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Lectins: To Combat Infections

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1. Introduction

The term "lectin" was coined by William Boyd in 1954 from the Greek word "legere" which means "to select" or "to bind". Lectins and hemagglutinins are proteins/glycoproteins of non-immune origin, which have at least one non-catalytic domain that exhibits reversible binding to specific monosaccharides or oligosaccharides (Lis and Sharon, 1986). The lectin-monosaccharide interactions are relatively very weak and the dissociation constants lie in millimolar range. However, in nature for the multimeric sugars the dissociation constants are several folds higher indicating that multiple protein-carbohyrate interactions are involved in the recognition and binding events (Ambrosi et al., 2005). Thus, lectins are multivalent in nature and can bind to the carbohydrate moieties on the surface of erythrocytes and agglutinate the erythrocytes, without altering the properties of the carbohydrates (Lam and Ng, 2011). Lectins are ubiquitous and are extensively distributed in nature. Many hundreds of these lectins have been isolated from varied sources like plants, viruses, bacteria, invertebrates and vertebrates but in all, lectins from different sources show little similarity. Lectins are invaluable tools for the detection, isolation, and characterization of glycoconjugates, primarily of glycoproteins, for histochemistry of cells and tissues and for the examination of changes that occur on cell surfaces during physiological and pathological processes, from cell differentiation to cancer (Sharon and Lis, 2004).

Cell identification and separation
Detection, isolation, and structural studies of glycoproteins
Investigation of carbohydrates on cells and subcellular organelles; histochemistry and cytochemistry
Mapping of neuronal pathways
Mitogenic stimulation of lymphocytes[b]
Purging of bone marrow for transplantation[b]
Selection of lectin-resistant mutants
Studies of glycoprotein biosynthesis

[a] Lectins from sources other than plants are rarely in use.
[b] In clinical use.
Source: Sharon and Lis, 2004

Table 1. Major applications of lectins[a]

Lectin Category	Definition
Merolectins	Proteins that consist exclusively of a single carbohydrate-binding domain. They are small, single-polypeptide proteins that are incapable of agglutinating cells because of their monovalent nature.
Hololectins	These are composed exclusively of carbohydrate binding domains, but contain at least two such domains.
Chimerolectins	These are fusion proteins composed of one or more carbohydrate-binding domains and an unrelated domain with a well-defined biological activity. Based on the number of sugar-binding sites, chimerolectins behave as either merolectins or homolectins.

Source: Van Damme and Peumans, 1996.

Table 2. Classification of lectins

Lectin name	Family	Glycan ligands
Plant lectins		
Concanavalin A (Con A; jack bean)	Leguminosae	Man/Glc
Wheat germ agglutinin (WGA; wheat)	Gramineae	(GlcNAc)1–3, Neu5Ac
Ricin (castor bean)	Euphorbiaceae	Gal
Phaseolus vulgaris (PHA; French bean)	Leguminosae	None known
Peanut agglutinin (PNA; peanut)	Leguminosae	Gal, Galb3GalNAca (T-antigen)
Soybean agglutinin (SBA; soybean)	Leguminosae	Gal/GalNAc
Pisum sativum (PSA; pea)	Leguminosae	Man/Glc
Lens culinaris (LCA; lentil)	Leguminosae	Man/Glc
Galanthus nivalus (GNA; snowdrop)	Amaryllidaceae	Man
Dolichos bifloris (DBA; horse gram) Leguminosae		GalNAca3GalNAc, GalNAc
Solanum tuberosum (STA; potato)		(GlcNAc)n
Animal lectins		
Asialoglycoprotein receptor (ASGPR) H1	C-type	Gal
Galectin-3	galectins	Gal
Sialoadhesin	I-type	Neu5Ac
Cation-dependent mannose-6-phosphate receptor (CD-MPR)	P-type	Man6P
C-reactive protein (CRP)	Pentraxins	Gal, Gal6P, galacturonic acid

Source: Ambrosi et al., 2005

Table 3. Examples of lectins, the families to which they belong and their glycan ligand specificities

Lectins are often classified based on saccharide-specificity. Though this conventional method is familiar and practically useful, it is not necessarily relevant for refined specificity. Lectins in the same category (e.g., galactose-specific lectins) show considerably different sugar-binding preferences. Moreover, an increasing number of lectins which never show high affinity to simple saccharides have been found. They can also be categorized according to the overall structures into merolectins, hololectins, chimerolectins and superlectins, or be grouped into different families (legume lectins, type II ribosome-inactivating proteins, monocot mannose-binding lectins, and other lectins).

The first protein showing inhibition of microorganisms was isolated from wheat flour in 1942 (Balls et al., 1942). However, it was found as late as 1980 by Duguid that *E. coli* possesses the ability to agglutinate erythrocytes and this ability is inhibited by mannose and methyl a-mannoside. Erzler in 1986 reported that lectins in higher plants defend against pathogenic bacteria and fungi by recognizing and immobilizing the infecting microorganisms via binding, thereby preventing their subsequent growth and multiplication. The role of lectins as those of the herbaceous Amaranthus in inhibiting bacteria and fungi has long been known (Bolle et al., 1996). Microbes have lectins that help in recognition and the blocking of these can prevent the infection has been established in mouse models. However, success of such treatments in humans has not been achieved yet (Sharon, 2006). Lately, with the emerging problem of multiple drug resistance, research in characterization of newer lectins to combat infections is gaining momentum.

