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Review

Plant lectins as potent Anti-coronaviruses, Anti-inflammatory, antinociceptive and antiulcer agents

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ABSTRACT

Lectins are defined as carbohydrate-binding proteins/glycoproteins of none immune origin, they are ubiquitous in nature, exist from bacteria to human cells. And due to their carbohydrate-binding recognition capacity, they have been a useful biological tool for the purification of glycoproteins and their subsequent characterization. Some plant lectins have also been revealed to own antinociceptive, antiulcer, and anti-inflammatory properties, where these features, in many instances, depending on the lectin carbohydrate-binding site. Coronavirus disease of 2019 (COVID-19) is a respiratory disease that struck the entire world leaving millions of people dead and more infected. Although COVID-19 vaccines have been made available, and quite a large number of world populations have already been immunized, the viral infection rates remained in acceleration, which continues to provoke major concern about the vaccines' efficacy. The belief in the ineffectiveness of the vaccine has been attributed in part to the recurrent mutations that occur in the epitope determinant fragments of the virus. Coronavirus envelope surface is extensively glycosylated being covered by more than sixty *N*-linked oligomannose, composite, and hybrid glycans with a core of Man3GlcNAc2Asn. In addition some *O*–linked glycans are also detected. Of these glyco-chains, many have also been exposed to several mutations, and a few remained conserved. Therefore, numerous plant lectins with a specificity directed towards these viral envelope sugars have been found to interact preferentially with them and are suggested to be scrutinized as a possible future tool to combat coronaviruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through blocking the viral attachment to the host cells. In this review, we will discuss the possible applications of plant lectins as anti-coronaviruses including SARS-CoV-2, antinociceptive, anti-inflammatory, and antiulcer agents with the proposed mechanism of their actions.

Contents

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1. Introduction

Cell surface glycoconjugates coat play a crucial role in several biological paths, such as cell–cell adhesion, inflammatory relocation, host-pathogen interactions, immune response initiation, and cancer metastasis ((Colgan et al. 1995; Gorelik et al. 2001; Hevey 2019; Nardy et al. 2016), and references therein). These processes are collectively mediated through carbohydrate-binding proteins that span the surface of the opposing cells (Brandley and Schnaar 1986).

Since ancient times, and to date plant parts such as leaves, barks, seeds, and roots have been used by human communities in the prevention and treatment of diseases, and for healthcare (Jones et al. 2018). In Africa and Asia over 90% of folk medicine protocols are comprised of plants, and the majority of these remedies are used by villagers or nomads who are often delocalized, and away from governmental medical facilities access. These plant products have been routinely used for treatments of various ailments such as infectious diseases caused by bacteria, fungi, and viruses, as well as non-communicable diseases including heart disease, cancer, diabetes, chronic lung conditions, etc. (Sofowora et al. 2013). It is generally thought that the presently in-use analgesia-inducing medications such as opioids and Non-steroidal anti-inflammatory drugs (NSAIDs) are not suitable for many patients due to their side effects and low efficiency (Ahmadiani et al. 1998). Consequently, the search for new drugs becomes necessary.

The fortuitous discovery made by the German doctoral student Peter Hermann Stillmark in 1888 that the castor bean (*Ricinus communis*) extract can agglutinate erythrocytes, a mechanism confirmed later to occur through erythrocytes' surface glycoconjugates, had signified the milestone for our existing understanding of plant carbohydrate-binding protein in particular, and its animal/microbial counterparts in general (Sharon and Lis 2004). These glycan interacting proteins were then termed lectin, "Legere" in Latin which means to choose or pick up. In subsequent years research has confirmed the presence of such proteins not merely in plant and animal cells but also in bacteria, viruses, yeast, and parasites where they could facilitate the attachment processes of these microbes to the glycoproteins and glycolipids, and permeate the host cell surface (Sharon and Lis 1997). By their feature or capacity of being able to interact with glycans, these proteins have been defined as any multivalent protein/glycoprotein that possesses at least a single non-catalytic domain that could interact reversibly with sugars or carbohydrates and thereby causes agglutination of the cells (Goldstein et al. 1980). Owing to their being furnished with such unique carbohydrate-binding site(s) lectins are assigned to perform many biological functions such as endocytosis, act as intracellular transport vehicles for glycoproteins, and regulate the protein content in the blood ((Dias et al. 2015) and the references cited therein). Nevertheless, animal lectin was discovered before plant lectin in 1872 but they were not recognized as glycan-binding protein (Kilpatrick 2002). Although animal and plant lectins share no apparent primary structure resemblances, they share the aptitude to interact and recognize specific glycan receptors emphasizing the role of these proteins in molecular recognition (Reyes-Montaño and Vega-Castro 2018). Animal and microbial lectins are found in comparatively lesser amounts as compared to the plant lectins, the latter being detected almost in every part of the plant; seeds, leaves, bark, stem, flower, roots, etc (Mishra et al. 2019). Although not all plants contain lectins, however, when present they may account for up to 10–12% of the total seeds soluble protein (Roopashree et al. 2006; Sathe and Deshpande 2003). The abundance of plant lectin (Spilatro et al. 1996), their ease to isolate (Mishra et al. 2019), and the accelerated advancement in preparation of affinity chromatographies that facilitated the purification of plant lectin in a single or two steps (Freeze 1995; O'Connor et al. 2017), have assisted in performing deep studies to solve their structures' ambiguity, possible biological effects, and clinical applications. While many plant lectins are sharing primary and secondary structures, they exhibit different biological effects which are probably ascribed to their varying glycan recognition specificities. Moreover, scientific proofs that present some plant lectins with antinociceptive, anti-inflammatory, antioxidant, and gastroprotective properties are also accumulating. While others are recognized to inhibit many microbes like viruses, parasites, nematodes, and bacteria (Breitenbach Barroso Coelho et al. 2018; Gaofu et al. 2008; Lusvarghi and Bewley 2016; Pinto et al. 2019; Vanderlei et al. 2010). Coronavirus is the main causative of COVID-19 the acute respiratory syndrome which originates from Wuhan China and caused an outbreak worldwide leaving million dead and infected (Hu et al. 2021). Many vaccines have been manufactured and approved worldwide to curb the disease's rapid mortality and morbidity rates. However, due to the accelerated frequencies of the virus spike protein mutations, the efficacy of these vaccines becomes questionable (Baraniuk 2021; Hayawi et al. 2021; Khan et al. 2021). However, the fact that the various *N*-linked glycosylation points of coronavirus-2 protein, which play a major role in the viral virulence are largely conserved, opened widely the window for the conceivable use of carbohydrate-binding agents such as lectins for targeting this virus' glycans, and thereby interfering with its initial binding stage to the host cell surface receptors (Ahmed et al. 2022; Barre et al. 2021; Martinez et al. 2021). In this review, we aim to discuss, in-depth, the potential applications of plant lectins to combat coronavirus diseases as well as their uses as, antiulcer, anti-inflammatory, and antinociceptive agents.

