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Leveraging Lucrative Lectins: An Explorative Review of the Biomedical Properties of Lectins

Preetha Nair[1], Saranya Jayaram[2]

[1]HOD & Associate Professor, Department of Biotechnology, Mount Carmel College, Autonomous, Bengaluru, Karnataka, India
[2]Assistant Professor, Department of Biotechnology, Mount Carmel College, Autonomous, Bengaluru, Karnataka, India

Abstract
Nature is a bountiful supplier of resources for all living beings. Moreover, nature has also been the recourse for numerous global problems including disorders and ailments. Natural product chemistry is the most sought-after field, probing into biological and industrial applications of different natural compounds isolated from sources like plants and microorganisms. Lectins, dating way back as to almost 130 years ago, have had a long standing in history in lieu of their numerous biomedical benefits. Marking the modern age of lectins in 1972, 'lectinology' came to be known as a potential field of research probing into various medical properties of lectins from different plants. These proteins display a plethora of benefits including wound-healing, anticoagulating, anti-nociceptive, antimicrobial, antiviral and immunomodulatory properties. The present review explores these lucrative properties of lectins and also discusses the current status of lectin-based antiviral therapeutics that hold immense potential for effective treatment of fastidious pathogens.

Keywords: Natural product chemistry, Lectins, Lectinology, Anti-nociceptive, Antiviral, Immunomodulatory.

1. Introduction

Over a century ago, dating back to almost 130 years back in history, Peter Hermann Stillmark initiated the first study of lectins in 1888 with the finding that Castor bean (*Ricinus communis*) seed extracts had the potential to agglutinate red blood cells [1]. Subsequently, the isolated lectin was given the name Ricin. Later, the United States and British military used ricin as potential weaponry during the World Wars I and II [2]. The purification of lectins from various plant sources marked the modern age of lectinology in 1972 [3] with rich sources of lectins being identified to be different parts of medicinal parts like their seeds, leaves, stems, tubers and roots [4].

Lectins belong to a diverse group of natural proteins that specifically and reversibly bind to carbohydrates like mono and oligosaccharides. These proteins contain two or more carbohydrate-binding sites and target the sugar complexes of glycoproteins. Lectins possess the property of agglutinating erythrocytes without altering the properties of the bound carbohydrates. Based on their binding specificities, lectins are classified as glucose/ mannose, L-fucose, galactose, N-acetylglucosamine, N-acetyl-D-galactosamine and sialic acids. Additionally, based on the number of binding sites, lectins are grouped as merolectins, chimerolectins, hololectins and superlectins [5].

The therapeutic applications of lectins are wide ranging, with novel advances in elucidating their *in vitro and in vivo* anti-viral applications. Lectins have highly potent anti-viral properties that can even target enveloped viruses having glycosylated envelop proteins [6]. Thus, lectins have been found to inhibit viral entry and production of viral proteins, thereby curtailing viral replication through their interaction with viral envelop proteins. Various studies have reported the *in vitro* anti-viral properties of lectin against coronaviruses and HIV [7]. Alongside therapeutic applications, lectins have also been widely employed as glycol-analytical biosensors as diagnostic tools for the detection of viral pathogens and infectious agents [8]. Examples of these include Concanavalin A (ConA) lectin that recognizes structural glycoproteins of arboviruses [9] and peanut lectin (PNA), *Dolichos biflorus* lectin (DBA), soybean lectin (SBA), *Helix pomatia* lectin (HPA) and *Ulex europaeus* lectin (UEA-1) that detect hepatitis-A virus (HAV) [10]. Plant lectins were reported for their anti-viral properties first in 1988 through the discovery that D-mannose-specific plant lectins blocked the *in vitro* binding of HIV [11]. The regulation of virus recognition and entry is controlled by a set of viral proteins called the glycosylated envelope proteins (GEP) which exert affinity towards host-cell surface proteins. Upon glycosylation, GEP (which comprises of transmembrane trimer, extracellular trimer, gp31 and gp120) undergo transformational changes that assist the viral entry and invasion into host cells that is further mediated by recognition of CD4+ cells. Antiviral lectins react with high-mannose glycan to bring about glycosylation of viral GEP and subsequently inhibit the structural reorganization of these GEP that results in the inhibition of viral entry into host cells [12]. The potential anti-HIV targets are considered to be few of the specific carbohydrate-binding lectins that block the host-viral interactions and inhibit viral entry into host cells [7]. Various studies have reported significant antiviral properties of lectins, namely leguminous lectins from *Dioclea lasiocarpa* (DLasiL) and *D. sclerocarpa* (DSclerL), *Canavalia/ brasiliensis* (ConBr) and *C. maritima* (ConM); and algal lectins from *Hypnea musciformis* (HML), *Amansia multifidi* (AML), *Solieria filiformis* (SfL), *Bryothamniom seaforthii* (BSL) and *Meristiella echinocarpa* (MEL) that have been found to be potent anti-viral agents against 18 different viruses including HIV and influenza virus [13].

