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Review

Plant lectins as prospective antiviral biomolecules in the search for COVID-19 eradication strategies

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ABSTRACT

Lectins or clusters of carbohydrate-binding proteins of non-immune origin are distributed chiefly in the Plantae. Lectins have potent anti-infectivity properties for several RNA viruses including SARS-CoV-2. The primary purpose of this review is to review the ability of lectins mediated potential biotherapeutic and bioprophylactic strategy against coronavirus causing COVID-19. Lectins have binding affinity to the glycans of SARS-COV-2 Spike glycoprotein that has N-glycosylation sites. Apart from this, the complement lectin pathway is a "first line host defense" against the viral infection that is activated by mannose-binding lectins. Mannose-binding lectins deficiency in serum influences innate immunity of the host and facilitates infectious diseases including COVID-19. Our accumulated evidence obtained from scientific databases particularly PubMed and Google Scholar databases indicate that mannose-specific/mannose-binding lectins (MBL) have potent efficacies like anti-infectivity, complement cascade induction, immunoadjuvants, DC-SIGN antagonists, or glycomimetic approach, which can prove useful in the strategy of COVID-19 combat along with the glycobiological aspects of SARS-CoV-2 infections and antiviral immunity. For example, plant-derived mannose-specific lectins BanLac, FRIL, Lentil, and GRFT from red algae can inhibit and neutralize SARS-CoV-2 infectivity, as confirmed with *in-vitro*, *in-vivo*, and *in-silico* assessments. Furthermore, Bangladesh has a noteworthy resource of antiviral medicinal plants as well as plant lectins. Intensifying research on the antiviral plant lectins, adopting a glyco-biotechnological approach, and with deeper insights into the "glycovirological" aspects may result in the designing of alternative and potent blueprints against the 21st century's biological pandemic of SARS-CoV-2 causing COVID-19

1. Introduction

Lectins are a diverse group of carbohydrate-binding natural proteins that bind reversibly to mono and oligosaccharides with high specificity [1]. The first study of lectin began more than 130 years ago in 1888 by Peter Hermann Stillmark with the finding that the seed extracts of *Ricinus communis* (Castor bean) can agglutinate red blood cells and the isolated lectin was named Ricin [2]. During World War I and II ricin was utilized as a potential weapon by the United States and British military, respectively [3]. The modern age of lectinology began in 1972 with the purification of lectins from different plant sources [4]. Seeds, tubers, leaves, stems, roots, and fruits of medicinal plants are rich sources to isolate and purify lectins [5], specially from the Leguminosae family [6], and large numbers of lectins are present in seed cotyledons [7].

Lectins can target the sugar complex of glycoproteins and all the lectins possess two or more carbohydrate-binding sites with the essential property of agglutinating ability to the erythrocytes without altering the carbohydrates properties [8]. Lectins can be classified based on binding

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Abbreviations: GEP, glycosylated envelope proteins; MBPL, mannose-binding plant lectin; MBL, mannose-binding lectin; sMBL, serum MBL; MASP, (MBL)-associated serine proteases; pdMBL, plasma-derived human mannose-binding lectin.

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specificity as glucose/mannose, galactose and N-acetyl-D-galactosamine, N-acetylglucosamine, L-fucose, and sialic acids [9]. Lectins may also be categorized into merolectins, holoectins, chimerolectins, and superlectins based on the number of binding sites [9]. Plant lectins can be classified into 12 families based on species and lectin domain [10]. Man-specific or mannose-specific lectins have specificity for mannose and mannose containing glycoproteins and they are widely present in all living organisms, and especially have been isolated and identified from plants, algae, fungi, and cyanobacteria [11].

The application of lectins is dependent on their properties, and some of the lectins derived from the natural resources have *in-vivo* and *in-vitro* antiviral activities [12]; therefore, some of these novel lectins have been considered for the potential development of therapeutic agents against viral infections [12]. Lectins are highly potent in virus neutralization activities and their modes of action can target enveloped viruses that share the feature of glycosylated proteins on their surfaces [13]. Thus, lectins can inhibit the replication of viruses by interacting with viral envelope proteins. Such antiviral lectins have extensively been evaluated *in-vitro* for their neutralization effects on different enveloped viruses including coronaviruses and HIV [13], because lectins can interfere with the virus entry and inhibit the viral proteins production [14]. Lectins have also been used as glyco-analytical tools in the development of biosensors for the diagnosis of infectious diseases and detection of viral pathogens [15]. Example includes, *Concanavalin* A (ConA) lectin can recognize the structural glycoproteins of the arboviruses [16]. In another study, five lectins such as *Dolichos biflorus* lectin (DBA), *Helix pomatia* lectin (HPA), peanut lectin (PNA), soybean lectin (SBA), and *Ulex europaeus* lectin (UEA-1) were evaluated for the detection of hepatitis A virus (HAV) and amongst the five lectins, SBA showed significant activity in the detection of HAV [17].

In addition, some lectins may have mitogenic activity that leads to systemic inflammation [18], and increase viral transmission because of their ability to activate T cells [19]. Lectin-induced mitogenicity can be overcome by attempting glycoengineering techniques such as BanLac, which was engineered to eliminate its mitogenicity by amino acid mutation at position 83–84 from histidine to threonine [19], without compromising antiviral activity against Ebola and influenza viruses [20, 21]. In another recent study published in April 2021, a site-specific engineered lectin based on structural insights, *Pseudomonas taiwanensis* lectin (PTL), reportedly enhanced antiviral activity against the influenza virus and such site-specific engineering of lectins can be a potential strategy to boost the antiviral activity of lectins [22]. The data from 2015 to 2020 showed that numerous potential antiviral lectins were discovered along with studies of structural modifications when needed [23].