2. The spike protein (S) glycosylation

The coronavirus comprises four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Spike protein (S) is the main structural protein antigen of SARS-CoV-2, which mediates the fusion of the coronaviruses into susceptible human cells through their interactions with the angiotensin-converting enzyme- 2 (ACE-2) receptor (Hsieh et al. 2005). However, unlike other SARS-CoV-2 viral proteins, it is accountable for triggering the host immune response, and the antibodies directed towards the S protein can bring about protective immunity against subsequent infections (Boechat et al. 2021). The S protein (180–200 kDa) is a homotrimer of two subunits S1 and S2, linked through a membrane-embedded serine 2 protease. S1 contains the receptor-binding site, while S 2 is devoted to the viral fusion of the host cells. Structural investigations of the S protein by cryo-EM and mass spectrometry revealed that S protein to be extensively glycosylated with as many as 66 *N*-glycosylation points (22 per monomer), covering the surface of the protein and assisting partly in mediating the virulence of the pathogen, and

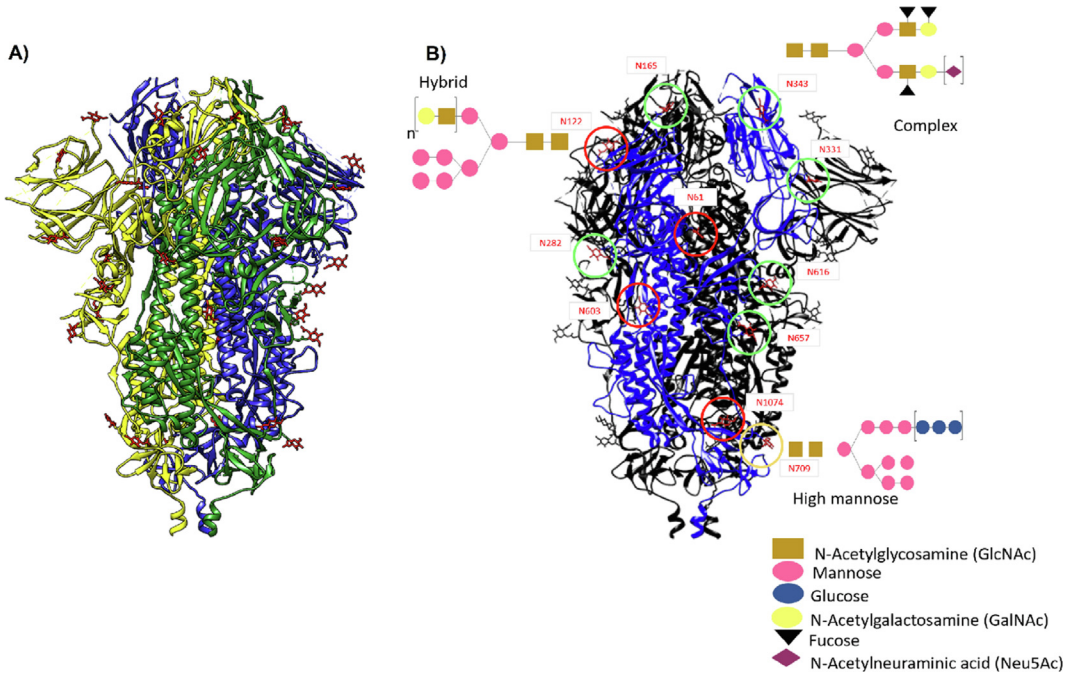

Fig. 1. Structural presentation of SARS-CoV-2 spike protein (S) (PDB ID: 6VXX). A) The homotrimer structure of the S-protein showing the *N*-glycans (Presented in red). B) The monomer of the S-protein A chain is highlighted in blue, of the 22 *N*-glycans, 11 were presented in 3 different types (hybrid, complex, and high mannose glycans), *O*-glycans are not shown. The 3D structures were visualized and edited using UCSF-Chimera 1.8v software.