Lectins isolated from banana have been proposed to possess antiviral properties due to their ability to bind to different types of glycans composed of high-density glycoproteins that are found on the surfaces of different viruses. In the case of influenza virus, lectins have been found to bind to hemagglutinin (HA) and neuraminidase (A), the key viral glycoproteins of influenza virus. Due to this interaction, lectins inhibit the replication cycle, release and aggregation of influenza virus that are brought about by the binding of these viral particles to sialic acid containing host cell receptors and endosomal membranes. On the downside, lectin induced inhibition of influenza virus has been proven to display certain inflammatory side-effects. These problems have been attempted to be circumvented by engineered banana lectins developed by the incorporation of single amino acid mutation from histidine 84 to threonine 84, namely H84T BanLec. Studies have reported this engineered banana lectin H84T BanLec to be highly effective against avian influenza virus *in vitro* and against pandemic, epidemic and fatal viral influenza virus *in* vivo when administered intranasally [14]. Furthermore, different reports have displayed the potential of mannose specific lectins to bind to corona virus in cases of severe acute respiratory syndromes thereby bringing about inhibition of viral attachment to host cells and subsequent development of viral life cycle [15]. Fructose binding lectins have been also extensively studied and have been suggested in anti-HIV formulations owing to their capability to inhibit the activity of HIV-1 RTase alongside inducing the expression of cytokine IFN-gamma [16]. The promising results of anti-

viral properties of lectins against influenza viruses are now propelling further in-depth studies of utilizing these beneficial carbohydrate-binding proteins to combat COVI-19. Recent applications involve nanotechnology-based approaches to utilize lectins in targeting various viruses. Beneficial features of nanotechnology comprise of targeted delivery, enhanced biosorption, better water solubility, greater bioavailability and improved bioactivity of drug compounds when formulated through nano-delivery systems. Different types of nanocarrier systems have been designed and tested for optimized delivery of drug compounds. Few prominent examples of these include nanogels, nanofibers, nanosuspensions, liposomes, nano-emulsions and nano-dimensional lipid transporters. Recent reports have demonstrated the use of nano carrier systems produced using gold nanoparticles that have been employed to trap lectins like BanLec [17], ricin B [18] and concanavalin A/ ConA [19]. Other studies have synthesized functionalized gold nanoparticles (generated from chicken egg white proteins) encapsulated within ovalbumin with their surfaces enriched with Galβ (1 → 4) GluNAc and hybrid mannose. These were used to specifically bind to different types of lectins like BanLec ricin B and ConA and the results revealed that this nanoparticle carrier system enabled selective release of lectins at the targeted sites [20].

2. Biomedical Properties of Lectins

Natural product chemistry has harnessed relatively more exclusive research attention in comparison to that gained by their chemical counterparts. This can be attributed to the multitude of advantageous properties of naturally derived drug compounds, like decreased or nil toxicity/ side-effects, enhanced bioavailability/ biosorption, efficacious bioactivity and specificity. Lectins belong to one such group of naturally occurring compounds that harbor a wide range of beneficial and biotechnological properties. These molecules are multidomain proteins that are non-immunogenic in origin but are capable of binding non-covalently and reversibly to specific sugars present individually or in groups as seen in glycoproteins and glycolipids. Lectins specifically bind to carbohydrates containing moieties by virtue of a carbohydrate binding domain, that is a specific polypeptide domain present in their structure. Hence, lectins are a means of attachment for different types of cells to other cells through the carbohydrate binding domain.

Present widely in plants, lectins also occur naturally in various species like bacteria, algae, protozoa, lichens and fungi and exert different biological roles. These ubiquitous proteins have the ability to interact with glycans on the cell surfaces thus aiding in agglutination of different cell types. This property of lectins has been exploited in biotechnological applications such as glycoconjugate-based cell physiology and pathology [21], in bio-flocculation, as drug targeting agents and probiotics [22]. Various types of lectins isolated from *Bauhinia* genus plants from the family Leguminosae have been reported to possess medicinal properties like antitumor, use as hemagglutination and chemotaxonomic markers. Plant lectins have been noted to elicit either pro- or anti-edematogenic processes in rats [23]. Presenting itself as one of the rare lectins due to its anticoagulant activity, studies on *Bauhinia forficata* Lectin (BFL) have reported this type of lectin to exhibit the property of prolonging coagulation time in *in vitro* tests that used agonists inducing platelet aggregation like epinephrine and ADP. This anticoagulant activity of BFL has been found to be independent of its sugar-binding property [24]. Lectins are also extensively used as anticancer agents and cancer detection tools due to their property to detect variations in the glycosylation profiles of cancer cells, which is usually one of the characteristic traits of tumor cells. They are also employed in drug delivery systems as recognition agents that lead the nanostructures

carrying the drug compounds specifically towards the cancer cells through lectin-based detection of the altered glycosylation patterns of the target cancer cells. Reports have displayed BFL toxicity towards MCF7 breast cancer cells *in vitro*. Growth inhibition of these cancer cells was found to be mediated through cell-cycle arrest in the G2/M phase caused due to inhibition of caspase-9 and fragmentation of DNA. Additionally, it was also found that BFL led to reduced adhesion of MCF7 cells to extracellular matrix compounds that are involved in the cancer pathways [25].