2. Lectins as tools in cell recognition

Lectins agglutinate cells and react with the glycoconjugates present on their surface. Cells at different stages of growth and differentiation express different glycoconjugates on their surface and this made lectins an important tool to investigate the cell pathology and physiology. James Sumner in 1919 isolated concanavalin A in crystalline form and in 1936, together with Howell, reported that it agglutinates cells such as erythrocytes and yeasts and that this agglutination is inhibited by sucrose, thus demonstrating for the first time the sugar specificity of lectins. Walter Morgan and Winifred Watkins in the early 1950s used blood type-specific hemagglutinins to show that the blood type A immunodeterminant is α-linked N-acetylgalactosamine and that the H(O) determinant is α-L-fucose. This was the first demonstration that cell surface carbohydrates can serve as carriers of biological information.

Several basic features of membranes were revealed, or their existence confirmed, with the aid of lectins. Singer and Nicolson using ferritin-conjugated concanavalin A and ricin as an electron microscopic probe found that the lectin derivatives bind specifically to the outer surface of the human and rabbit erythrocyte membrane and concluded that the oligosaccharides of the plasma membrane of eukaryotic cells are asymmetrically distributed (1971). Vincent Marchesi used ferritin-labeled phytohemagglutinin (PHA) and showed that glycophorin is oriented in such a way that its carbohydrate-carrying segment is exposed to the external medium, whereas the other segments of the same molecule are embedded in the lipid bilayer or protrude into the cytoplasm (Sharon, 2007).

It was later found that lectin-induced clustering and patching of the corresponding membrane receptors on lymphocytes and other kinds of cell, as illustrated for example by

the treatment with fluorescein-labeled concanavalin A of rat or mouse lymphocytes (Inbar and Sachs, 1973). Reorganization of cell surface carbohydrates was later shown to be required for various activities of lectins on cells such as mitogenic stimulation and induction of apoptosis. There is increasing evidence that changes in cellular glycosylation attend alterations in cell behaviour in both normal and in pathological processes, and that this may be of particular interest in malignancy. The malignant cells differ from the normal cells in the distribution of carbohydrates on the outer surface; many of these have an affinity for lectins (Brooks et al., 2001, Kannan et al., 2003). The reports of Inbar and Sachs also proved that lectins agglutinated malignantly transformed cells but not their normal parental cells (1973). They provided compelling evidence that cancer might be associated with a change in cell surface sugars, an idea that only a few years before had been considered completely unfounded. It was also found that SBA (specific for galactose and N-acetylgalactosamine) also possesses the remarkable ability to distinguish between normal and malignant cells (Sharon, 2007). Numerous subsequent studies have demonstrated that high susceptibility to agglutination by lectins is a property shared by many, albeit not all, malignant cells. The herbal *Viscum album* (Mistletoe) lectin (ML-1), has been shown to have antitumoral activity because of its ability to modulate and activate natural killer cells (Joshi, S, 1993). ML-1 also induces apoptosis in myelomonocytic leukemia (Joshi, S et al., 1994). Another herbal medicine *Agaricus bisporus* lectin (ABL), has also been shown to reverse the proliferation of colorectal and breast cancer cells in humans (Yu L et al., 1983).

Bacterial lectins are typically elongated submicroscopic multi-protein appendages, known as fimbriae (or pili) which mediate their adhesion to glycocalyx. Adhesion appears to prevent bacterium removal by intestinal peristalsis, facilitating colonization of the small intestine. Lectins from human pathogens like *E.coli*, *Actinomyces naeslundii*, *C. jejuni*, *E. cloacae*, *H. influenzae*, *H. pylori*, *K. pneumoniae*, *N. gonorrhoea*, *N. meningitides*, *S. mutans* and *P. aeruginosa* with diverse specificities have been isolated and characterized. An individual bacterium may co-express more than one lectin, e.g., certain strains of *E. coli* are both mannose and galabiose specific and those of *H. pylori* recognize simultaneously the tri- and tetrasaccharide. The major function of the enterobacterial surface lectins, as that of similar lectins of other microorganisms, is to mediate the adhesion of the organisms to host cells, an initial stage of infection. This has been extensively demonstrated both in vitro, in studies with isolated cells and cell cultures, and in vivo in experimental animals, and is supported in some cases also by clinical data. It is best documented for *E. coli* type 1 and P fimbriae (Bergsten et al., 2005). P-fimbriae have been shown to enhance the early establishment of *E. coli* in the human urinary tract, and a strong association has been found between the presence of P-fimbriae with disease severity, suggesting that adherence mediated by these organelles has a direct effect on mucosal inflammation in vivo (Sauer et al., 2000). Concerning the type 1 fimbriae, it has been reported that mutants of *E. coli* deficient in Fim H, the carbohydrate-binding subunit of the fimbriae, are unable to cause cystitis in monkeys (Sauer et al., 2000). Attachment of a pathogen to a tissue does not of itself initiate disease. It must be coupled to specific responses that lead to infection. Adherence of P-fimbriated *E. coli* or of the isolated P fimbriae to galabiose of uroepithelial cells induces a two-way flow of biological crosstalk via the lectin bridge, affecting both partners. Following adherence, the target cells are activated, with resultant production of cytokines that engender acute

inflammation and other symptoms of disease, while in the bacteria the interaction leads to up-regulation of signal transduction systems that allow responses to the changing environment (Sharon, 2006).