1.1. *Antiviral plant lectins and their modes of action*

The contribution of plant lectins as antiviral activity was first reported in 1988 wherein D-mannose-specific plant lectins blocked the binding of HIV *in-vitro* [24]. Glycosylated envelope proteins (GEP) are a particular protein for the regulation of virus recognition and virus entry. They exert affinity for cell-surface proteins of host cells, and therefore the antiviral lectins react with the high-mannose glycan to trigger glycosylation of viral GEP [12]. A glycosylated envelope protein complex of HIV has transmembrane trimer, gp31 and extracellular trimer, gp120 that contain N-linked oligosaccharide attachment sites. These structures assist viral evasion of the host immune system and entry into

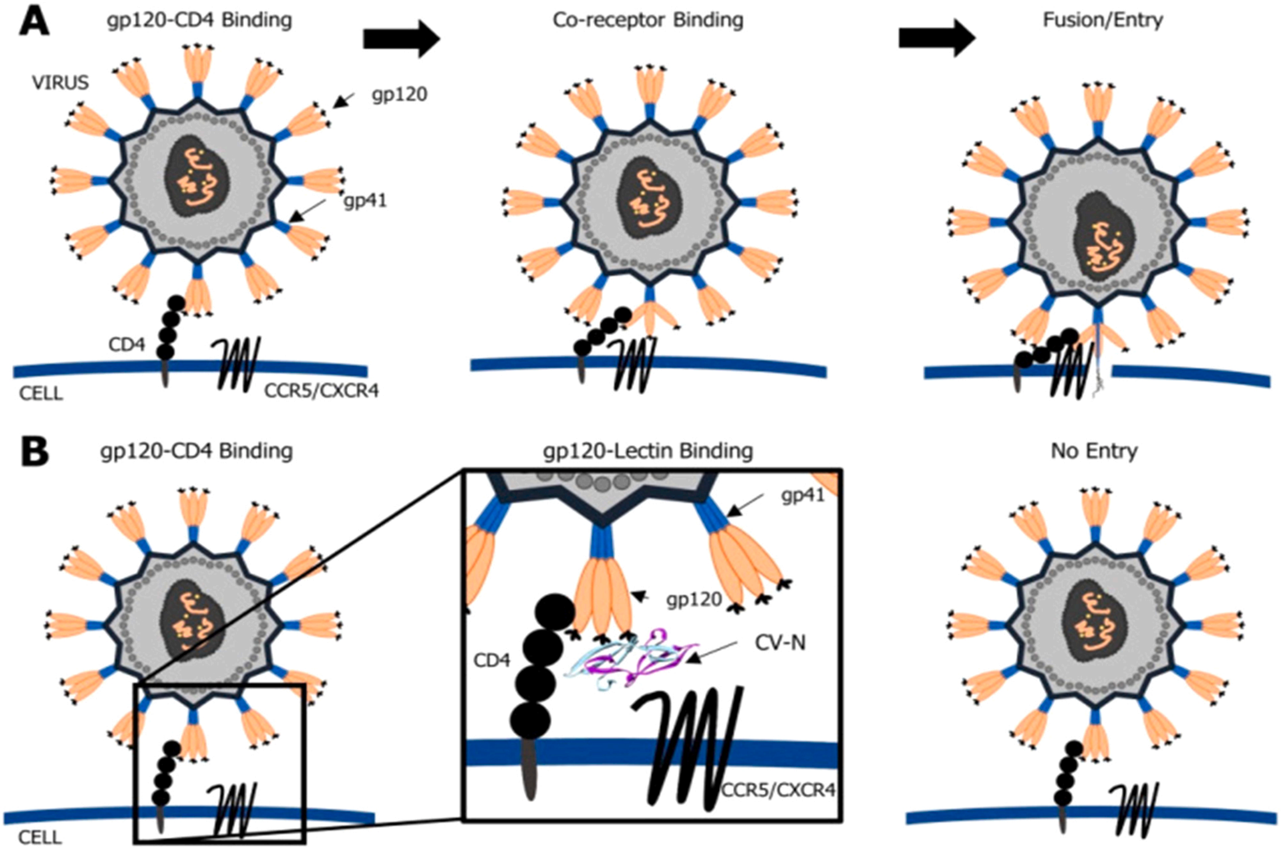

Fig. 1. "Schematic representation of viral infection (A) and the role of cyanobacterial lectin, cyanovirin (CV-N) on inhibition of viral entry and fusion (B). CV-N blocks the interaction between the viral gp120 and the CD4 receptor on the host cell. It prevents the interaction with the associated co-receptors CXCR4/CCR5. As a consequence, the virus cannot enter into the cell."
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the host cells, mediated by recognition of CD4+ triggering. The antiviral lectins inhibit the conformational reorganization of the glycosylated envelope protein complex and thus result in suppressing virus entry into host cells [12,25]. Specific carbohydrate-binding lectins are considered as potential anti-HIV agents which can block the host-virus interactions at their earliest stage because of the glycosylated action of the viral envelope proteins [26]. The following figure, Fig. 1, represents the role of cyanobacterial lectin against viral infection.

Since antiviral medicinal plants and their bioactive compounds are potential sources that may play a significant role in the development of COVID-19 biotherapeutics [28–31], we documented some plant lectins from reported antiviral medicinal plants available in Bangladesh in Table 1.

The *in-vitro* antiviral potency of bioactive compounds or drugs can be determined by the two most commonly reported parameters such as EC_{50} (EC for effective concentration), the concentration of bioactive compounds (drugs) in cell culture media that provides 50% maximal protection against virus induced cytopathicity and IC_{50} (IC for inhibitory concentration), the concentration of bioactive compounds (drugs) that yields 50% of the maximum inhibitory effect.

In a study of antiviral activity, Gondim and coauthors have evaluated 4 leguminous lectins, namely *Canavalia /brasiliensis* (ConBr), *C. maritima* (ConM), *Dioclea lasiocarpa* (DLasiL) and *D. sclerocarpa* (DSclerL), and 5 algal lectins: *Amansia multifida* (AML), *Bryothamniom seaforthii* (BSL), *Hypnea musciformis* (HML), *Meristiella echinocarpa* (MEL) and *Solieria filiformis* (SfL) from the Brazilian biodiversity, which are active against 18 different viruses, including influenza viruses and HIV. On the basis of EC_{50} values, the most potential lectins were DLasiL and DSclerL, which showed EC_{50} values ranging from 9 nM to 46 nM for HIV-1 and respiratory syncytial virus, respectively; DSclerL, ConBr and ConM showed EC_{50} ranging from 0.4 to 6 nM against influenza A virus strain H3N2 and influenza B virus, and DLasiL showed EC_{50} of 5 nM against feline coronavirus [128]. In a review study published in August 2021, Carneiro and co-authors have demonstrated antimicrobial applications of patented lectins and listed some patented lectins that exhibited *in-vitro* antiviral activity [129] (see Table 2).

2. Potentials of lectins against SARS-CoV-2 infectivity

Lectins can be used to identify and characterize the structure of glycans [130]. Glycans are the carbohydrate portion of glycoproteins which have crucial roles in the immune system of humans [131] and pathobiology of viral infections [132]. Antiviral lectins can block the entry of virus by binding to glycans from either the virus or host cell [129]. Antiviral lectins can bind to the viral Spike (S) protein of SARS-CoV [116]; specifically, lectins like mannose/glucose and N-acetylglucosamine (GlcNAc)- specific lectins have been found to inhibit entry of several coronaviruses such as SARS-CoV [133,134], MERS-CoV [135], and other coronaviruses [136,137].