Contributing further to the field of therapeutics, lectins are also being utilized for their hemagglutination properties. Fungal species are among the major sources of lectins that have unique and novel biotechnological applications. About 80% of the fungal lectins are extracted from mushrooms [26] including edible mushrooms [27] and agglutinins have been isolated from Australian [28], Japanese [29] and South-East Asian mushrooms [30] apart from British higher fungi [31]. Agglutination assays using enzyme-treated or native erythrocytes are generally used to detect the agglutination property of lectins. Using these tests, the agglutination property of various mushroom lectins has been widely reported. Few reports have demonstrated a preferential hemagglutination property of mushroom lectins over animal erythrocytes as compared to the human erythrocytes [32]. Mushroom lectins also find numerous other therapeutic applications such as antiproliferative, antioxidant, antimicrobial and immune-stimulating agents. These lectins specifically identify the altered glycans on cancer cells and thus facilitate the detection of tumor cells [33]. Mushroom lectins have also been reported to display antiproliferative effects against HT29 human colon cancer cells that comprise of elevated amounts of GlcNAc residues and facilitate tumor cells death through inhibition of cell proliferation through arrest of cell cycle [34-36]. Thus, mushroom lectins act as markers to identify these elevated amounts of GlcNAc residues thereby helping detect and differentiate tumor cells from normal cells. Another mushroom lectin namely *Agrocybe aegerita* lectin (AAL and AAL2) also has been found to exhibit anticancer activity against human cancer cell lines like breast, sarcoma, colon, gastric, sarcoma and hepatoma [37]. AAL has been found to bind enhanced levels of hyaluronan present in the stroma of 4T1 breast cancer cells, thus specifically targeting these tumor cells and inducing caspase-3/7-dependant apoptosis of these tumor cells *in vitro* [38]. Advanced technologies have further improved this detection tool by designing recombinant AAL comprising of altered fucose binding ability that has a potential to be used as an oncofetal marker for liver cells [39]. Thus, mushroom lectins are now being widely used as promising tools for the detection of tumor cells and as potential anticancer agents.

Adding further to the plethora of therapeutic properties elicited by mushroom lectins, mitogenic activity is another prominent property displayed by lectins isolated from various mushrooms, which has been noted since historic studies. The specific-binding of mushroom lectins to cell-surface specific glycans induces various membranous changes that trigger intracellular cascades leading to cellular mitotic division [40]. This hence leads to cellular transformation from inactive to active state of proliferation and mitosis. These activation patterns have been extensively studied and few of them have been reported to have been brought about by different pathways associated with calcium-calcineurin-nuclear factor of activated T-cells [41] or with activation of InSP3 ionsitol receptors [42]. At very low concentrations such as 0.01µg/mL, bolesatine, a mushroom lectin extracted from *Boletus satanus* has shown to exhibit remarkable mitogenic activity towards human lymphocytes [43]. Similarly, very low concentrations of mushroom lectins extracted from *Lentinus edodes* [44], *Volvariella volvacea* [45] and *Flammulina velutipes* [46] have been demonstrated to evoke mitogenicity in murine splenocytes.

Applications of lectins in wound healing are yet another group of well-documented applications of these compounds. Different studies have reported an accelerated process of wound healing by topical application of lectins on the site of injured tissues. Native and recombinant *Bauhinia variegate* lectins (BVL) have demonstrated wound healing properties upon topical application on mice with surgically induced wounds. Based on the analyses of wound size, histology and epithelialization, the accelerated rate of wound healing brought about by BVL was noted to be around 7 days post the operative procedure of wound induction in these mice [47]. Hence, this property of lectins are promising traits that are being explored for extended applications of lectins in designing drugs for faster scar and wound healing.

2.1. Immunomodulatory properties of lectins

Owing to the wide range of properties exhibited by lectins, they are touted to be the quintessential proteins that have the property to interact with a wide range of cellular surface glycoproteins and other signaling molecules, thereby playing a crucial role in different types of cell-signaling pathways.

Studies have reported the anti-inflammatory effects of *Bauhinia bauhinioides* lectins (BBL) in carrageenan-induced edema formation in rats through their ability to compromise neutrophil rolling and adhesion that further decreases the rate of release of primary cytokines like TNF-α and IL-1β [48]. Additionally, *Bauhinia monandra* leaf lectin (BmolL) was also reported to reduce inflammatory response in rats [49].