The FimH subunits of both *E. coli* and *K. pneumoniae* are 88% homologous, yet they have different specificities (Gupta et al., 2009). They mediate not only bacterial adhesion, but also invasion of human bladder and intestinal, respectively. In contrast, adhesion mediated by PapG, the lectin subunit of P fimbriae, did not initiate bacterial internalization. *E. coli* strains that cause urinary tract infections are not strictly extracellular pathogens and FimH can directly trigger host cell signalling cascades that lead to bacterial internalization. Type 1 fimbriae are instrumental also in the attachment of *E. coli* to human polymorphonuclear cells and human and mouse macrophages, in the absence of opsonins. This is often followed by the ingestion and killing of the bacteria, a phenomenon named "lectinophagocytosis" (Ofek and Sharon, 2000), an early example of innate immunity; it may function in vivo, for example in sites poor in opsonins, and in the peritoneal cavity. Indeed, injection of type 1 fimbriated *E. coli* into the peritoneal cavity of mice led to the activation of the peritoneal macrophages; no activation was observed in the presence of methyl α-mannoside or when non-fimbriated bacteria were used (Bernhard et al., 1992). Enterobacteria can attach by their surface lectins to mast cells as well, with resultant activation of the target cells and production of high levels of certain cytokines, in particular TNF-α (Malviya and Abraham, 2001). Activation of mast cells can also be induced by purified type 1 fimbriae, and by FimH. The cytokines released by the activated mast cells cause rapid recruitment of neutrophils into the site of infection, resulting in early clearance of the bacteria. As expected, mice lacking mast cells were significantly less efficient in clearing intranasal or intraperitoneal infection caused by *K. pneumoniae.*

Specific binding of lectin to Chlamydial cell wall structures is demonstrated by the binding of Galanthus nivalis lectin (GNA). Binding of sialic acid residues to peanut agglutinin (PNA), and jackfruit lectin (JFL), were also found in two Chlamydial glycopeptides (Siridewa, et al., 1993). The study suggests that lectins may be of use as therapeutic agents to keep Chlamydial organisms from entering human cells, thus rendering them more susceptible to immune system elimination.

3. Antibacterial effect of lectins

3.1 Direct inhibition of lectin

Quite recently novel lectins are usually tested for any potential antimicrobial activity. A novel galactoside binding lectin from *Bothrops leucurus* snake venom was purified and it exhibited antibacterial effect against the human pathogenic Gram positive bacteria *Staphylococcus aureus*, *Enterococcus faecalis* and *Bacillus subtilis* (Nunes et al., 2011). *Archidendron jiringa* seed lectin showed inhibitory activity against *B. subtilis* and *S. aureus* but did not show any activity against *E.coli* and *P. aeruginosa* (Charungchitrak et al., 2010). Lectins have been islated from serum, plasma, skin mucus and egg of fishes (Jensen et al., 1997;, Ottinger et al., 1999; Dong et al., 2004; Tasumi et al., 2004). A galactose binding lectin has been isolated from Indian catfish *Clarias batrachus*. The lectin agglutinated *E.coli*, *P aeruginosa* and *Klebsiella* strains (Dutta et al., 2005).

Plant (tissue)	Lectin specificity	Antibacterial activity
Eugenia uniflora (seeds)	Carbohydrate complex	*Bacillus subtilis, Corynebacterium bovis, Escherichia coli, Klebsiella sp., Pseudomonas aeruginosa, Streptococcus sp., Staphylococcus aureus*
Myracrodruon urundeuva (heartwood)	GlcNAc	*B. subtilis, Corynebacterium callunae, E. coli, Klebsiella pneumoniae, P. aeruginosa, S. aureus, Streptococcus faecalis.*
Phthirusa pyrifolia (leaf)	Fru-1,6-P2	*B. subtilis, K. pneumoniae, Staphylococcus epidermidis, S. faecalis*

Table 4. Lectins with antibacterial activity, Source: Paiva et al., 2010.

3.2 Lectins against the virulence properties of pathogenic bacteria

The use of lectins in antiadhesion therapy has already been proposed in the literature (Ofek et al., 2003; Mody et al., 2005).This may be of particular importance for controlling diseases where opportunistic pathogens are involved and bacterial adhesion is critical, followed by attainment of sedentary mode of bacterial lifestyle (biofilms) like in oral infections. The acquired enamel pellicle is an organic and acellular film formed by selective adsorption of salivary molecules to the teeth (Yin et al., 2005). Oral bacteria adhere to this pellicle during the initial events of dental plaque formation (Saxton 1973; Yao et al., 2001), a crucial event to dental caries, pathology that represents a health expenditure of several billion dollars per year in the United States alone (Global Oral Health 2006). As bacterial adhesion to the acquired pellicle is one of the primary stages of plaque formation which may lead to caries (Scheie, 1994), it is reasonable to suppose that avoiding adhesion could be a good method to prevent this disease at early stages. Lectins may be good candidates to carry out this approach, as the adherence of bacteria to host cells is, in many cases, mediated by lectin-like adhesins on the bacterial surface that recognize carbohydrate receptors (Ofek and Sharon 1990; Hytonen et al., 2000). Marine algal lectins are especially interesting for biological applications because they have generally lower molecular masses as compared with most land plant lectins. An additional benefit might be that small algal lectin molecules may be expected to be less antigenic than the larger land plant lectins (Rogers and Hori, 1993). Further, they possess great stability on account of their several disulfide bridges and present high specificity for complex carbohydrates and glycoconjugates, especially for mucins (Ainouz et al., 1995; Sampaio et al., 1998; Nagano et al., 2005). The ability of two algal lectins BSL and BTL to bind to the SHA beads and their effectiveness in decreasing the adhesion of streptococci to the pellicle: BSL showed statistically significant results (<0 01), especially for *S. mutans*, whose adhesion was decreased almost totally; while BTL achieved this type of result for only two strains (*S. sobrinus* and *S. mitis*) (Teixeira et al., 2007)