at the same time shielding the susceptible viral receptor-binding domain (RBD) against the neutralizing human antibodies (Huang et al. 2021; Shajahan et al. 2021) Fig. 1. Of distinct interest, the glycosylation points as N165 and N234 (mannose-rich glycans) are located at the vicinity of the ACE-2 RBD, they have been revealed by all-atom molecular dynamic simulation (MD) to play a role in the ACE2-S protein interaction. Point mutation of N165A and N234A, which resulted in glycosylation depletion at these sites, reduced effectively the receptor-glycan interaction, though didn't utterly nullify it. These results underlined the possible importance

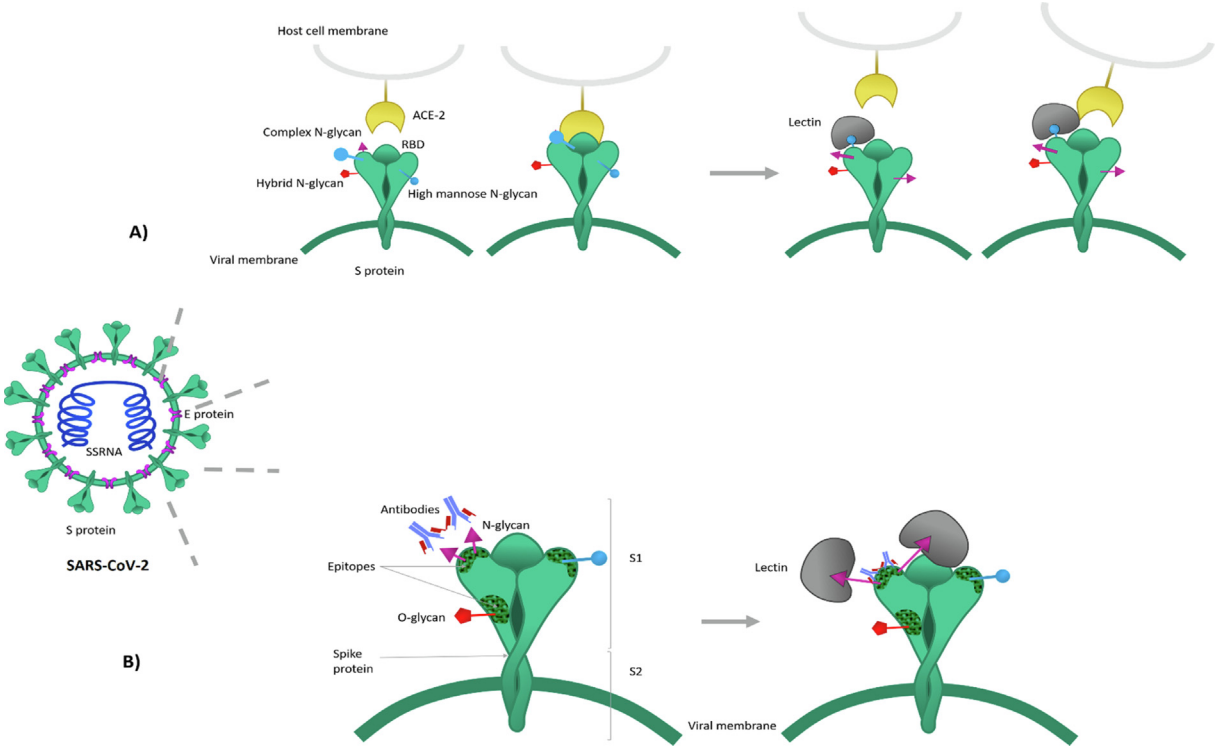

Fig. 2. Lectins assumed mechanism of action against SARS-CoV-2. A) ACE-2 recognition of by the viral S-protein and interference of plant lectin. B) Action of plant lectin on exposing of the virus epitope determinant site. The Virus *N*-glycan shield the virus epitope determinant and prevent the antibodies recognition. Upon lectin binding, conformational changes occur and lead to exposing the epitope site.

of these glycosylation points in suitably orienting the conformation of the receptor-binding domain of the virus ((Zhao et al. 2021) and references cited therein). Through using different expression vectors, several workers have reported recurrent mutations at *N*-glycans (Shajahan et al. 2021). Nonetheless, 19 glycosylation sites were proven to remain conserved. *O*-glycosylation has also been shown to occur, however, to a limited extent (Hayawi et al. 2021). Expression of SARS-CoV-2 genome on human cell line HEK-293 offered varied complex glycosylation patterns, habitually of the mannose-rich type glycan.