The glucose/mannose-specific plant lectin FRIL, derived from *Lablab purpureus,* is effective both *in-vivo* and *in-vitro* for neutralizing SARS-CoV-2 binding to complex-type-N-glycans on viral glycoproteins [138]. Another plant lectin which is mannose-specific, lentil, isolated from *Lens culinaris,* showed strong inhibitory SARS-CoV-2 activity at the early steps of infections by blocking the ACE2-S trimer binding to oligomannose-type glycans and N-acetylglucosamine at glycosylation sites N165, N234, and N343, which are located around the receptor binding domain [139].

The agal lectin, GRFT (Griffithsin), derived from red algae *Griffithsia* sp., is a high mannose-specific lectin, which significantly inhibits SARS-CoV-2 pseudovirus infection *in-vitro* with an IC_{50} of 63 nmol/L compared to remdesivir with effective concentration of 0.77 μmol/L; GRFT also inhibits SARS-CoV-2 S-mediated cell to cell fusion with an IC_{50} of 323 nmol/L [140]. GRFT has also been reported to inhibit SARS-CoV infectivity in previous *in-vivo* and *in-vitro* studies [133]. The following table, Table 3 lists some algae-derived mannose-specific antiviral lectins that have been reported to be potent inhibitors of different RNA viruses summarized by Alam et al. [141], and can be potent inhibitors of coronaviruses as well.

From molecular docking and MD simulation studies, Banana derived mannose-specific lectin, BanLec, can target N-glycans of the Spike glycoproteins to neutralize SARS-CoV-2 infectivity [142]. The following table, Table 4 is listed with some antiviral plant lectins, which are reportedly potent inhibitor of coronaviruses by targeting both the early virus replication cycle and the end of the infectious virus cycle (modified from Bah et al. [143]).

The antiviral medicinal plant *Withania somnifera* (L.) Dunal*,* which is called Indian ginseng has potential for COVID-19 management [127]. An *in-silico* docking and molecular dynamics results have showed its (phytochemicals of *W. somnifera*) ability to inhibit SARS-CoV-2 host entry and replication [144], and the plant has effective roles on the host ACE2 receptor complex and receptor binding domain (RBD) of virus [145]. It is worth noting that a mannose-specific lectin was isolated from leaves of *W. somnifera* [125].

2.1. Lectin mediated DC-SIGN antagonists and glycomimetic approach

C-type lectins, which according to their property of Ca^{2+} dependent carbohydrate-binding lectins, were identified as the key susceptibility factors that interact with multiple viruses, and then induce infection [146]. DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) is such a mannose-specific C-type lectin and pathogen recognition receptor of human innate immune system expressed in dendritic cells [147]. DC-SIGN can recognize N-linked high-mannose oligosaccharides and branched fucosylated structures [148]. It has been reported that DC-SIGN can act as an alternative receptor for SARS-COV-2 entry, therefore enhancing infectivity [149,150]. The glycomimetic antagonists of DC-SIGN and L-SIGN which is another C-type lectin, highly expressed in human type II alveolar cells and the endothelial cells of the lung, liver, and lymph nodes can be promising candidates for the inhibition of SARS-CoV-2 entry to host cell receptors [150]. Therefore, DC-SIGN antagonist that act as a glycomimetic approach, are potential anti-infectives [151], and several glycomimetics are already in clinical trials [152]. *In-vitro* assays have confirmed ability of the plasma-derived human mannose-binding lectin to block binding of SARS-CoV to DC-SIGN [153]. Furthermore, the algal lectin GRFT and cyanobacterial lectins Cyanovirin-N, and Scytovirin can block HIV-1 binding to the DC-SIGN receptor and the DC-SIGN-mediated HIV-1 infection of CD4(+) cells [154].

2.2. Mannose-binding lectins and SARS-CoV-2 possible interactions

The SARS-CoV-2 Spike (S) glycoprotein has S1 and S2 subunits linked through transmembrane protease serine 2 (TMPRSS2) and furin cleavage sites [155]. The S1 subunit is involved in the attachment to host cell receptors facilitated by a receptor binding domain (RBD), and S2 is involved in the fusion of cellular membranes in between virus and human [155]. The entry of SARS-CoV-2 into human host cells is shown schematically in Fig. 2.

Watanabe et al. [157] and Zhou et al. [158] has identified the location of 22 N-linked highly glycosylated sites where glycans are attached to the SARS-CoV-2 Spike glycoproteins and the types of sugar at each site. High mannose-type glycans were identified on the site N234 of the S glycoprotein of SARS-CoV-2, and Complex-type N-glycans and high mannose-type glycans were identified at the sites N165, N331, and N343 [155]. The SARS-CoV-2 Spike proteins are coated with sugars (glycans) [158]; neutralization of the sugar-coated Spike protein by using lectins, which behaves as sugar-binding proteins, can be a promising strategy for the COVID-19 therapeutics. For instance, the two mannose-specific mammalian lectins (Clec4g and CD209c) strongly bind to the N-glycan site N343 of the SARS-CoV-2 Spike protein, which can be visualized and quantified using atomic force microscopy [159].

Table 1
Source of plant lectins from reported *in-vivo*, *in-vitro* and *in-silico* antiviral medicinal plants available in Bangladesh.