The streptococcal cell wall contains four major antigenic polymers: peptidoglycan, group and type-specific polysaccharides, proteins and the glycerol form of teichoic and lipoteichoic acids. We studied lectins from edible sources and different specificities to the different

components of the cell wall of oral pathogen, *Streptococcus mutans*. Lectins from *Canavalia ensiformis* (ConA), *Trigonella foenumgraecum* (TFA), *Triticum aestivum* (WGA), *Arachis hypogaea* (PNA), *Cajanus cajan* (CCL), *Phaseolus vulgaris* (PHA) and *Pisum sativum* (PSA) were tested against the growth and biofilm formation of *S. mutans* on saliva coated surface. None of these lectins inhibit the bacterial growth even up to a concentration of 1000mg/ml. However, all the lectins inhibited the biofilm formation by *S.mutans in-vitro*. Amongst these, lectins with Mannose/Glucose (ConA, TFA, CCL and PSA) specificity showed the highest inhibitory effect on the biofilm formation while lectins with N-acetylglucosamine specificity (WGA and PHA) and N-acetylgalactosamine specificity (PNA) also showed inhibition, albeit to a lesser degree (Islam et al., 2009).

Organism	**Target tissue**	**Carbohydrate**	**For m[b]**
C. jejuni[c]	Intestinal	Fucα2GalβGlcNAc	GP
E. coli Type 1	Urinary	Manα3Manα6Man	GP
P	Urinary	Galα4Gal	GSL
S	Neural	NeuAc (α2–3)Galβ3GalNAc	GSL
CFA/1	Intestinal	NeuAc (α2–8)–	GP
F1C[d]	Urinary	GalNAcβ4Galβ	GSL
F17[e]	Urinary	GlcNAc	GP
K1	Endothelial	GlcNAcβ4GlcNAc	GP
K99	Intestinal	NeuAc(α2–3)Galβ4Glc	GSL
H. influenzae	Respiratory	$[NeuAc(\alpha2–3)]_{0,1}$Galβ4GlcNAcβ3Galβ4GlcNAc	GSL
H. pylori	Stomach	NeuAc(α2–3)Galβ4GlcNAc	GP
		Fucα2Galβ3(Fucα4)Gal	GP
K. pneumoniae	Respiratory	Man	GP
N. gonorrhoea	Genital	Galβ4Glc(NAc)	GSL
N. meningitidis	Respiratory	$[NeuAc(\alpha2–3)]_{0,1}$Galβ4GlcNAcβ3Galβ4GlcNAc	GSL
P. aeruginosa[f]	Respiratory	L-Fuc	GP
	Respiratory	Galβ3Glc(NAc)β3Galβ4Glc	GSL
S. typhimurium	Intestinal	Man	GP
S. pneumoniae	Respiratory	$[NeuAc(\alpha2–3)]_{0,1}$Galβ4GlcNAcβ3Galβ4GlcNAc	GSL
S. suis	Respiratory	Galα4Galβ4Glc	GSL

Source: Gupta et al., 2009.

Table 5. Carbohydrates as attachment sites for bacterial pathogens on animal tissues[a]

A surface glycoprotein of *S.mutans* of 60 kDa (with mannose and N-acetylgalactosamine) has been known to involve in saliva and bacterial interaction. The lesser adherence in the presence of glucose/mannose and galactosamine specific lectins could be because of the interaction with this protein. The PHA and WGA lectin binds to a constituent of the peptidoglycan of the cell wall (Sharon and Lis 2003). The attachment of bacteria is mediated by glucan binding lectin (GBL) and the presence of lectin in the growth media perhaps leads to competition between GBL of bacteria and plant lectins for the attachment sites on salive-coated plates resulting in less binding of the cells. With regard to bacterial surface lectins

that often play a role in the initial step of adherence, plant lectins by interfering in this process show a promising future as anti-adherence agents (Islam et al., 2009). A schematic description of how lectins might inhibit attachment of bacteria to the host tissue is shown in Figure 1 (Ghazarian et al., 2011).

Use of bacterial lectin inhibitors such as mannose to prevent the adhesion of *Eschericia coli* to bladder epithelial cells has been employed in clinical practice for some time. Other bioglycans, such as that from *Crenomytalus grayanus* (mussels), has been found to considerably decrease the adhesion of the bacteria *Eschericia coli*, *Staphylococcus aureus* and P*seudomonas aeruginosa* (Zaporozhets et al., 1994). Plant lectins such as those from *Datura stramonium*, *Robinia pseudoacacia* and *Dolichos biflorus* agglutinated Streptococcal Group C bacterial cells (Kellens et al., 1994) which prevents them from adhering to human cell surfaces.