2.1. The use of lectins to target SARS-CoV spike glycoprotein

In the search for appropriate and effective treatment for SARS-CoV-2 infection, drug repurposing has already been underway. Inclusion of the antimalarial drugs such as chloroquine and hydroxychloroquine in COVID-19 treatment protocol has made a considerable debate before they were withdrawn after proven futile (Altulea et al. 2021; Ferner and Aronson 2020). Anticancer drugs have also been proposed to be promising against viral replication however, higher toxicity described with the administration of such drugs is criticized (El Bairi et al. 2020). As stated the heavily glycosylated SARS-CoV-2 S protein surface made it a tempting choice for glycan-binding proteins (lectins) especially those of plausible interaction with these glycans. It is largely believed that they will likely hinder the attachment of the virus to the host cells by inducing a conformational change that would favour uncovering the epitope recognition site of the virus, thereby neutralizing the virulence effect by the triggered immune response (Fig. 2). At the vicinity to the RBD of the spike protein, the presence of two glycosylation sequences N165 and N234 which mainly comprised of Man3 GlcNAc core could represent an excellent target for plant lectins with complex-type biantennary oligo-mannosyl saccharides. Almost four decades ago, Greig and Bouillant had revealed extensive binding of Concanavalin A (ConA); the lectin from the *Canavalia ensiformis* to encephalomyelitis virus, a Coronavirus. Removal of the viral surface glycans by snake venom phospholipase A abolished ConA-virus interactions, emphasizing the importance of the sugar chains in the viral attachment process (Greig and Bouillant 1977).

On the other hand, *Urtica dioica* agglutinin (UDA); the lectin purified from the Nettle (*Urtica dioica* L.), is a small 8.7 kDa protein with a specificity directed towards N, N′, N″- tri-acetylchitotriose (polymer of acetylated acetylglucosamines). This peptide lectin besides its sugar-binding site also had a hydrophobic binding region adjacent to its carbohydrate-binding site (Shibuya et al. 1986). It inhibits the SARS-CoV replication cycle by interfering with the viral attachment to the host cell probably through binding to spike protein *N*-acetylglucosamine (GlcNAc) units (Kumaki et al. 2011; Saul et al. 2000). Investigating the effect of the mannose-binding lectin *griffithsin* against MERS-CoV infection revealed that *griffithsin* even though displaying no apparent cytotoxicity, offered a strong inhibitory effect on MERS-CoV infection through binding to the mannose-rich viral spike protein (Millet et al. 2016). The same lectin, in several other publications, was demonstrated to exhibit a broad antiviral spectrum. HIV-1 *N*-linked glycosylation sites on the gp-120 were affirmed to be recognized by *griffithsin*, the binding of lectin would lead to a change in the structure of gp-120, which would result in exposing the virus CD4 binding site (Alexandre et al. 2011; Fischer et al. 2019). Similar results were obtained for banana (*Musa acuminata*) lectin which could inhibit HIV-1 by recognizing the mannose-rich gp-120 viral outer layer glycoprotein in a range of picomole quantities, hence interfering with the viral adherence to the human cell (Swanson et al. 2010). Testing a collection of 33 plant lectins with different specificities indicated that the strongest antiviral activity was principally confined among lectins with mannose-binding specificity (Keyaerts et al. 2007). Using *Vero B4* cells, the Wheat Germ Agglutinin (WGA) purified from *Triticum vulgaris* exhibited antiviral activity not only against the initially emerged SARS-CoV-2, but also its recent major two variants *Alpha* and *Beta* were found effective with IC_{50} of < 10 ng/mL at both the pre-incubation period with the virus or during the viral infection. Interestingly, this lectin had a narrow specificity that was merely directed towards coronaviruses as it had no effect with other non-coronaviruses causing respiratory tract distresses (Auth et al. 2021). In a very recent publication, Barre and his colleagues studied the viral envelope shielding glycans of several viruses like Ebola, herpes simplex, human cytomegalovirus, human immunodeficiency, influenza, chikungunya, Lassa, MERS-CoV, SARS-CoV, SARS-CoV-2, and Zika, which exhibited high coat glycans heterogeneities. Based on that they have suggested some homodimeric mannose-specific legume lectins with a high affinity for α1,6-fucosylated Man3 3GlcNAc2 core. They have concluded that lectins from *Pisum sativum, Lens culinaris, Lathyrus ochrus, Canavalia ensiformis, Pterocarpus angolensis,* and *Vicia faba* could be classified to offer the best SARS-CoV-2 spike envelope binding capacity (Barre et al. 2021; Garcia-Pino et al. 2007). However, since these lectins merely bind to the mannose-rich glycan receptors on the viral envelope surface and don't interfere with the inside viral genome, they did not consider them as coronavirus replication inhibitors, but from a future perspective point of view, could be used in preventing the viral attachment to the host cells and therefore block the initial stages in the virulence processes. Table 1 shows different plant/algal lectins with reported antiviral activity including the recent publications concerning SARS-CoV-2.