Botanical name	Family	Used plant part	Lectin identification, isolation and purification (reference)	Specificity	Antiviral activity (reference)
Abelmoschus esculentus (L.) Moench	Malvaceae	Seed	[32]	Non-specified	Not reported
Abrus precatorius L.	Fabaceae	Seed	[33]	Galactose	Coronavirus[34]
Aegle marmelos (L.) Correa	Rutaceae	Fruit pulp	[35]	N-acetylgalactosamine, Mannose and sialic acid	Coxsackie viruses B1–B6, BmNPV[36,37]
Alisma plantago-aquatica var. *orientale* Sam.	Alismataceae	Rhizome	[38]	Non-specified	HBV, HSV-1[39,40]
Amaranthus viridis L.	Amaranthaceae	Seed	[41]	T-antigen and N-acetyl-D-lactosamine	Measles virus[42]
Areca catechu L.	Arecaceae	Nut	[43]	Non-specified	HIV-1, NDV[44,45]
Artocarpus heterophyllus Lam.	Moraceae	Seed	[46]	Galactose and N-acetylgalactosamine	HIV, HSV-2, CMV, HCV [47–49]
Bauhinia variegata L.	Fabaceae	Seed	[50]	Glucose/Galactose	Coxsackievirus B3, Rotavirus [51,52]
Benincasa hispida (Thunb.) Cogn.	Cucurbitaceae	Fruit	[53]	N-acetylglucosamine	Not reported
Butea monosperma (Lam.) Taub	Leguminosae	Seed	[54,55]	N-acetylgalactosamine, N-acetyl D-galactosamine, galactose and lactose	Unknown[56]
Cajanus cajan (L.) Millsp.	Fabaceae	Root	[57]	Mannose/glucose	Measles virus[58]
Cassia fistula L.	Fabaceae	Seed	[59]	Galactose	IBR[60]
Clitoria ternatea L.	Fabaceae	Seed	[61]	Galactose and N-acetylgalactosamine	MCV, HSV[62]
Coccinia indica Wight & Arn.	Cucurbitaceae	Fruit	[63]	Chito	HBV[64]
Corchorus olitorius L.	Tiliaceae	Leaf	[65]	Glucose/mannose, galactose	Measles virus[66]
Cucurbita maxima Duchesne	Cucurbitaceae	Seed kernels	[67]	Galactose	Not reported
Datura stramonium L.	Solanaceae	Seed	[68]	N-Acetylglucosamine	Potato virus X[69]
Erythrina variegata L.	Fabaceae	seed	[70,71]	Galactose, N-acetylgalactosamine	Not reported
Glycyrrhiza glabra L.	Fabaceae	Root	[72]	Non-specified	HAV, HBV, HCV, HIV, SARS-CoV[73,74]
Kaempferia rotunda L.	Zingiberaceae	Rhizome	[75]	Mannose	H5N1[76]
Kaempferia parviflora Wall. ex Baker	Zingiberaceae	Rhizome	[77]	Non-specified	HIV-1, HCV, HCMV[78]
Lathyrus sativus L.	Fabaceae	Seed	[79]	Mannose	Not reported
Litchi chinensis Sonn.	Sapindaceae	Seed	[80]	Glucose/mannose	HSV-1[81]
Mangifera indica L.	Anacardiaceae	Fruit seed	[82]	Non-specified	HSV, influenza virus[83,84]
Momordica charantia L	Cucurbitaceae	Seed	[85]	Galactose/ N-Acetylgalactosamine	HIV, HSV-1, H1N1, H3N2, H5N1[86–88]
Mucuna pruriens (L.) DC.	Fabaceae	Seed	[89]	Mannose	HCV[90]
Musa paradisiaca L.	Musaceae	Ripe fruit pulp	[91]	Mannose	HSV-1, HSV-2[91]
Oryza sativa L.	Poaceae	–	[82]	N-Acetylglucosamine	CMV, HSV[92,93]
Phaseolus vulgaris L.	Fabaceae	Seed	[94,95]	Galactose	HIV-1 RT[94,95]
Psidium guajava L.	Myrtaceae	Fruit	[96]	Galactose	H1N1[97]
Pisum sativum L.	Fabaceae	Seed	[82,98]	Mannose/galatose	HCV, ADV[98,99]
Pterocarpus indicus Willd	Fabaceae	Seed	[100]	Mannose/glucose	Dengue virus[101]
Senna tora (L.) Roxb.	Fabaceae	Seed	[102]	Mannose/Galactose	SARS-CoV 3CL protease[103]
Senna occidentalis (L.) Link	Fabaceae	Seed	[104]	Non-specified	BHV-1, SHV-1[105]
Sesbania bispinosa (Jacq.) W.Wight	Fabaceae	Stem	[106]	Glucose	Not reported
Solanum lycopersicum L.	Solanaceae	Fruit	[107]	N-acetylglucosamine	Not reported
Solanum melongena L.	Solanaceae	Fruit	[108]	Non-specified	HSV-1[109]
Tamarindus indica L.	Fabaceae	Seed	[110]	Mannose/maltose	NDV, mosaic viruses[111, 112]
Trichosanthes cucumerina L.	Cucurbitaceae	Seed	[113]	Galactose	Not reported
Trichosanthes dioica Roxb.	Cucurbitaceae	Seed	[114]	Galactose and N-acetylgalactosamine	Not reported
Urtica dioica L.	Urticaceae	Root	[115]	N-acetylglucosamine	SARS-CoV; HIV, CMV, RSV, H1N1[12,116,117]
Vigna mungo (L.) Hepper	Fabaceae	Seed	[118]	Galactose	Urdbean Leaf Crinkle Virus [119]
Vigna radiata (L.) R. Wilczek	Fabaceae	Seed	[120]	Galactose	Influenza A virus, HSV-1, RSV [121,122]
Vigna unguiculata (L.) Walp	Fabaceae	Seed	[123]	Non-specified	HIV[124]
Withania somnifera (L.) Dunal	Solanaceae	Leaf	[125]	Mannose	SARS-CoV-2, HIV, HSV, H1N1[126,127]

HSV= Herpes simplex virus; HAV= Hepatitis A virus; HBV= Hepatitis B virus; HCV= Hepatitis C virus; CMV= Cytomegalovirus; RSV= Respiratory Syncytial Virus; ADV= Adenoviruses; MCV= Molluscum contagiosum virus; BmNPV= Bombyx mori nucleopolyhedrovirus; IBR= Infectious Bovine Rhinotracheitis; HIV= Human immunodeficiency viruses; H1N1, H3N2, H5N1= Subtypes of Influenza A virus; NDV= Newcastle disease virus; BHV= Bovine herpesvirus-1; SHV= swine herpesvirus 1.

Table 2
List of some patented lectins that exhibited antiviral activity.

Name of lectin	Virus
Momordica balsamina lectin (MOMO30)	HIV-1
Mistletoe lectin I (ml-I)	HSV-1, Ad5
Singapore mistletoe lectin (SML)	DENV
Sambucus nigra agglutinin IV (SNA IV)	Influenza A
Sambucus nigra agglutinin V (SNA V)	Influenza A
Sambucus nigra protein derived from lectin (SNL RP	Influenza A
Vicia villosa agglutinin (VVA-G)	Influenza A
Wisteria floribunda lectin (WFL)	Influenza A
Aleuria aurantia lectin (AAL)	Influenza A
Aspergillus oryzae lectin (AOL)	Influenza A

HIV-1= human immunodeficiency virus 1; HSV-1= herpes simplex virus 1; Ad5= adenovirus 5; DENV= dengue virus.
Modified from Carneiro et al. [129].

