Fig. 6** A,B: Lateral view (A) and top view (B) of the molecular surface of the glycosylated homo-trimeric spike from SARS-CoV-2 in the closed conformation (PDB code 6VXX). The N-glycan chains decorating the spike are colored cyan, except for N-glycans linked to N165 and N343 residues, which are colored magenta and yellow, respectively. Once recognized by lectins, these N-glycans, located in close vicinity of the RBDs (red circles), should create some steric hindrance susceptible to prevent the spike to anchor properly to the ACE2 receptor.
of the complex type and high-mannose type N-glycans were modeled using the GlyProt server (http://www.glycosciences.de/modeling/glyprot/php/main.php) [51], and represented in CPK (spherical space-filings models designed by Corey, Pauling and Koltun) on the molecular surface of the envelope glycoproteins.

Cartoons for high-mannose N-glycans, complex N-glycans, hybrid N-glycans and O-glycans, were built and represented with the DrawGlycan SNFG package for Mac [52]. Colored symbols were used to represent Fuc (red triangle), Gal (yellow circle), Glc (blue circle), GalNAc (yellow square), GlcNAc (blue square), Man (green circle) and sialic acid/Neu5Ac (purple diamond), respectively.

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