3. Plant lectins as antinocieptive and anti-inflammatory agaents

Apart from the booming development that has arisen in recent years accompanied by studious progress in pharmaceutical biotechnology and the development of drugs manufacturing, the need for effective and powerful analgesics is in continuous demand (Khan et al. 2020). A great number of currently prescribed drugs were initially extracted from medicinal plants like morphine, thebaine, and the recently isolated and commercialized serratiopeptidase (Bhagat et al. 2013; Jehan et al. 2017). Local communities from different countries, especially in Africa and Asia are customed to practice the use of several plants parts for pain relief and reducing inflammation. It was estimated that 65% and 90% of Indian and Sudanese populations depend on traditional medicine for their healthcare, respectively (Karar and Kuhnert 2017; Prashantkumar and Vidyasagar 2008). Clove (*Syzygium aromaticum)* buds are routinely used by natives to relieve toothache, treating experimental animals with clove aqueous extract is reported to significantly increase the latency period upon thermal stimuli (hotplate test), confirming the analgesics property of the plant (Kamkar Asl et al. 2013). The aromatic herb peppermint leaves are used on daily basis to soothe an upset stomach (Uritu et al. 2018). Examining the anti-inflammatory and antinociceptive properties of mint oil extracted from three species *Mentha piperita* L. var. *pallescens*, *Mentha spicata* L. subsp. *Crispata,* and *Mentha suaveolens* Ehrh resulted in a significant pain reduction (Mogosan et al. 2017). While many plant crude aqueous extracts have been tested for their antinociceptive properties and gave a positive significant outcome, very few publications were devoted to isolating the active ingredient responsible for such effect. To evaluate lectin anti-nociceptive properties in mice or rat models, variable methods such as abdominal writhing, formalin and the hotplate tests are largely accepted. Whereas the anti-inflammatory reactions are often assessed by

Table 1
Plant /algal lectins with antiviral activities.

Plant/algae Latin name	Family	Plant part	subunit / Mr	Specificity	Virus inhibited	References
Grateloupia chiangii	Halymeniaceae	Whole	Monomer/25 kDa	Mannose	Influenza virus, HIV type 1, and herpes	(Hwang et al. 2020)
Pandanus amaryllifolius Roxb.	Pandanaceae	Leaf	Monomer/8kDa	Mannose	Herpes simplex virus type-1, influenza virus, N1H1	(Ooi et al. 2004)
Phaseolus vulgaris L.	Fabaceae	Seed	Homodimer/ 30 kDa	Complex	HIV-1	(Sharma et al. 2009)
Capparis spinosa L.	Capparaceae	Seed	Homodimer/ 31 kDa	Raffinose, lactose, rhamnose and galactose	HIV-1	(Lam et al. 2009)
Lablab purpureus (L.) Sweet	Fabaceae	Seed	Pentamer (varying associations) / 67 kDa	glucose/mannose	Influenza, SARS-CoV-2	(Liu et al. 2020; Mo et al. 1999)
Polygonatum odoratum (Mill.) Druce	Asparagales	Rhizome	Homotetramer/ 12 kDa	mannose	Herpes Simplex Virus	(Yang et al. 2011)
Clematis montana Buch.-Ham. ex DC.	Ranunculaceae	Stem	Homodimer/ 12 kDa	Complex of mannose units glycans	HIV, HIV-1, HIV-2, Influenza A H1N1, Influenza A H3N2, Influenza B, Para-influenza-3 and virus reovirus-1	(Peng et al. 2009)
Myrianthus holstii Engl.	Urticaceae	Stem, Root	Monomer/9kDa	*N*-acetylglucosamine	HIV-1RF	(Charan et al. 2000)
Musa acuminata Colla *	Musaceae	Fruit	Homodimer/ 13 kDa		MERS-CoV, SARS-CoV-2 including variants Alpha and Beta	(David et al. 2022; Koshte et al. 1990)
Lens culinaris Medik.	Fabaceae	Seed	Heterodimer/17 & 4 kDa	oligomannose-type glycans and GlcNAc	SARS-COV-2 variants	(Chan et al. 2015; Wang et al. 2021)
Triticum aestivum L.	Pooideae	Seed	Monomer/23 kDa	*N*-acetyl-D-glucosamine	SARS-CoV-2 including variants Alpha and Beta	(Auth et al. 2021; LeVine et al. 1972)
Maackia amurensis Rupr.	Fabaceae	Seed	Heterodimer/32 & 37 kDa	Sialic acid	SARS-CoV-2	(Sheehan et al. 2020; Van Damme et al. 1997)
Urtica dioica	Urticaceae	Rhizomes	Monomer /8.5 KDa	*N*-acetylglucosamine	HIV-1	(Gordts et al. 2015)
Nicotiana tabacum	Solanaceae	Leaf	Monomer/19 KDa	*N*-acetylglucosamine	HIV-1	(Gordts et al. 2015)
Galanthus nivalis	Amaryllidaceae	Bulb	Tetramer (13 KDa/monomer)	Mannose-specififc	HIV-1, HIV-2	(Balzarini et al. 2004)
Hippeastrum hybrid	Amaryllidaceae	Bulb	Homomtetramer /14 KDa/monomer	Mannose-specific	HIV-1, HIV-2	(Balzarini et al. 2004)
Tamaridus insica	Fabaceae	seed	Monomer / 34 kDa	*N*-acetyl glucosamine	Chikungunya virus	(Kaur et al. 2019)