Table 3
List of mannose specific antiviral lectins derived from marine algae.

Name of antiviral lectin	Algae source
Microvirin	*Microcystis aeruginosa* (Kützing) Lemmermann
Cyanovirin	*Nostoc ellipsosporum* Rabenhorst ex Bornet & Flahault
AML, BSL, HML, MEL, Sfl	*Amansia multifida* J.V.Lamouroux, *Bryothamnion seaforthii* (Turner) Kützing, *Hypnea musciformis* (Wulfen) Lamouroux, *Meristiella echinocarpa* (J.E. Areschoug) D.P.Cheney & P.W. Gabrielson and *Solieria filiformis* (Kützing) Gabrielson
ESA-2	*Eucheuma serra* (J.Agardh) J.Agardh
KAA-2	*Kappaphycus alvarezii* (Doty) Doty ex P.C.Silva
BCA	*Boodlea coacta* (Dicke) Murray and De Toni
HRL40	*Halimeda renschii* Hauck
MVL	*Microcystis viridis* (A.Braun) Lemmermann
Scytovirin	*Scytonema varium* Kützing ex Bornet & Flahault

Table 4
List of antiviral lectins derived from plant sources.

Name of lectin	Plant source	Specificity	Anti-viral activity
EAPL	*Phaseolus vulgaris* L.	Galactose	HIV-1
DBL	*Musa acuminata* L. (Del Monte banana)	Fructose	HIV-1
APA	*Allium ampeloprasum* L.	Mannose	SARS-CoV
SGBSL	*Glycine max* (L.) Merr.	Melibiose	HIV-1
PAL	*Pholiota adipose* (Batsch) P.Kumm. mushroom	Inulin	HIV-1
TDL	*Typhonium divaricatum* (L.) Decne	Mannose	HSV-2
CLL	*Crinum latifolium* L.	Mannose	Pox virus

High mannose-specific seaweed lectins have the ability to interfere both with the virus entry in the host cell and virus release from the host cell by targeting the Spike glycoprotein and heavily glycosylated ACE2 receptor [160]. ACE2 stands for Angiotensin converting enzyme 2, is expressed in human organs and play a chief role in the entry of SARS-CoV-2 [161] by binding of S1 subunit to ACE2 receptors [162] (see Fig. 2 as well) and the molecular mechanisms of SARS-CoV-2 binding to the ACE2 receptor has been discussed by Ramírez Hernández et al. [163].

An *in-vitro* study [153] showed that plasma-derived human mannose-binding lectin (pdMBL) selectively binds to SARS Spike (SARS-S) glycoprotein and can inhibit SARS-CoV infection in susceptible cell lines. This experiment has identified a single N- glycosylation site, N330, on S glycoprotein as the target for the specific interactions between pdMBL and SARS-CoV. Comparably, Mannose-binding plant lectins (MBPLs) can interfere during virus entry by binding to the high-mannose type N-glycans of SARS-CoV Spike (S) protein, and by blocking viral attachment to the host cell [116,164] wherein N-linked glycosylation plays a critical role in the specific interaction between the MBPLs and SARS-CoV Spike glycoprotein [165].

It is worth noting that the lower levels of serum mannose-binding lectin (sMBL) in human blood is associated with the occurrence of many infectious diseases including SARS, as MBL has a pivotal role in innate immune response [166,167]. Mannose-binding lectin deficiency (< 70 ng/ml) in serum has been reported in 25 patients with viral upper respiratory infections and in 13 patients with immunodeficiencies [168]. A case report study of a 2-times COVID-19 affected patient showed MBL deficiency (< 50 ng/ml), which indicated that patients with decreased levels of MBL may have greater risk of COVID-19 re-infection than the general people [169]. Serum MBL levels test in COVID-19 patients should be carried out (by using a sample of the patient's blood and Enzyme-linked immunosorbent assay) to avoid critical conditions and targeting the mannose-binding pathway (see Fig. 3) can be a potential treatment for COVID-19 as well for thrombosis in COVID-19 [170]. Changes in the MBL2 gene can lead to MBL (produced in the liver) deficiency that is very common in the general population and reduced MBL levels in blood serum (< 500 ng/ml) may be considered as susceptibility for recurrent infection including respiratory tract infections by pathogens as well as to inflammatory and autoimmune diseases [171].

A clinical investigation of 284 PCR-confirmed COVID-19 patients and 100 healthy controls revealed that mannose-binding lectin 2 (MBL2) gene B variant is common in patients with COVID-19 cases compared to the control group because MBL2 gene is related to lower levels of MBL [174]. Changes in mannose-binding lectin (MBL)- associated serine proteases, MASP-1 and/or MASP-2 levels have been related with COVID-19 risk factors such as sex, diabetes, kidney, cardiovascular, cerebrovascular, and chronic obstructive pulmonary disease (COPD), and association of MASPs and COVID-19 comorbidities has been demonstrated by Bumiller-Bini et al. [173]. Human coronaviruses SARS, MERS, and SARS-CoV-2-induced hyperactivation of MASP-2 aggravates lung injury, and this hyperactivation of MASP-2 is caused through a direct interaction between MASP-2 and coronavirus nucleocapsid protein [175].

Moreover, mannose-binding lectins induce complement cascade, which is a defense against invading pathogens in mucosal immunity [176] and trigger the production of pro-inflammatory cytokines [177]. The complement pathway in SARS-CoV-2 infection has been mentioned as having a "double-edged sword"; it can control mild or asymptomatic cases in COVID-19, but exacerbate local and systemic damage in severe COVID-19 [178]. Complement pathways in SARS-CoV-2 infection has been demonstrated by Bumiller-Bini et al. [173] and shown in Fig. 3.

However, in COVID-19 therapeutic strategy, the complement cascade pathway, particularly lectin pathway has received negligible attention [179] dues to the complex pattern of immune dysregulation in COVID-19 patients with acute respiratory failure [180]. Since serum MBL has a key role in innate immunity [181], and can inhibit SARS-CoV *in-vitro* [166] by preventing ACE2 binding with Spike glycoprotein and also enhances phagocytosis function as an opsonin [182], thus MBPLs may offer potent and alternative biotherapeutic and bioprophylactic strategy against SARS-CoV-2 infections. The following Fig. 4 demonstrates potential role of mannose-binding lectins in prevention of SARS-CoV-2.