Mushroom lectins have also been widely studied for their therapeutic applications. Through their specific identification and interaction with altered glycans on cancer cells, these lectins bind to tumor cells and induce immunomodulatory activities that further inhibit cellular process leading to tumor cell death. Few of the mushroom lectins have also been identified to exhibit immunomodulatory effects by their ability to stimulate proliferation of macrophages, lymphocytes and monocytes in mouse spleen [50]. They have also been known to inhibit allergic reactions by augmenting the T-helper-1 (Th1) cell mediated cytokine production. Recent studies have shown that fungal lectins isolated from *Latiporus sulphureus* interact with toll-like-receptor-4 to stimulate macrophages to produce cytokines, nitric oxide and tumor necrosis factor–α [51]. While nitric oxide helps in defense against pathogenic microorganisms [52], TNF–α plays a crucial role in cell proliferation, differentiation, inflammation and apoptosis [53]. Mushroom lectins are known to be involved in regulating the immune response mainly through the macrophages [51], which are the foremost immune cells that also phagocytose distorted cells upon external stimuli like infections, inflammations and tumors [52]. Macrophages get activated through several signaling pathways that get triggered after mushroom lectins bind to cellular glycoprotein-based receptors [54]. This is succeeded by the production of nitric oxide, interleukin factors, nitric oxide synthase and tumor necrosis factor–α [40]. Cytokine production in various cells like basophils, eosinophils, neutrophils and monocytes/ macrophages help in regulating the immune cells and response. To cite a few, studies have reported that lectins isolated from *Agaricus bisporus* exhibited inhibitory effects against macrophages. Furthermore, this fungal lectin binds to the o-glycans (containing T-antigen and sialyl-T-antigen) present on the surface of macrophages leading to the obstruction of the Akt signaling pathway and production of cytokines and nitric oxide [55].

Lectins have also gained popularity for being utilized as tools in therapeutics and for understanding the routes involved in pathways related to inflammation. Various *in vitro* reports have demonstrated the potential of *Bauhinia forficata* lectins (BFL) to delay coagulation time by regulating the intrinsic coagulation cascade through mechanisms independent of its sugar-binding property [24]. In the field of

therapeutics, lectins are of great utility for the diagnosis and treatment of cancer. Altered glycation profiles of cancer cells being one of the hallmarks of carcinogenesis, helps utilize lectins to specifically detect and therapeutically target tumor cells. BFL has been proven to display *in vitro* toxic effects against MCF-7 breast cancer cell line through the induction of DNA fragmentation and inhibition of caspase-9 thereby causing a cell-cycle arrest in the G2/M stage [25]. Furthermore, using recombinant DNA technology, BFL has been subjected to different types of gene editing techniques to produce recombinant forms of BFL that have the property to cause cytotoxicity towards different types of human cancer cell lines like NCI-60 [56], A549, RXF393, OVCAR-8 and T-47D [25].

2.2. Anti-nociceptive properties of lectins

Different lectins have continually displayed wide ranging therapeutic applications, with one of their interesting applications being that of anti-nociceptive agents. Lectins isolated from red algae *Amansia multifidi* namely LEC have been reported to naturally display potent central and peripheral anti-nociceptive properties [57]. Another such lectin, namely *Pterocladiella capillacea* lectin (PcL) also has been reported to exhibit peripheral action having anti-nociceptive properties [58]. Another red algal based lectin called *Hypnea cervicornis* agglutinin (HCA) has also been reported to exhibit anti-hypernociceptive properties when administered in rats by inhibiting neutrophil migration and increasing the production of nitric oxide [59].

2.3. Antimicrobial properties of lectins

Gram positive bacteria contain murein (N-acetylmuramic acid and N-acetyl-glucosamine residues), teichoic acids and other surface glycoproteins that are specifically recognized by lectins [60]. Studies have shown potent antibacterial activity of lectin extracted from *Gymnopilus spectabilis* against gran positive pathogenic bacteria like *Staphylococcus aureus*. Another such lectin from *Sparassis latifolia* has demonstrated broad spectrum antibacterial properties. The specific binding of these lectins with the glycoproteins and lipopolysaccharides on the surface of the bacterial cell walls facilitates their antibacterial activity [61].

Plant lectins are extensively utilized as antibacterial agents not only due to their growth-inhibiting properties towards bacteria, but also through their property of reducing the colonization of bacterial populations. This feature is exhibited by lectins by targeting and impeding biofilm formation, cell adhesion and colonial agglomeration of bacterial cells. Hence, by utilizing this feature of lectins, novel therapeutics have been popularly designed to cater to the production of plant lectin based antibiofilm forming drugs that are widely used especially in the prevention of dental carries caused due to biofilm formed by oral bacteria on the surface of the teeth [62]. Reports have demonstrated the ability of BVL to inhibit bacterial biofilm formation of human indigenous mucosal flora *Streptococcus mutans* and *sanguis* [63] that are also known to cause dental carries during. Upon further studies it was understood that these lectins exhibited their anti-biofilm forming capabilities by binding to and deactivating the bacterial cell surface glycoproteins that are primarily involved in the bacterial adsorption to the surface of biofilm and other cells [64].

Mushroom lectins have been identified to display antifungal activities like that reported by *Aleuria aurantia* lectin that inhibits *Mucor racemosus* by binding to L-fucose present on its cell wall [65]. Few other such reports include crude lectin extracts of *Gymnopilus spectabilis* and *Schizophyllum commune* displaying significant antifungal activity against *Aspergillus niger* [66-67]. The antifungal property of

these lectins has been hypothesized to be brought about by their specificity towards N-acetylglucosamine that is the repeating unit of chitin present on the fungal cell wall. Laminarin and mannan that also constitute fungal cell walls, have also been found to be targeted by lectins extracted from *Sparassis latifolia* that exert their antifungal activity by inhibiting yeast cells and hyphae-forming fungi. Thus, the fungal cell wall components majorly aid in the specific binding of lectins that cause disruptions in cell way synthesis and nutrient uptake thereby resulting in the inhibition of fungal growth. Leguminous plant lectins have also been reported for their noteworthy antifungal properties. *Pisum sativum* lectin [68] has been reported to demonstrate significant antifungal properties. It has been hypothesized that these lectins exhibit affinity towards chitin and inhibit fungal cell wall synthesis resulting in displaying non-lethal type of antifungal properties [69].