* Genetically engineered lectin with preserved antiviral activity however with a reduced mitogenic capacity (Swanson et al. 2010).

challenging animals with carrageenan, dextran or serotonin to induce paw oedema. Neutrophils and leukocytes' migration to the peritoneal cavity is followed to confirm the lectin anti-inflammatory action (Nunes et al. 2009). An affinity-purified galactose-specific lectin isolated from the leaves of *Bauhinia monandra* exhibited antinociceptive and anti-inflammatory in a dose-dependent manner when mice were challenged with 1% carrageenan-induced inflammation and 0.8% acetic acid-induced abdominal writhing. At a concentration of 60 mg lectin/kg mice, there was a 60% inflammation reduction. Whereas 71.3% agony reduction was recorded in the case of acetic acid pain induction. The authors concluded their results by attributing the routine use of this plant in traditional medicine as an anti-inflammatory and analgesic agent to the presence of lectin in this plant (Campos et al. 2016). A heterodimer lectin-like protein with an ambiguous sugar specificity purified from the seeds of *Clitoria fairchildiana* displayed no apparent toxicity to human RBCs, owned an anti-inflammatory activity of 64% attenuation in the mice paws oedema caused by administration of carrageenan. Moreover, the lectin was successful in inhibiting neutrophils migration. This lectin had also shown a 72% diminution in the mice's abdominal writhing when the pain is induced by acetic acid and therefore is considered to possess both anti-inflammatory and antinociceptive characteristics (Leite et al. 2012). Several algal lectins were also characterized by their analgesic and sometimes anti-inflammatory properties such as *Caulerpa cupressoides* lectin, this protein could decrease the effect of the writhing induced by acetic acid to up to 86%, however, it was not being able to produce significant antinociceptive effects in the hot plate experiment, indicating the sole involvement of the peripheral rather than central acting mechanism (Vanderlei et al. 2010). The antinociceptive properties of lectins have been, in many instances, attributed to the probable inhibition of inflammation producing molecules such as bradykinin, prostaglandins, substance P, and some cytokines, such as IL-1β and TNFα which will lead to activation of chemosensitive nociceptors and hence induction of pain (Vanderlei et al. 2010). Similar observations were also noticed with the marine red algae *Pterocladiella capillacea* lectin (Silva et al 2010). The writhing effect induced by acetic acid was significantly reduced when *Amansia multifida* Lamouroux lectin was administered along with the glycoprotein avidin at 1 mg/kg. The authors ascribed the occurred attenuation in the antinociceptive property to the blockage of the lectin's active site by the inhibitory glycoprotein avidin, therefore concluding the involvement of the lectin sugar-binding site in

Table 2
Plant lectins with reported anti-inflammatory and antinociceptive activities.