4. Antiviral effect of lectin

The surfaces of retroviruses such as human immunodeficiency virus (HIV) and many other enveloped viruses are covered by virally-encoded glycoproteins. Glycoproteins gp120 and gp41 present on the HIV envelope are heavily glycosylated, with glycans estimated to contribute almost 50% of the molecular weight of gp120 (Mizuochi et al., 1988; Ji et al., 2006). The antiviral activity of lectins appears to depend on their ability to bind mannose-containing oligosaccharides present on the surface of viral envelope glycoproteins. Agents that specifically and strongly interact with the glycans may disturb interactions between the proteins of the viral envelope and the cells of the host (Botos & Wlodawer, 2005; Balzarini, 2006). Sugar-binding proteins can crosslink glycans on the viral surface (Sacchettini et al., 2001; Shenoy et al., 2002) and prevent further interactions with the co-receptors. Unlike the majority of current antiviral therapeutics that act through inhibition of the viral life cycle, lectins can prevent penetration of the host cells by the viruses. Antiviral lectins are best suited to topical applications and can exhibit lower toxicity than many currently used antiviral therapeutics. Additionally, these proteins are often resistant to high temperatures and low pH, as well as being odorless, which are favorable properties for potential microbicide drugs. Antiviral activity of a number of lectins that bind high-mannose carbohydrates has been described in the past. Examples of such lectins include jacalin (O'Keefe et al., 1997), concanavalin A (Hansen et al., 1989), Urtica diocia agglutinin (Balzarini et al., 1992), Myrianthus holstii lectin (Charan et al., 2000), and Narcissus pseudonarcissus lectin (Balzarini et al., 1991). However, lectins derived from marine organisms, a rich source of natural antiviral products (Tziveleka et al., 2003), such as CV-N (Boyd et al., 1997), SVN (Bokesch et al., 2003), MVL (Bewley et al., 2004) and GRFT (Mori et al., 2005), exhibit the highest activity among the lectins that have been investigated so far (Ziółkowska NE and Wlodawer A 2006). Some lectins found in algae, such as cyanovirin-N (CV-N) (Boyd et al., 1997; Esser et al., 1999; Barrientos et al., 2003; O'Keefe et al., 2003; Helleet al., 2006); scytovirin (SVN) (Bokesch et al., 2003), Microcystis viridis lectin (MVL) (Bewley et al., 2004), and griffithsin (GRFT) (Mori et al., 2005; Ziółkowska et al., 2006) exhibit significant activity against human immunodeficiency virus (HIV) and other enveloped viruses, which makes them particularly promising targets for the development as novel antiviral drugs (De Clercq, 2005; Reeves & Piefer, 2005)

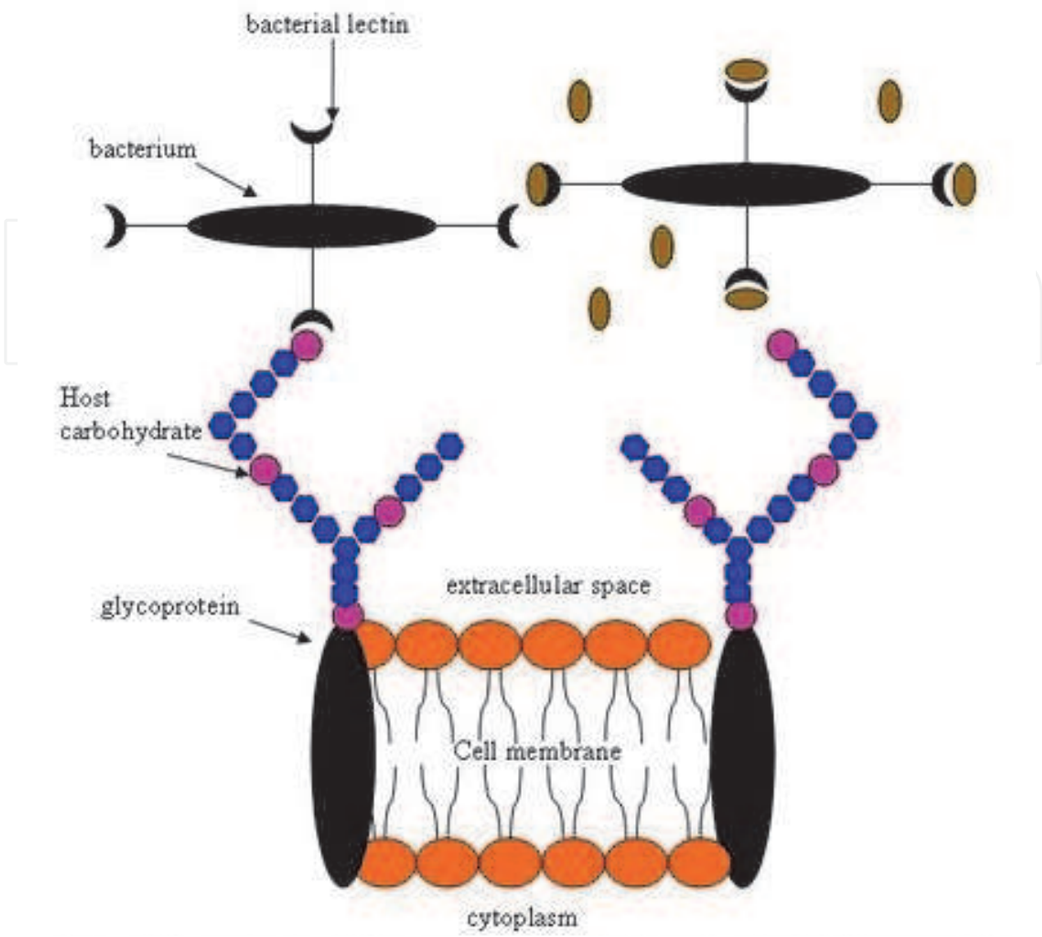

Fig. 1. Representation of bacterial lectins binding to the host cell (left) and specific lectins, used as drug interfering with this bacteria-host interaction (right)

Keyaerts et al., (2007) described the antiviral activity of plant lectins with specificity for different glycan structures against the severe acute respiratory syndrome coronavirus (SARS-CoV) and the feline infectious peritonitis virus (FIPV) in vitro. The SARS-CoV emerged in 2002 as an important cause of severe lower respiratory tract infection in humans, and FIPV infection causes a chronic and often fatal peritonitis in cats. A unique collection of 33 plant lectins with different specificities were evaluated. The plant lectins possessed marked antiviral properties against both coronaviruses with EC50 values in the lower microgram/ml range (middle nanomolar range), being non-toxic (CC50) at 50–100 μg/ml. The strongest anti-coronavirus activity was found predominantly among the mannose-binding lectins. In addition, a number of galactose-, N-acetylgalactosamine-, glucose-, and N-acetylglucosamine-specific plant agglutinines exhibited anti-coronaviral activity. A significant correlation (with an r-value of 0.70) between the EC50 values of the 10 mannose-specific plant lectins effective against the two coronaviruses was found. In contrast, little correlation was seen between the activities of other types of lectins. Two targets of possible antiviral intervention were identified in the replication cycle of SARS-CoV. The first target is located early in the replication cycle, most probably viral attachment, and the second target is located at the end of the infectious virus cycle (Keyaerts et al., 2007).