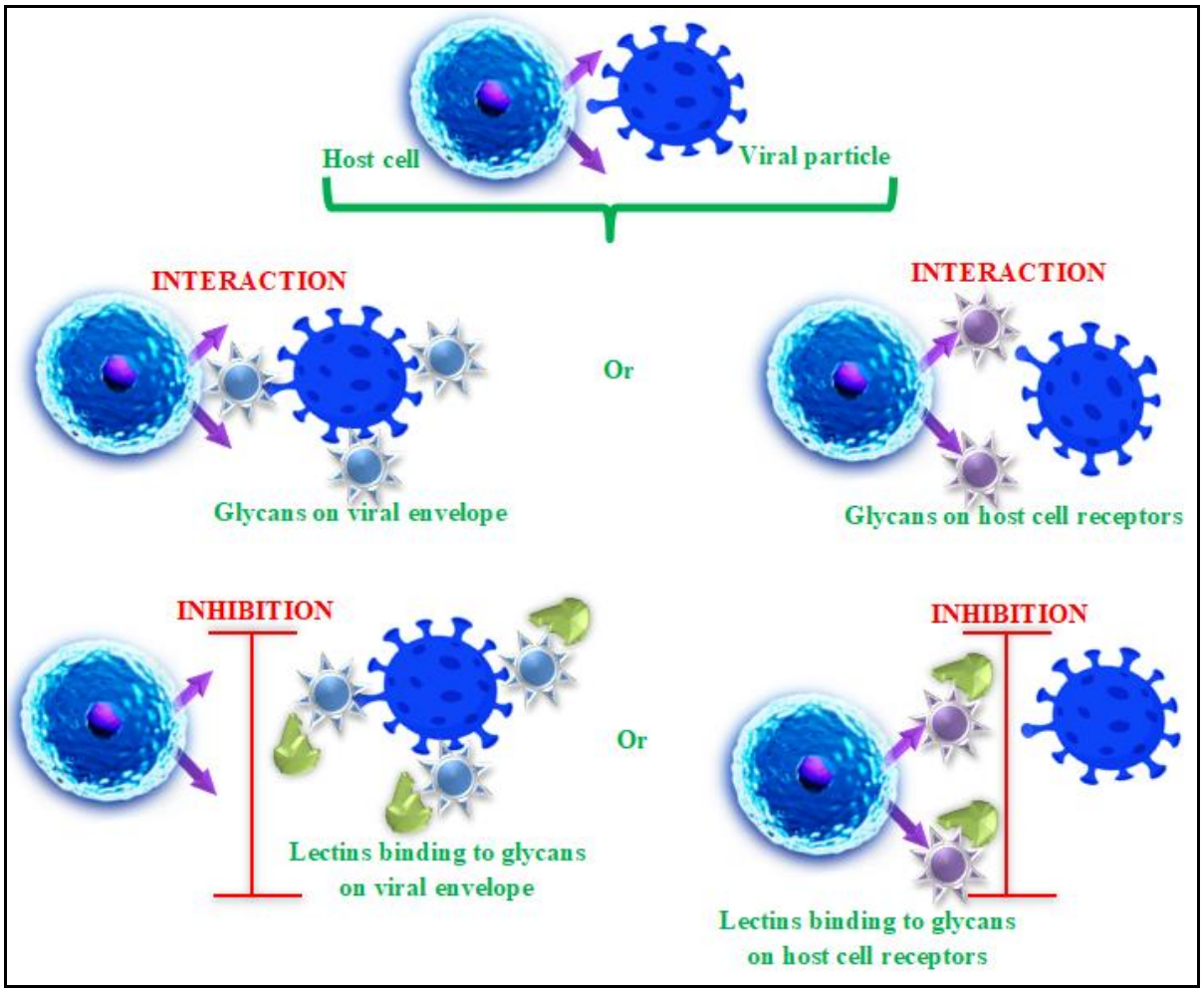
2.4. Antiviral properties of lectins

Lectins have been popularly explored for their bioactive properties, especially against viral pathogens. With the global increase in the cases of viral pandemics, the need for more bioactive ingredients with the potential as potent anti-viral agents, is of paramount importance. Among the various types of lectins, plant lectins have been widely studied for their extensive range of therapeutic properties including significant anti-viral activities. In glycobiology, lectins constitute the most studied category of molecules.

Plant proteins comprising of at least one non-catalytic domain that accurately and reversibly bind to oligosaccharides are referred to as plant lectins. Plant lectins are categorized into 12 families based on the structure of their carbohydrate recognition domains and are grouped into 2 broad groups based on their expression patterns. Lectins are known to have numerous functions in plants with their major roles comprising of binding to glycans for defense, signaling and stress response [70]. They are also known to take part in the host plant's immune mechanisms along with regulating plant-microbial interactions [71]. Experimental data has proven lectins to display wide ranging stability towards enzymes, temperature and pH. Additionally, through interactions with glycans, lectins have been proposed to modulate their virulence against pathogens. Since most of the pathogenic viruses comprise of glycoproteins having mannose glycans integral to their viral entry into host cells, recent advances in therapeutics is focusing on utilizing mannose-binding lectins as potential broad-spectrum antiviral agents that potentially will inhibit the viral interaction with and subsequent entry into host cells. A brief pictorial depiction of this mechanism is represented in figure 1.