Source	Plant/algae Latin name	Family	Plant part	Subunit / Mr	Sugar specificity	Activity	References
	Andira anthelmia	Fabaceae	seed	Heterotrimer 20, 17, 15, 13 kDa	Mannose	Anti-inflammatory	(Do Nascimento et al. 2021)
	Bauhinia monandra	Fabaceae	leaves	Monomer 33 kDa	Galactose	Anti-inflammatory and antinociceptive	(Coelho et al., 2000; Campos et al.,2016)
PLant Lectins	*Dioclea guianensis* Benth.	Fabaceae	Seed	Two isolectins of 47 and 100 kDa, Heterotridimers 12,18 & 30 kDa	Mannose/glucose	Anti-inflammatory	(Assreuy et al. 1997; Vasconcelos IM et al. 1991)
	Dioclea grandiflora Benth.	Fabaceae	Seed	Three isolectins 25–26 kDa 13–14 kDa 8–9 kDa	Mannose/glucose	Anti-inflammatory	(Assreuy et al. 1997; Moreira et al. 1983)
	Dioclea violacea Benth.	Fabaceae	Seed	Heterotrimer 11.7, 15.8 and 29.5 kDa	Mannose/glucose	Anti-inflammatory & Antinociceptive	(Assreuy et al. 1997; Holanda et al. 2009; Renato et al. 1996)
	Dioclea virgata (Rich.) Amshoff	Fabaceae	Seed	Heterotrimer 30.9, 16.2 & 12 kDa	Mannose/glucose	Anti-inflammatory	(Assreuy et al. 1997; Márcio et al. 1996)
	Clitoria fairchildiana	Fabaceae	Seeds	Heterodimer 100, 116 kDa	Unspecific to known sugars and glyconjugates	Anti-inflammatory /antinociceptive	(Leite et al. 2012)
	Cratylia floribunda Benth.	Fabaceae	Seed	Heterotrimers 29–30 kDa 16–18 kDa 12–13 kDa	Mannose/glucose	Anti-inflammatory	(Assreuy et al. 1997; Oliveira et al. 1991)
	Canna limbata	Cannaceae	Seed	Homodimer of 21 kDa	*N*-acetylglucosamine	Anti-inflammatory Antinociceptive	(Araújo et al. 2013)
	Parkia biglobosa (Jacq.) G.Don	Fabaceae	Seed	Homodimer 46 kDa	Mannose/glucose	Anti-inflammatory Antinociceptive	(Silva et al. 2013)
	Parkia playcephala	Fabaceae	seed	Monomer 48 kDa	Mannose/glucose	Antinociceptive	(De Oliveira Leite et al. 2020)
	Praecitrullus fistulosus	Cucurbitaceae	Phloem exudates	Semi-Purified	ND	Anti-inflammatory	(Madhu and sharada 2019)
	Crataeva tapia L.	Capparaceae	Bark	Heterodimer 21 and 40 kDa	Mannose/glucose	Anti-inflammatory Antinociceptive	(Araújo et al. 2011; Araújo et al. 2012)
	Lonchocarpus campestris Mart. ex Benth.	Fabaceae	Seed	Two Isolectins 10 & 25 kDa	Mannose	Anti-inflammatory Antinociceptive	(De Freitas Pires et al. 2019)
	Machaerium acutifolium Vogel	Fabaceae	Seed	Heterotrimer 29, 13, & 8 kDa	Mannose/ *N*-acetyl-glucosamine	Antinociceptive	(Santos et al. 2019)
	Microgranna vacciniifolia	Polypodiaceae	Rhizome	Monomer 54 kDa	Glucose	Anti-inflammatory Antinociceptive	(Cavalcante da Silva et al. 2021)
	Mucuna pruriens	Fabaceae	Seeds	Monomer 60 kDa	Complex specificity	Anti-inflammatory Antinociceptive	(Lacerda et al. 2015)
	Tetracarpidium conophorum	Euphorbiaceae	seeds	Heterodimer 17 and 34 kDa	Lactose/galactose	Anti-inflammatory Anti-inflammatory and Antinociceptive	(Oladokun et al. , 2019)
	Schinus terebinthifolia	Anacardiaceae	Leaf	Monomer 12.4–14 kDa kDa	Chitin	Anti-inflammatory and Antinociceptive	(Gomes et al., 2013; De-souza et al. 2019; Ramos et al. 2020)
	Luetzelburgia auriculata	Fabacaea	seeds	Homotetramer 123.5 kDa	*N*-acetyl-D-galactosamine	Anti-inflammatory	(Oliveira et al., 2002; Alencar et al., 2010)
	Synadenium carinatum	Euphorbiaceae	Latex	Heterodimer 28 and 30 kDa	Galactose	Anti-inflammatory	(Rogerio et al. 2007)
Algal Lectins	*Bryothamnion triquetrum*	Alsidieae	Whole	Monomer 9 kDa	Mucin	Anti-inflammatory	(Fontenelle et al. 2018)
	Solieria filiformis	Solieriaceae	Whole	Monomer 28 kDa	Complex glycan	Anti-inflammatory	(Abreu et al. 2016)

Table 2 (*continued*)

Source	Plant/algae Latin name	Family	Plant part	Subunit / Mr	Sugar specificity	Activity	References
	Caulerpa cupressoides	Caulerpaceae	Whole	Homodimer 23 kDa	Lactose	Antinociceptive Anti-inflammatory Antinociceptive	(Vanderlei et al. 2010)
	Hypnea cervicornis	Gigartinaceae	Whole	Heterodimer 9.1, 9.9 kDa	Complex glycan	Anti-inflammatory Antinociceptive	(Bitencourt Fda et al. 2008)

ND: No information available.