The carbohydrate binding profile of the red algal lectin KAA-2 from *Kappaphycus alvarezii* was studied by Sato et al (2011). They tested the anti-influenza virus activity of KAA-2 against various strains including the recent pandemic H1N1-2009 influenza virus. KAA-2 inhibited infection of various influenza strains with EC50s of low nanomolar levels. Immunofluorescence microscopy using an anti-influenza antibody demonstrated that the antiviral activity of KAA-2 was exerted by interference with virus entry into host cells. This mechanism was further confirmed by evidence of direct binding of KAA-2 to a viral envelope protein, hemagglutinin (HA), using an ELISA assay. These results indicate that this lectin could be a useful antiviral agent (Sato Y et al., 2011).

5. Antifungal effects of lectins

Despite the large numbers of lectins and hemagglutinins that have been purified, only a few of them manifested antifungal activity (Table 5). The expression of *Gastrodia elata* lectins in the vascular cells of roots and stems was strongly induced by the fungus *Trichoderma viride*, indicating that lectin is an important defense protein in plants (Sá et al., 2009). Following insertion of the precursor gene of stinging nettle isolectin I into tobacco, the germination of spores of *Botrytis cinerea*, *Colletotrichum lindemuthianum*, and *T. viride* was significantly reduced (Does et al., 1999). Thus, lectins may be introduced into plants to protect them from fungal attack.

Plant lectins can neither bind to glycoconjugates on the fungal membranes nor penetrate the cytoplasm owing to the cell wall barrier. It is not likely that lectins directly inhibit fungal growth by modifying fungal membrane structure and/or permeability. However, there may be indirect effects produced by the binding of lectins to carbohydrates on the fungal cell wall surface. Chitinase-free chitin-binding stinging nettle (*Urtica dioica* lectin) impeded fungal growth. Cell wall synthesis was interrupted because of attenuated chitin synthesis and/or deposition (Van Parijs et al., 1991). The effects of nettle lectin on fungal cell wall and hyphal morphology suggest that the nettle lectin regulates endomycorrhizal colonization of the rhizomes. Severa1 other plant lectins inhibit fungal growth. The first group includes small chitin-binding merolectins with one chitin-binding domain, e.g., hevein from rubber tree latex (Van Parijs et al., 1991) and chitin-binding polypeptide from *Amaranthus caudatus* seeds (Broekaert et al., 1992). The only plant lectins that can be considered as fungicidal proteins are the chimerolectins belonging to the class I chitinases. However, the antifungal activity of these proteins is ascribed to their catalytic domain.

6. Lectins and the immune system

To initiate immune responses against infection, the surface receptors on antigen presenting cells must recognise the corresponding molecules on infectious agents. Pattern recognition receptors (PRR) which include C-type lectin like receptor (CLR) recognise and interact with carbohydrate moieties of many pathogens. Despite the presence of a highly conserved domain, C-type lectins are functionally diverse and have been implicated in various processes including cell adhesion, tissue integration and remodelling, platelet activation, complement activation, pathogen recognition, endocytosis, and phagocytosis.

Natural source of lectin	Fungal species inhibited	Sugar specificity	Reference
Amaranthus viridis (Green Amaranth) seeds	*Botrytis cinerea, Fusarium oxysporum*	Asialofetuin, fetuin, T-antigen, N-acetyl-d-lactosamine, N-acetyl-d-galactosamine	Kaur et al.2006
Astragalus mongholicus (huangqi) roots	*Borrytis cinerea, Colletrichum sp., Droschslara turia, Fusarium oxysporum*	d-galactose, lactose	Yan et al.2005
Capparis spinosa (caper) seeds	*Valsa mali*	D(+)galactose, α-lactose, raffinose, rhamnose, L(+)-arabinose, D(+)glucosamine	Lam et al.2009
Capsicum frutescens (red cluster pepper) seeds	*Aspergillus flavus, Fusarium moniliforme*	d-mannose, glucose	Ngai and Ng 2007
Curcuma amarissima Roscoe (wei ji ku jiang-huang) Rhizomes	*Colectrotrichum cassiicola, Exserohilum turicicum, Fusarium oxysporum*	Not found	Kheeree et al. 2010
Dendrobium findlayanum (orchid) pseudobulbs	*Alternaria alternata, Colletrichum sp.*	Not found	Sattayasai et al. 2009
Phaselous vulgaris cv " flageolet bean" seeds	*Mycosphaerella arachidicola*	Not found	Xia and Ng 2005
Phaselous vulgaris cv "French bean 35" seeds	*Valsa mali*	Not found	Lam and Ng 2010
Phaseolus coccineus seeds	*Gibberalla sanbinetti, Helminthosporium maydis, Rhizoctonia solani, Sclerotinia sclerotiorum*	Sialic acid	Chen et al.2009
Phaseolus vulgaris cv "red kidney bean" seeds	*Coprinus comatus, Fusarium oxysporum, Rhizoctonia solani*	Lactoferrin, ovalbumin, thyroglobulin	Ye et al. 2001
Pouteria torta (pouteria trees/eggfruits) seeds	*Saccharomyces carevisiae, C. musae, Fusarium oxysporum*	Fetuin, asialofetuin, heparin, orosomucoid, ovoalbumin	Boleti et al.2007
Talisia esculenta (pitomba) seeds	*Microsporum canis*	d-mannose	Pinheiro et al. 2009