2.3. Glycosylation for the SARS-CoV-2 antiviral therapeutics and vaccines design

Glycosylation is a ubiquitous post-translational modification of proteins that plays significant roles both in the virus life cycle for stability, antigenicity and infectivity, and in glycans of the host cell receptors for the attachment and entry of the virus [183]. N-glycosylation or N-acetylglucosamine (GlcNAc) and O-glycosylation or N-acetylgalactosamine (GalNAc) are mainly two types of glycosylation sites [183]. Lectins can be used as microarray for high-throughput glycosylation analysis that can aid to screen glycan patterns of therapeutic

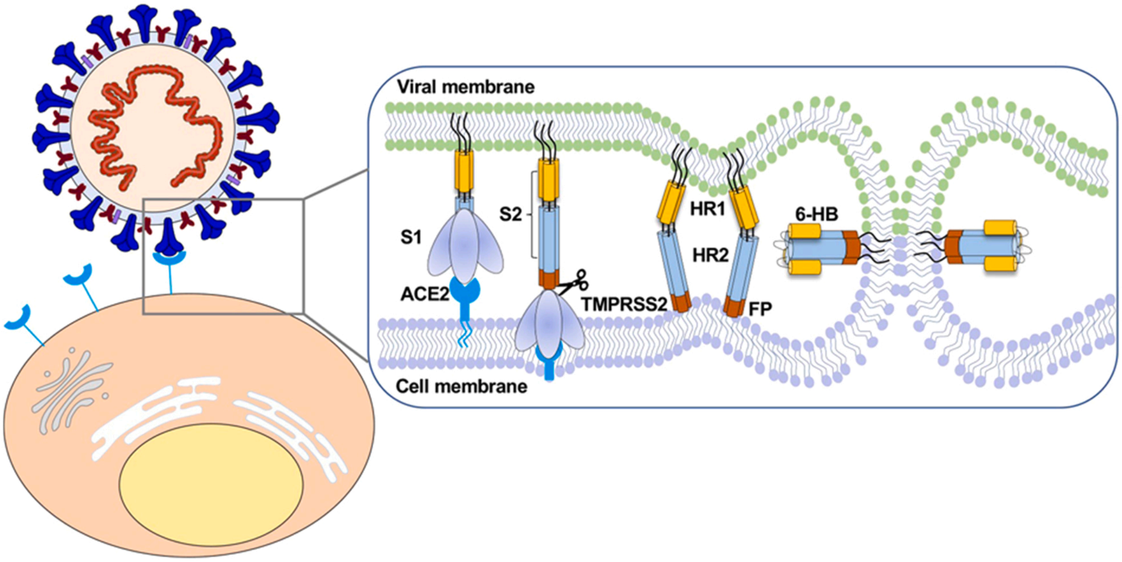

Fig. 2. "Diagram of SARS-CoV-2 entry into host cells. S protein binding to ACE2 receptor and virus attachment to the cell; S protein cleaved by TMPRSS2 produces S1 and S2 subunits. HR1 and HR2 of the S2 subunit gradually approach each other and form a six-helix bundle (6-HB), which causes the virus envelope and host cell membrane to complete fusion."
Adapted from Zhang et al. [156] with permission.