the obtained analgesic effect (Neves et al. 2007). To examine the involvement of the opioid system, the analgesic morphine was used, and to block the thermal stimuli, the morphine antagonist naloxone was administered which resulted in complete reserve of the morphine effect indicating the involvement of the opioid receptor in the pain sensation (Neves et al. 2007). The red seaweed *Bryothamnion triquetrum* lectin was found potent at 10 mg/kg in inhibiting paw oedema induced by both carrageenan and dextran. This anti-inflammatory response was linked by inhibiting the neutrophil migration towards the peritoneal fluid (Fontenelle et al. 2018). A mannose-specific lectin isolated from the seeds of *Andira anthelmia* expressed a potent antinociceptive property; it inhibited mice writhings caused by parenteral administration of 0.7% acetic acid by about 68% in as low as 10 μg/kg dose, this effect was neutralized in presence of mannose (Nascimento et al. 2016). To wrap up, many legume lectins discussed in this review were proven to attenuate the inflammatory response including the lectin isolated from *Canavalia boliviana* seeds in a reaction mediated by the lectin binding site (Figueiredo et al. 2009), however, astonishingly, *Canavalia virosa* seed lectin which was purified by affinity interaction to Sephadex®-G50 (polymer of glucose units), was rather found to trigger inflammation when injected subcutaneously into mice paw. The noticed paw oedema produced by lectin administration was dramatically reverted when the lectin was initially incubated with its haptenic sugar glucose, indicating the role of sugar affinity site in the observed inflammatory reaction (Osterne et al. 2017). Another interesting work on *Lonchocarpus araripensis* seed lectin published by a Brazilian group, where the *N*-acetyl-D-glucosamine (GlcNAc) specific lectin demonstrated antinociceptive effect through a unique mechanism involving the nitric oxide pathway, additionally the same protein was also characterized by GlcNAc specific anti-inflammatory property, inhibiting the neutrophil migration to the intraperitoneal cavity of the experimental animal. The administration of the anti-steroidal drug niflumic acid, instead of initiating an analgesic effect, aggravates the pain sensation. Since this drug is used as a calcium-activated chloride channel blocker, the involvement of the calcium channel, in this case, as a first-ever report, is apparent (Assreuy et al. 2020; De Freitas Pires et al. 2019). Similarly, the pretreatment of the animal with Cannabinoid receptor 1 (CB-1) and receptor 2 (CB-2) antagonist AM251 and AM630 respectively overturned the antinociceptive effect of *Lonchocarpus araripensis* seed lectin, emphasizing the contribution of endocannabinoid receptor (Amorim et al. 2021). Table 2 presents to date literature compilation of plant lectins with both antinociceptive and anti-inflammatory effects. Mechanistically, plant lectins can exert their anti-inflammatory response by interfering with the pro-inflammatory cascade in either of two different ways. They can inhibit vascular inflammation mediated through competitive binding of lectin with the glycosylation molecules found at the surface of the white blood cells, thus preventing them from interacting with selectin molecules and inducing cell transmigration to the site of inflammation. Or by inhibiting the cytokines and chemokines production related to white blood cells migration (Alencar et al. 1999; Jandúet al. 2017).

4. Plant lectins as antiulcer

An ulcer is defined as a pain that originates from damage that occurs in the internal coating of the stomach or small intestine, when the problem is associated with stomach mucosal lesions it is termed gastric ulcer which is caused by acid secretion or pepsin (Sverdén et al. 2019). In Nigeria, natives routinely use *Carica papaya* seeds flour for the treatment of peptic ulcers, whereas in Sudan *Acacia Senegal* and *Aerva javanica* are known for their healing effect of peptic ulcers (Karar and Kuhnert 2017). In the exper-

imental models, many gastric-lesion inducers have been employed such as ethanol, Indomethacin and Aspirin. A homotetrameric galactose-binding lectin purified from *Artocarpus incise* conventionally named *frutalin* was successful in providing considerable protection against both ethanol and indomethacin gastric injury in mice, however in a dose-unrelated manner where a lectin at a concentration as low as 500 μg/kg was able to produce potent protection. Yet, the pre-treatment with the α2- receptor antagonist Yohimbine didn't revert or attenuate *frutalin* protection against ethanol lesions which indicated no involvement of α2-receptor in the caused action of the lectin. Simultaneously administration of glibenclamide, a K_{+ATP} channel inhibitor, resulted in a partial however significant reduction of the action *frutalin,* demonstrating the influence of K_{+ATP} channel in shielding the stomach lining against the external mucosal attacker (De Vasconcellos Abdon et al. 2012). A rabbit erythrocytes specific seeds lectin purified from the Brazilian plant *Mucuna pruriens* (L.) DC (MpLec), was also examined for its protective effect against ethanol-induced gastro-damage in mice. The lectin was able to provide a significant reduction in stomach lesions in comparison to control, however, pre-treatment with Yohimbine abolished the MpLec protective effect, which emphasize the role of α2 adrenoceptors in the attained defensive mechanism (Pinto et al. 2019). Another interesting highly stable GlcNAc specific seeds lectin, which agglutinates only the human A-blood group was capable of reducing the ethanol damage by up to 63%. The lectin was administered at three different doses 10, 100 and 1000 μg/kg, even though all of them lead to a significant outcome, major protection was offered by the 1000 μg/kg dose.

5. Conclusion

The information on the great potency of plant lectins on microorganisms such as bacteria, viruses, parasites, and fungi as well as their reported action as antioxidants, antinociceptive, antitumors and antiulcer have been accumulating. And due to their peculiar sugar recognition site that compliments in minute details with the acknowledged tumor cellular glycan changes, clinical trials on their possible application as a drug shuttle for cancer treatment are underway (Wijetunge et al. 2018; Wode et al. 2020). Some of their unfavourable characteristics such as large molecular weight which will likely induce immunogenicity and toxicity may limit the widespread use of these interesting proteins in drug applications. Therefore the suggestion of the implementation of small molecular weight lectins is promising and may pave the way to overcome the immunogenic hurdle. While there is still much to be investigated and disclosed about the *in-vivo* and *in-vitro* triggered biological effects of plant lectins, the currently ongoing research on genetically engineered lectins with reduced undesired activity without resulting in major structural alterations may retain hope in future applications of plant lectin in drug synthesis and applications. Additionally, our laboratory's ongoing research activities on many lectins from tropical medicinal plants with extreme thermal and chemical stability hold significant probabilities of thrilling discoveries shortly.

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