Studies have reported the anti-HIV action of lectins brought about by their interaction with the HIV envelope glycoproteins rich in mannose glycans [72]. Other studies have reported the reaction between D-mannose lectin from *Gerardia savaglia* with the side chain of gp120 envelope protein of HIV-1 thus inhibiting the viral infection in H9 host cells [73]. The general mechanisms of lectin mediated anti-viral action include binding to viral envelope glycoproteins, blocking host cell receptors and inhibiting viral polymerase enzymes. Fungal lectin extracted from *Pleurotus ostreatus* has been reported to exhibit the potential of activating HBV-specific T cell responses. *Pleurotus ostreatus* lectins upregulate the expression of signaling molecules like TLR-6 and IL-1β involved in the immune signaling pathways in dendritic cells. Through this mechanism, *Pleurotus ostreatus* lectins activate humoral immunity thereby acting as prospective treatment options for HBV [74].

Figure 1: Mechanism of viral glycan mediated interaction and lectin mediated inhibition of interaction between host cell receptors and viral particles.



Plant lectins have also been found to mediate anti-corona viral activity by inhibiting the spike protein of the virus which subsequently hinders viral attachment to host cells, replication and release of viral particles [15]. Red algal lectins, *i.e.* Rhodophyceae lectins belong to another popular group of lectins used for their extensive range of biomedical applications. Their varied therapeutic properties have been attributed to their carbohydrate specificity towards various viral disorders like HIV, influenza, hepatitis, herpes, coronavirus and others. Griffithsin, a lectin derived from red algae *Griffithsia* sp. and abbreviated as GRFT displays high mannose-rich N-linked glycan specific affinity and strong anti-viral activity against HIV [75]. Experimental reports investigating the anti-HIV-1 mode of action of GRF have revealed that it involves specific binding to high-mannose rich viral surface glycoprotein gp120. This results in the subsequent binding of gp120 to host CD4+ T-helper cells [76]. Various *in vitro* and animal model-based studies have revealed a broad spectrum and targeted antiviral action of GRF against HIV-1 which is also further favored by certain modes of administration over others [77]. Another potent viral disease, namely Hepatitis C that is caused by Hepatitis C virus (HCV), results in severe liver damage in affected humans. GRFT is known to also interact with the N-linked high-mannose oligosaccharides present on the HCV envelope glycoproteins and inhibit the viral interaction with host hepatocytes *in vitro* thus preventing HCV infection *in vivo* [78]. Being correctly defined as a broad-spectrum antiviral agent, GRFT has also been reported to exhibit significant inhibition of other viruses like Herpes Simplex Virus-2 (HSV-2) and Human Papilloma Virus (HPV). The HSV-2 envelope

glycoproteins namely gB, gD, gH and gL are the key players for successful entry of HSV into host cells. GRFT has been reported to specifically interact with, bind to and inhibit gD thus occluding this glycoprotein from further interaction with host cell receptor. Hence this disrupts the interaction of HSV glycoproteins with the host cells thereby mitigating viral entry into host cells [79]. Similar mechanisms of specific and strong binding of GRF with the high-mannose N-glycans present on viral envelope surface glycoproteins have been reported as the anti-viral mode of action of this lectin also against pathogens like SARS-CoV thereby preventing viral entry into host cells [80].

3. Role of Glycosylation in Viral Infectivity and Lectin Based Antiviral Agents

One of the major global causes of infections and morbidity is that contributed by infectious enveloped viruses like HIV, coronavirus, etc. These types of viruses are characterized by the presence of envelope glycoproteins that are densely glycosylated with a huge proportion of high-mannose-type glycans (HMGs) that specifically protect these viruses from host immune neutralization. Through the action of these surface glycoproteins the viruses interact with the host cell receptors and subsequently gain cellular entry. Lectins thus gain exclusive importance as antiviral agents due to their high specificity towards different types of glycans. To compensate for the weak interactions between lectins and monosaccharides, certain types of lectins are polymeric proteins in which each of the subunits help enhance the affinity of lectin towards viral envelope proteins.

Cell surface receptors generally are known to facilitate viral entry by binding to the viral envelope glycoproteins also referred to as HMGs. Hence, lectins have been considered to have undergone co-evolution with viruses due to their targeted specificity towards viral envelope glycans through their carbohydrate recognition domains (CRDs). This thus forms the basis of the underlying mechanisms of most lectin based antiviral drugs. Their antiviral properties are further enhanced by the multimeric and multivalent lectins that significantly magnify the CRDs based viral binding mode of action among lectins. A pictorial overview of this is represented in figure 2.