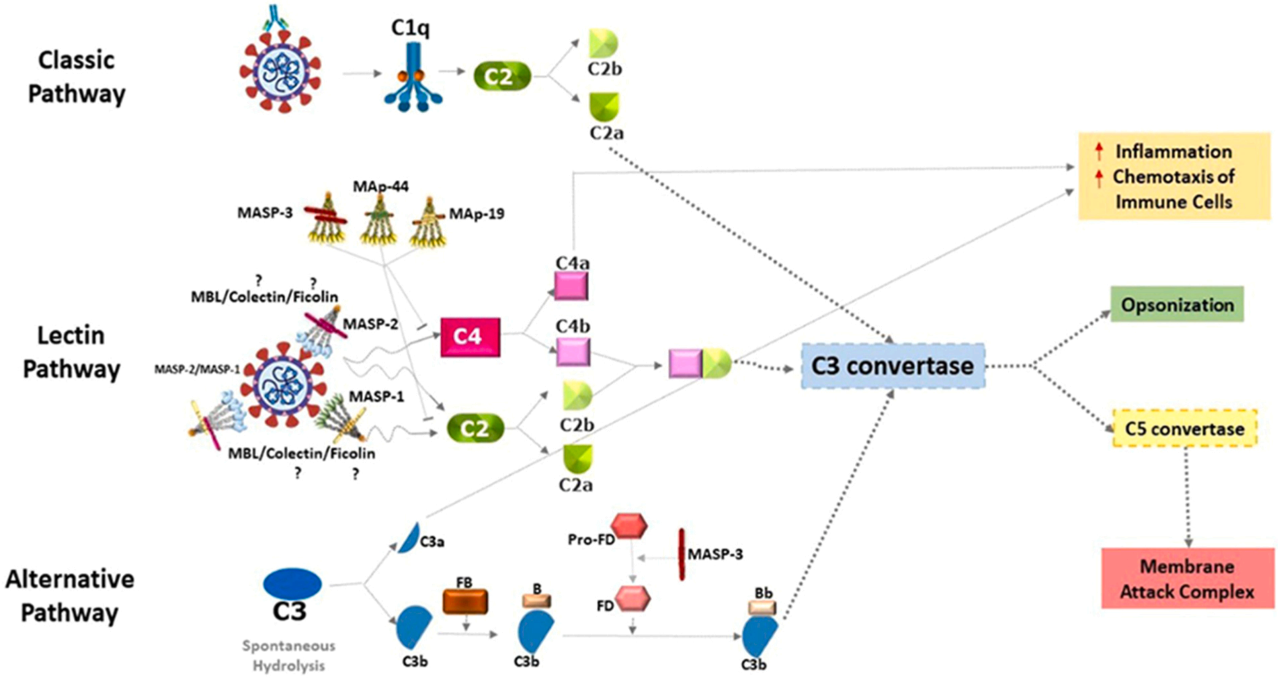

Fig. 3. "Complement pathways in SARS-CoV-2 infection. The activation of the classical pathway occurs through the C1 complex, after recognition of antibodies complexed to SARS-CoV-2. This leads to the cleavage of the C2 component into C2a and C2b. C2a joins the common pathway of the three complement pathways to form the C3 convertase. After binding of MBL/MASP complexes to the surface of pathogens, MASP-1 autoactivates, transactivates MASP-2, and C2 and C4 components are cleaved (C2 and C4 by MASP-2 and C2 by MASP-1), generating the C3 convertase. The alternative pathway is initiated by the spontaneous hydrolysis of component C3, generating C3a and C3b. C3b binds to factor B and is cleaved by factor D, forming the C3 convertase of the alternative pathway. After this step, the three pathways converge into a single pathway. The C3 convertase enzyme cleaves component C3 into C3a and C3b. C3a and C4a are anaphylatoxins that contribute to an increase in inflammatory processes and to the chemotaxis of neutrophils and macrophages (red arrows), while C3b performs viral opsonization. The formation of C5 convertase occurs in different ways through the three pathways, but all generate C5a and C5b. C5a is an anaphylatoxin (as also C3a) that contributes to inflammatory processes, and regulates innate and adaptive immune responses [172], while C5b joins the last C6-C9 components of the cascade and forms the membrane attack complex." (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Adapted from Bumiller-Bini et al. [173] with permission, and some modifications in the text body.

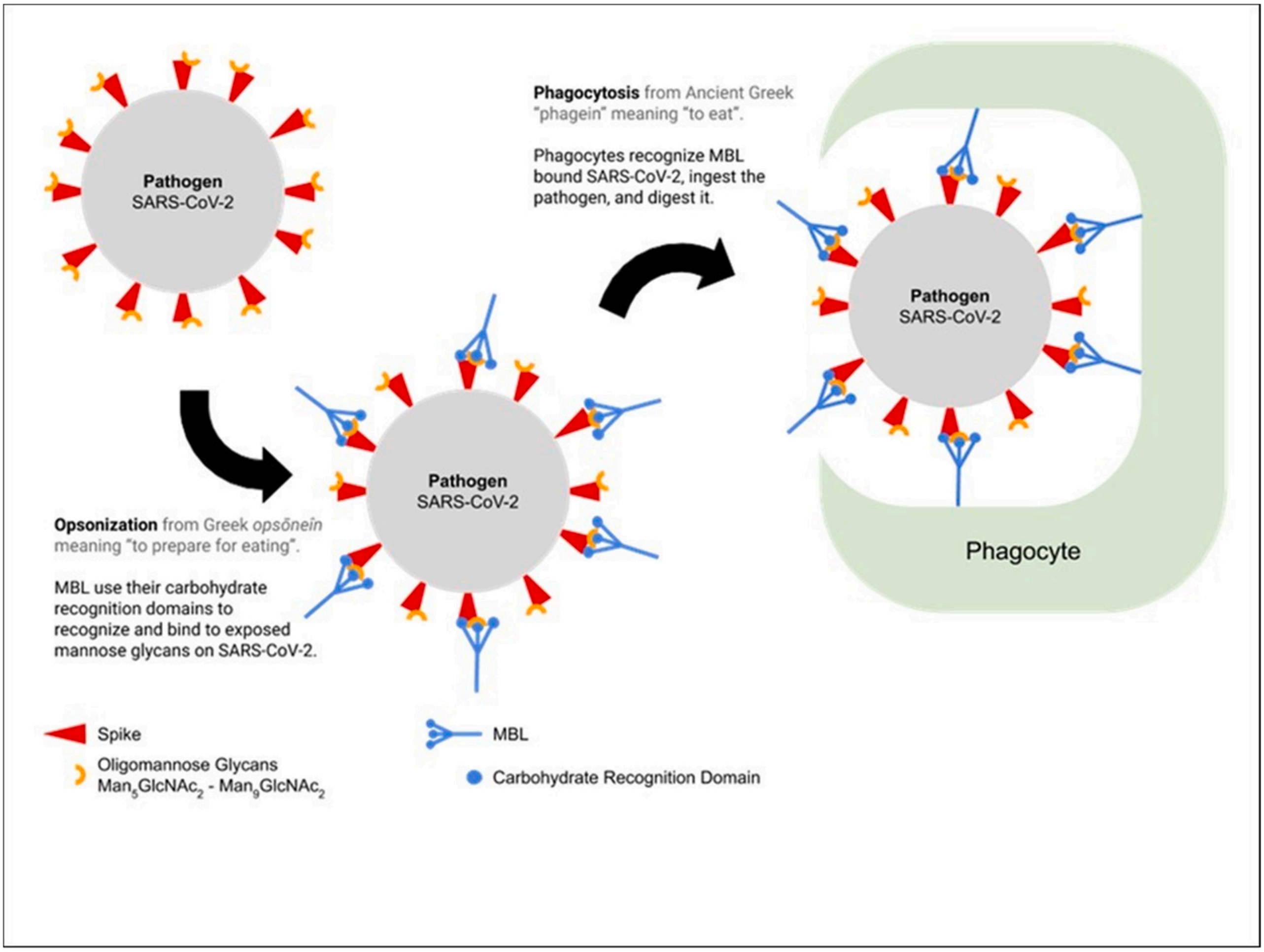

Fig. 4. "MBL binding and complement activation enhances phagocytosis by acting as an opsonin." Adapted from Lau [206] with permission.

glycoproteins [184,185]. Viral pathogens use glycans and lectins for the replication and spread, but recent advances in glycobiological research showed that specific glycan-lectin interactions on the basis of viral infectivity and antiviral immunity, can be useful in antiviral strategy [131].

Numerous studies have been performed on Lectins as antimicrobial agents and virucidal agents against several enveloped viruses [186] considering glycan-lectin interactions in antiviral strategies [131]. Besides the ones mentioned before, anti-viral lectins have been isolated from various plants like *Scilla campanulata*, *Narcissus pseudonarcissus*, *Galanthus nivalis*, *Polygonatum cyrtonema*, as reviewed by Mitchell et al. [12].

Lectins have been used in immunotherapeutic studies for potential prophylactic and therapeutic strategies against microbial infectious diseases, especially plant lectins [187,188]. Lectins from mushroom [189,190], and sea mussel [191] have also been demonstrated to exhibit immunomodulatory activities. Since lectins have exhibited immunomodulatory properties, they can also be used as vaccine bio-adjuvants to improve the efficacy of immunization [192], which has been demonstrated in the laboratory against enveloped viruses such as influenza, hepatitis, and herpes virus, for example see Table 5.