Natural source of lectin	Fungal species inhibited	Sugar specificity	Reference
Withania somnifera (Ashwagandha/Indian ginseng/Winter cherry/Ajagandha/Kanaje Hindi/Amukkuram) leaves	*Fusarium moniliforme, Macrophomina phaseolina*	Not found	Ghosh 2009
Zea mays (maize) endosperm	*Aspergillus flavus*	D(+)galactose	Baker et al.,2009

Table 6. Examples of lectins with antifungal activity, Source: Lam and Ng, 2011

6.1 Mannose Receptor

The MR binds a broad array of microorganisms, including *Candida albicans, Pneumocystis carinii*, *Leishmania donovani*, *Mycobacterium tuberculosis*, and capsular polysaccharides of *Klebisella pneumoniae* and *Streptococcus pneumonia* (Chakraborty et al., 2001; Ezekowitz et al., 1991; Marodi et al., 1991; O'Riordan et al., 1995; Schlesinger, 1993; Zamze et al., 2002). The receptor recognises mannose, fucose or N-acetylglucosamine sugar residues on the surfaces of these microorganisms (Largent et al., 1984) and carbohydrate recognition is mediated by CTLDs 4–8 (Taylor et al., 1992). The MR has been implicated in the phagocytic uptake of pathogens, but there are limited examples actually demonstrating MR-dependent phagocytosis.

6.2 Dectin-1

Dectin-1 is a type II transmembrane protein that is classified as a Group V non-classical C-type lectin and lacks the conserved residues involved in the ligation of calcium that are usually required to co-ordinate carbohydrate binding. Dectin-1 was initially identified as a dendritic cell specific receptor that modulates T cell function through recognition of an unidentified ligand (Ariizumi et al., 2000; Grunebach et al., 2002). It was subsequently reidentified as a receptor for β-glucans, which are carbohydrate polymers found primarily in the cell walls of fungi, but also in plants and some bacteria (Brown and Gordon, 2001, 2003). Dectin-1 can recognise a number of fungal species, including *C. albicans*, *P. carinii*, *Saccharomyces cerevisiae*, *Coccidioides posadasii* and *Aspergillus fumigatus* (Brown et al., 2003; Gersuk et al., 2006; Saijo et al., 2007; Steele et al., 2003, 2005; Taylor et al., 2007; Viriyakosol et al., 2005).The ligation of Dectin-1 also triggers intracellular signalling resulting in a variety of cellular responses, including phagocytosis.

6.3 DC-SIGN (CD209)

DC-SIGN is a type II transmembrane protein that is classified as a Group II C-type lectin. DC-SIGN was originally identified as a receptor for intercellular adhesion molecule-3 (ICAM-3) that facilitates DC-mediated T-cell proliferation and binds HIV-1 (Geijtenbeek et al., 2000a, b). It has since been reported that the receptor interacts with a range of pathogens, including *M. tuberculosis*, *C. albicans*, *Helicobacter pylori*, *Schistosoma mansoni* and *A. fumigatus* (Appelmelk et al., 2003; Cambi et al., 2008; Geijtenbeek et al., 2000b, 2003; Serrano-Gomez et al., 2004; Tailleux et al., 2003; van Die et al., 2003). There have been no reports of a

mechanism for DC-SIGN mediated phagocytosis. However, activation of DC-SIGN triggers Rho-GTPase (Hodges et al., 2007) making it conceivable that Rho could be involved in phagocytosis mediated by this receptor.

6.4 Mannose-binding lectin (MBL)

Mannose-binding lectin (MBL) is a Group III C-type lectin belonging to the collectins (Holmskov et al., 2003), which are a group of soluble oligomeric proteins containing collagenous regions and CTLDs. MBL is secreted into the blood stream as a large multimeric complex and is primarily produced by the liver, although other sites of production, such as the intestine, have been proposed (Uemura et al., 2002). It recognises carbohydrates such as mannose, glucose, l-fucose, N-acetyl-mannosamine (ManNAc), and N-acetyl-glucosamine (GlcNAc). Oligomerisation of MBL enables high avidity binding to repetitive carbohydrate ligands, such as those present on a variety of microbial surfaces, including *E. coli*, *Klebisella aerogenes*, *Neisseria meningitides*, *Staphylococcus aureus*, *S. pneumoniae*, *A. fumigatus* and *C. albicans* (Davies et al., 2000; Neth et al., 2000; Schelenz et al., 1995; Tabona et al., 1995; van Emmerik et al., 1994).MBL has also been proposed to function directly as an opsonin by binding to carbohydrates on pathogens and then interacting with MBL receptors on phagocytic cells, promoting microbial uptake and stimulating immune responses (Kuhlman et al., 1989). It was shown in a recent study that MBL modifies cytokine responses through a novel cooperation with TLR2/6 in the phagosome (Ip et al., 2008).