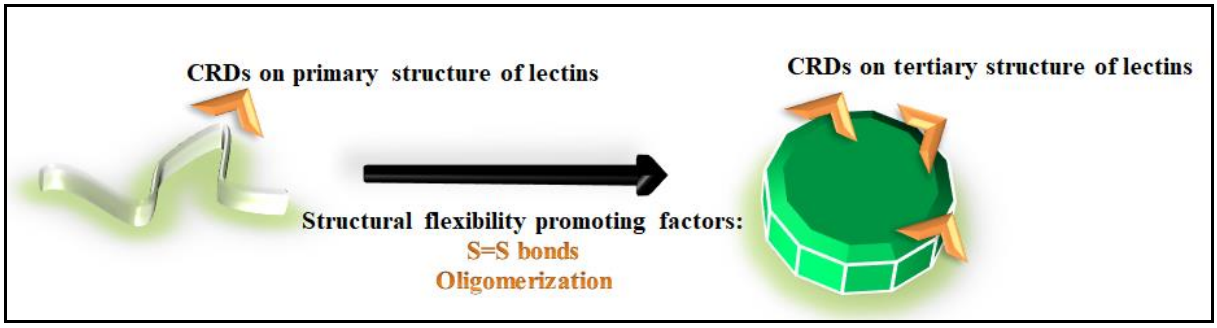
The general mechanisms of antimicrobial action displayed by lectins has been attributed to their property to bind to glycan rich epitopes on pathogens, resulting in various effects of pathogen neutralization that include bacterial cell agglutination, induction of toxicity towards pathogenic cells followed by their lysis. A deep insight into the mode of action of lectins towards neutralizing pathogens forms that basis of designing efficient, robust and specific diagnostic and therapeutic strategies targeting microbial diseases. Advancements in therapeutics have facilitated the utilization of lectins conjugated with drug delivery systems to enhance their potency as antimicrobial agents. Reports have demonstrated efficient usage of lectins isolated from Arachis hypogaea and conjugated with nanoparticles deployed for oral immunization by the targeted neutralization of hepatitis-B surface antigen (HBsAg) [81].

One of the lectins isolated from banana exhibiting potent anti-HIV activity, BanLec, has been shown to display the ability to bind to mannose structures present on the viral envelope thereby blocking the viral entry into host cells. Recent experiments have revealed BanLec to display a tetrameric stoichiometry comprising of 2 carbohydrate-binding sites for each of its monomers. The independent ability of each of these monomers to bind to high mannose glycans on the viral envelope with high affinity has been reported to be a noteworthy mechanism through which these lectins strongly neutralize HIV [82]. Corroborating with these findings are numerous other studies that have reported the specificity of lectins to bind to HIV-1 viral envelope glycoprotein 120 (gp120) bringing about prevention of viral entry into host immune cells. Cyanovirin-N (CV-N), a lectin originating from blue-green algae, has been reported

to possess CRDs specific towards different mannose moieties present on gp120 [83]. Another lectin with high similarity with CV-N is microvirin (MVN) that has a bacterial origin. Various experimental reports have shown significant antiviral activity of MVN towards HIV-1 and HCV [84]. Recent advancements are being employed to design antiviral agents acting as archetypes of lectins by altering their mannose-rich glycan binding properties. Pradimicin-A (PRM-A), an antifungal antibiotic, is among the first groups of "artificial lectins" that displays predominant binding towards HMGs on viral envelope. This is being considered as one of the promising drug candidates targeted against HIV-1/2 and Simian Immunodeficiency Viruses (SIVs) [85].

Another potent virus causing globally high levels of morbidity and mortality is the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2). These virus particles are enveloped in 2 layers by surface glycoproteins that facilitate its adhesion, entry and invasion into host cells. Two of the most important surface glycoproteins on this viral envelope include the spike (S) and membrane (M) proteins. GRFT has been widely recognized as a potent lectin based antiviral agent that specifically recognizes these mannose-rich glycans on the surface of coronavirus and aids in preventing subsequent viral entry and pathogenesis in host cells [86]. Another similar lectin, namely *Lens culinaris* agglutinin (LCA) has demonstrated potent antiviral properties against SARS-CoV2 pseudovirus [87].

Figure 2: Amino acid arrangement of CRDs on lectin protein structure.