Lectins are potential biomolecules that can induce IL-12, IFN-γ, and T helper type 1 (Th1) protective immunity against viral infections and can also modulate the expression of toll-like receptors (TLRs) which initiate the early immune recognition of the pathogens and the release of proinflammatory cytokines [193]. Current reports strongly suggest that glycobiological and/or "glycovirological" contribution, particularly in glycan-lectin interactions can help for highly effective COVID-19 vaccines and drugs development [131,132] and focusing on glycosylation of Spike glycoprotein can be a novel strategy in the development of both anti-viral vaccine and anti-viral drugs designs against SARS-CoV-2 [157,183,194].

Table 5
Reported lectins used as adjuvants in the antiviral vaccine strategy.

Name of Lectin [source]	Specificity	Administration route in mice	Vaccine category against viruses
AAL [*Agrocybe aegerita* (V. Brig.) Singer]	N-acetylglucosamine	subcutaneous injection	Inactivated vaccine for H9N2 virus
POL [*Pleurotus ostreatus* (Jacq.) P. Kumm.]	N-acetylgalactosamine	Intramuscular injection	DNA vaccine for Hepatitis B virus
KML-C [*Viscum album coloratum* (Kom.) Nakai]	Galactose/N-acetylgalactosamine	Intranasal route	Inactivated vaccine for H1N1 virus
MLI, MLII, MLIII [*Viscum album* L.]	Galactose/N-acetylgalactosamine	Intranasal route	Subunit vaccine for Herpes simplex virus

Modified from Nascimento da Silva et al. [193].

3. Concluding remarks

The idea of Lectin-based specific drug delivery was first reported in 1988 *via* the use of tomato lectin (TL) to target the luminal surface of the small intestine [4]. The lectin-based drug targeting system can be attained *via* two mechanisms: (i) direct lectin targeting system, which includes carbohydrate molecules that are recognized by endogenous cell surface lectins, and (ii) reverse lectin targeting system, which include exogenous lectins that recognize synthesized carbohydrate molecules on glycolipids and glycoproteins [4,195–197]. Ribosome inactivating lectins (Ulex europaeus I and Wheat Germ Agglutinin) containing HIV peptides, hepatitis B surface antigen, TLR receptor were used as bioactive molecules for drug targeting as excipients in vaccine application [198]. Antiviral lectins are potential microbicide molecules for their exhibition of lower toxicity than any other currently used antiviral therapeutics, best for topical applications, odorless, resistant to low pH and high temperatures [143]. Furthermore, rigorous characterization and identification of glycosylation motifs in viral glycoproteins are essential to the design of vaccines and anti-viral drugs [199].

COVID-19 is an infectious disease caused by the zoonotic virus SARS-CoV-2, which has created catastrophe among *Homo sapiens* worldwide. Scientists and health experts are still working to find out effective therapeutics and vaccines that can eradicate COVID-19. To date, there are six WHO-recognized experimental vaccines available but their efficacy is still under consideration due to continuous SARS-CoV-2 mutations and wane of immunity over time. Bangladesh has also joined the global COVID-19 vaccine race with developing an mRNA-based vaccine candidate [200] with hopes for human trials in November 2021 after completion of successful clinical trials that is happening on non-human primates and monkeys [201].

Numerous attempts have been made with the hope of glycan-based effective antiviral molecules for preventing 2019-nCoV infections. According to our information obtained from established databases, mannose-binding lectins (MBL) have been found to be highly effective against coronaviruses, and mannose-binding plant lectins should have significance for its potent antiviral properties particularly against SARS-CoV-2 as MBL has properties of anti-infectivity, immunoadjuvant, DC-SIGN antagonist, or glycomimetic approach, and specially MBL induces complement cascade pathway, which is a first-line host defense, but MBL has been given limited attention in the COVID-19 biotherapeutic and bioprophylactic strategy. Moreover, decreased levels of serum MBL is a susceptible factor for severe COVID-19 infections and MBL levels in COVID-19 patients should be diagnosed to avoid greater risk of re-infection and disease severity.

Nonetheless, researchers are working hard on plant-based COVID-19 vaccine development *via* glycoengineering technology and plant-based vaccines have low cost production, rapidity, scalability, and safety [202]. The pharmacological properties and stability, solubility, bioavailability, pharmacokinetics, and immunogenicity of glycosylated biotherapeutics can be determined by the glyco-biotechnological approach, which can propel scientific research to the development of the next generation of biotherapeutics and glycoengineered vaccines [203]. In addition, antiviral lectins for COVID-19 may suffer from low sale production, high cost purification and manufacturing process that can be resolved by the applications of plant biotechnology, as for example molecular farming or transient expression of Griffithsin and Cyanovirin-N in plants [204] as well as Griffithsin (GRFT) in engineered *Escherichia coli* [205].

To be a consideration, “glycovirology” is an emerging discipline covering both glycobiology and virology, and Bangladesh is a resource of anti-viral medicinal plants with lectins. Altogether, deeper insights into “glycovirological” aspects, antiviral lectins, and glyco-biotechnology may lead to developing highly effective next-generation antiviral biotherapeutic and bioprophylactic against the 21st century’s biological pandemic of SARS-CoV-2 causing COVID-19 and quite possibly other new emerging viruses.

4. Methodological approach in literature search

The authors have performed translating mind derived research questions to keywords in pursuit of specific evidence-based literature to accumulate further information on antiviral lectins against COVID-19. The literature search was performed in PubMed, Google Scholar, Google Search databases by randomly using below keywords: (lectins and coronavirus; lectins and SARS-CoV; medicinal plants and antiviral activity; antiviral plan lectins; molecular mechanisms of actions of antiviral lectins; bioactive compounds and SARS-coronavirus; glycans-lectin interactions for antiviral therapy; glycan and lectins interplay; classifications of lectins; *etc.*).

The articles were screened and included for this review are proof of concept studies that paid attention to the involvement of inhibitory activity of lectins against SARS-CoV, the antiviral mechanisms of actions of lectins, and studies related to antiviral plant lectins. Furthermore, we also focused on all the relevant articles that were investigated lectins for the antiviral activity. Finally, this review deals with the literature discussion on the potential role of glycosylation for the designing of biotherapeutics and vaccines against SARS-CoV-2.

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CRediT authorship contribution statement

Md. Nasir Ahmed: Conceptualization, Visualization, Writing – original draft. **Rownak Jahan:** Validation, Writing – review & editing. **Veeranoot Nissapatorn:** Writing – review & editing. **Polrat Wilairatana:** Funding acquisition. **Mohammed Rahmatullah:** Supervision, Validation, Writing – review & editing.

Conflict of interest statement

The authors declare have no conflict of interest.

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