7. Lectins and drug delivery

The concept of lectin-mediated specific drug delivery was proposed by Woodley and Naisbett in 1988 (Bies et al., 2004). Delivery of targeted therapeutics via direct and reverse drug delivery systems (DDS) to specific sites provides numerous advantages over traditional non-targeted therapeutics (Rek et al., 2009). Targeted drug delivery increases the efficacy of treatment by enhancing drug exposure to targeted sites while limiting side effects of drugs on normal and healthy tissues (Rek et al., 2009). Furthermore, specific drug delivery increases the uptake and internalization of therapeutics that have reduced cellular permeability (Rek et al., 2009). Lectin based drug-targeting can be done in two ways. In the first approach, carbohydrate moieties form a part of DDS. The carbohydrate tag drives the drug to the endogenous lectins present on the cell surface. In the second approach, lectins are present on the drug surface and it interacts with the glycosylated surfaces of the cells (Gabor et al., 2004). Considering the fact that epithelial cells contain a thin layer of mucus which has mucins that are highly glycosylated proteins, the lectin-encapsulated drug strategy offers great potential. As non-specific interactions are susceptible to changes in pH and to interactions with food digesta, which probably reduce the mucoadhesive effect, specific mucoadhesiva of the second generation seem to be preferable. The second target is the glycocalyx of the absorptive epithelium. In case of identical oligosaccharide structures of the mucin and the glycocalyx, partitioning of the formulation to the cell surface is facilitated due to full reversibility of the mucin–lectin interaction. In case of lectin-matching carbohydrates only at the glycocalyx, the formulation has to penetrate the mucuos layer. Both pathways result in fixation of the drug delivery system closer to the site of absorption. That way cytoadhesion will increase the concentration gradient between the extracellular and intracellular compartment, which facilitates at least passive diffusion of the drug into

the cell. The third target is represented by glycosylated receptors at the cell membrane. The binding of some lectins, such as WGA to the EGF-receptor, induces active receptor mediated endocytosis, which can improve cytoinvasion of prodrugs as well as nanoscaled carrier systems (Gabor, 2004).

In an approach towards pulmonary delivery, lectinised liposomes (130–170 nm in diameter) were screened for binding to alveolar type II epithelial cells (Bruck et al., 2001). As compared to plain liposomes, the binding to A549 cells increased 6–11-fold upon surface modification with wheat germ agglutinin (WGA), Concanavalin A (ConA) or soybean agglutinin. The binding was not affected by a synthetic lung surfactant and no cytotoxic effect of the free lectins or the lectinised liposomes was observed. Upon incubation with primary cultured human alveolar epithelial cells, which exhibit barrier functions, the WGA-liposomes were not only bound but also taken up into the cells. In search for non-viral vectors for gene therapy of cystic fibrosis and as a basis for lectin-mediated gene transfer, 32 lectins were screened for binding and uptake into living human airway epithelium (Yi et al., 2001). Whereas ConA was internalised within 1 h, the lectins from *Erythrina cristagalli* and *Glycine max*, peanut lectin, and Jacalin were taken up into the epithelium within 4 h. The endocytosis of WGA was minimal even after 4 h. Irrespective of the specificity of the lectin–carbohydrate interaction; the internalised lectins exhibited a non-selective binding pattern on the epithelium. Only peanut lectin bound to subpopulations of ciliated and non-ciliated cells.

Owing to their remarkable specificities, plant lectins with affinities for the carbohydrates on microbial cell surface are already well characterised. Given the potential of porphyrins to act as antimicrobials it is pertinent to ask whether lectins could be used *in vivo* to specifically deliver porphyrins into pathogenic microbial cells, thereby improving the efficacy of the treatment, reducing the concentration of the drug required to be introduced into the system and thereby reducing the possible side-effects. In particular, lectins could be successful oral and mucosal drug delivery agents. Not only are a large number of lectins part of our everyday diet, but also several of them are known to survive the harsh conditions of human gastro-intestinal tract. Similarly, attempts have been made to use lectins in ocular drug delivery. Specific hydrophobic binding sites on lectins provide the ideal opportunity to expand the use of these molecules in targeted therapy (Komath et al., 2006).

8. Conclusions

Lectins are ubiquitous in nature and have garnered much attention due to specificity of its interaction with the carbohydrates. Glycosylation is a key step in many cellular processes and with more reports about the change in cell-surface carbohydrates in different pathological conditions, research about exploiting lectins as a therapeutic tool is now at the forefront. Lectins are now routinely used in the identification and purification of glycoproteins. Their use in blood typing as well as in clinical diagnostics is well established. Many lectins show antibacterial, antiviral or antifungal activities in-vitro. However, clinical trials need to be done for establishing their therapeutic effect and optimising their dosage delivery. As microbes use their surface lectins for attachment to the host tissue, dietary/therapeutic lectins may interfere in this interaction. Thus lectins can be used anti-adhesion agents and prevent the colonization of the microbe and hence the establishment of the infection. In the immune system, endogenous lectins play a role in ligand recognition and hence are an important component of the host's defense against microbes. Given their

ability to specifically target different cell types, they have always been looked upon as useful candidates for targeted drug delivery. Research utilizing lectins as carriers of monoclonal antibodies or specific chemotherapeutic agents has been conducted. Alongwith the beneficial effect, lectins have been reported to have caused severe allergic reactions. Most of the information on the acute toxicity of lectins in humans has been derived from observations of incidences of accidental poisoning. Since no experimental data is available to show the possible adverse effects of lectins on humans but can be inferred from experiments with laboratory animals. Although results obtained with mice, rats or pigs cannot simply be extrapolated to humans, the observed effects on the gut and other organs of these animals demonstrate the possible toxicity of the lectins. Thus lectin-based therapeutics for combating infections is very promising owing to its highly selective nature, provided the dosage is well below the toxic limits.

9. References

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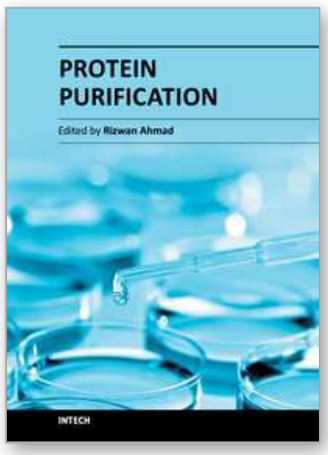

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