3.1. Current status of antiviral lectin-based therapeutics

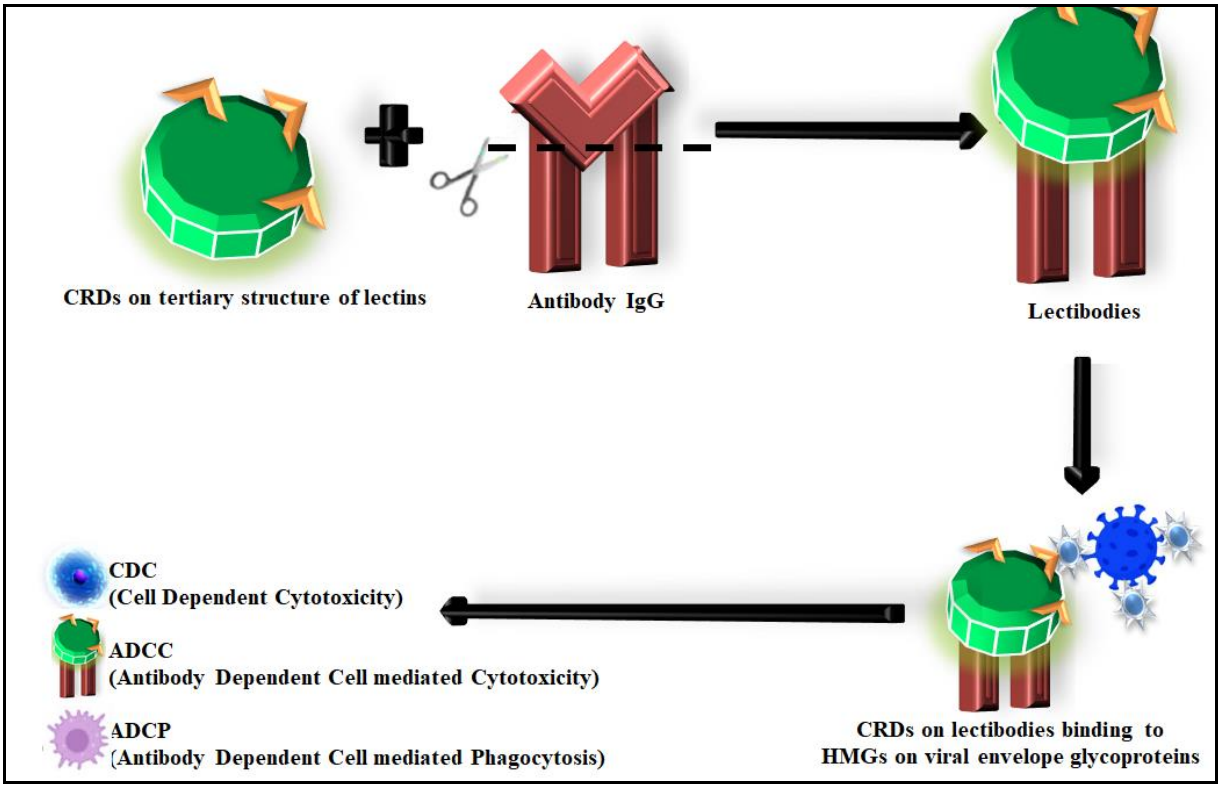
Lectins are quintessential proteins that have widespread applications as diagnostic and therapeutic agents. However, they also are accompanied by certain disadvantageous features that limit their biomedical applications. Few of the disadvantageous chemical features include their small size, vulnerability to host enzyme catalyzed proteolysis and short stability in host environment. Additionally, few of their disadvantageous biological features include pro-inflammatory properties, mitogenicity and cytotoxicity [88]. To overcome these challenges, different approaches in protein engineering have been employed to enhance the potency of lectin-based drug systems while lowering or eliminating their disadvantages.

One of such prominently employed research techniques is the production of lectibodies, *i.e.* a fusion of lectins with the crystallizable fragment (Fc) of Immunoglobulin G (IgG). These lectibodies hence act as carbohydrate-targeting antibodies that bind to viral envelope glycoproteins. In the infected host system, these lectibodies hence trigger effector functions that include antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody dependent cell-mediated phagocytosis (ADCP) [89]. A brief depiction of this technique is represented in figure 3. Different clinical trials have been reported to being performed at different stages that aim to target neutralizing

SARS-CoV through lectibodies [90]. Other clinical reports have demonstrated few potent lectibodies, namely CVN-Fc that targets HIV, HCV and Ebola [91].

Viruses being tricky organisms by themselves, due to their complicated nature of existence, have always posed as fastidious micro-organisms to be tackled. Viral infections are hence among the group of complicated types of infections to be combated by host immunity as well as by antiviral drugs. Various approaches have always been employed to target different types of viruses. With advances in technology, lectins have been recognized as potent antiviral agents because they effectively target the viral binding to host cell surface, thus preventing the first and most important line of entry of viruses into host cells. Further advancements in protein engineering are proving to be helpful in designing effective lectin based antiviral drugs with least or nil disadvantages. To validate these advancements in research, plenty of clinical trials and testing would be required to standardize the efficacy of lectin based antiviral drug delivery systems with nil or least side effects.

Figure 3: Basic principle of structure and mode of action of lectibodies.



4. Conclusion and Further Scope

The present day of modern medicine and therapeutics has demonstrated the exponential rate at which technology has advanced in catering to human needs, in the context of detection and treatment of ailments and disorders. Nevertheless, natural product chemistry has always stood its ground in proving that using natural compounds as therapeutic agents will always prove to be a robust way to address different types of issues related to human health. Lectins, being widely known for their wide-spectrum medical applications including wound-healing, anticoagulating, anti-nociceptive, antimicrobial, antiviral and immunomodulatory properties, are a treasure trove of novel bioactive compounds that can widely be used in the field of therapeutics. There lies immense potential around lectin-based antiviral therapeutics. Advancements in protein engineering, targeted drug designing and other areas, have facilitated further

research into effectively using the immunomodulatory and antiviral properties of lectins, in the line of treatment for different disorders. These advances in research will certainly require validation through clinical trials and tests to enable the standardization of lectin based therapeutic systems.

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