Lectins are widely distributed proteins having ability of binding selectively and reversibly with carbohydrates moieties and glycoconjugates. Although lectins have been reported from different biological sources, the legume lectins are the best-characterized family of plant lectins. Legume lectins are a large family of homologous proteins with considerable similarity in amino acid sequence and their tertiary structures. Despite having strong sequence conservation, these lectins show remarkable variability in carbohydrate specificity and quaternary structures. The ability of legume lectins in recognizing glycans and glycoconjugates on cells and other intracellular structures make them a valuable research tool in glycomic research. Due to variability in binding with glycans, glycoconjugates and multiple biological functions, legume lectins are the subject of intense research for their diverse application in different fields such as glycobiology, biomedical research and crop improvement. The present review specially focuses on structural and functional characteristics of legume lectins along with their potential areas of application.

Keywords. Legume lectins; carbohydrate specificity; biological functions; antiviral function; biomedical research

Abbreviations: BFL, Bauhinia forficata Lectin; CRD, Carbohydrate recognition domains; ConA, Concanavalin A; ConBr, Canavalia brasiliensis Lectin; Cramoll, Cratylia mollis Lectin; DBL, Dolichos biflorus Lectin; DLL, Dolichos lablab Lectin; DVL, Dioclea virgata Lectin; ECL, Erythrina cristagalli Lectin; EcorL, Erythrina corallodendron Lectin; FRIL, Flt3 receptor-interacting lectin; Fuc, Fucose; Gal, Galactose; GalNAc, N-acetyl-D-galactosamine; Glec, Glucose; GlecNAc, N-Acetyl-D-glucosamine; GSL, Griffonia simplicifolia Lectin; LCA, Lens culinaris Agglutinin; LTA, Lotus tetragonolobus Lectin; MAL, Maackia amurensis Lectin; Man, Mannose; PHA, Phytohaemagglutinin agglutinin; PNA, Peanut agglutinin; PSA, Pisum sativum Agglutinin; RPbAI, Robinia pseudoacacia Lectin; SBA, Soyabean agglutinin; SPL, Spatholobus parviflorus Lectin; TCLL, Tamarind chitinase like lectin; TLR, Toll like receptor; TxLC-I, Tulipa hybrid lectin I; UEA, Ulex europeus Agglutinin; VFL, Vicia faba Lectin; VML, Vatairea macrocarpa Lectin; WFA, Wisteria floribunda Agglutinin; WGA, Wheat germ agglutinin.

1. Introduction

Lectins recognize and bind carbohydrate moieties and glycoconjugates selectively and reversibly without changing the structure of glycan. The carbohydrate specificity of lectins distinguishes these proteins from other proteins. Lectins are ubiquitous present in nature and their presence has been detected from different biological sources of which plant lectins are thoroughly investigated (Van Damme 2014; Cavada et al. 2019).

Plant lectins constitute a heterogeneous group owing to their biochemical and physicochemical properties, evolutionary relationships, molecular structure, and carbohydrate specificity. They have been known to play important cellular and biological functions for which lectins have always been a subject of intense research (Ingale and Hivrale 2013). Though many lectins have been investigated from different plants, legume lectins are the extensively investigated plant lectin family (Cavada et al. 2020). These lectins have
been reported in higher amounts from seeds but they also present in lesser amounts in vegetative parts of the plants. Legume lectins are one of the important families of homologous proteins and share high sequence and structural similarity (Grandhi et al. 2015). Relationships between the sequences of legume lectins within the same family suggest that these lectins most probably arose from divergent evolution from a single common ancestor. Till date, several lectins from different legumes have been investigated in detail to study their structural and functional characteristics. The existence of carbohydrate-binding domain (CRD; Procópio et al. 2017a) is an important factor for their biological properties and their future biomedical and biotechnological applications. Legume lectins show strong relatedness in primary structure and tertiary structure. Despite this, they show variation in carbohydrate specificities and quaternary structure (Grandhi et al. 2015; Lagarda-Diaz et al. 2017). The variability in carbohydrate-binding specificities of legume lectins makes them a potential tool in glycobiology (Coelho et al. 2017). This review provides a comprehensive and up to date information on structural and biological properties, technological interventions and areas of potential applications of legume lectins.

2. Lectin classes and distribution

More than a century ago, Stillmark (1888) gave the first description of lectins while investigating the effect of castor bean extract (Ricinus communis) on red blood cells. He gave the name ricin to the proteins causing agglutination of red blood cells. Later, another lectin named as ‘abrin’ was isolated from Abrus precatorius seeds. Boyd and Shapleigh introduced the term lectin in the year 1954. The word lectin is taken up from a Latin verb ‘legere’ which has the meaning of ‘to pick up or to choose’ (Boyd and Shapleigh 1954). Since the first insight of lectins, numerous lectins from different plants have been isolated and investigated. ConA was the first lectin, isolated in its pure form by Summner (1936) from Jack bean seeds (Canavalia ensiformis). ConA was also the first lectin whose primary and 3D structures were resolved (Edelman et al. 1972; Hardman and Ainsworth 1972). Lima bean lectin was the first plant lectin that had shown blood group specificity (Boyd and Reguera 1949).

Although, lectins have been reported from varied sources, plant lectins constitute a heterogeneous group of glycoproteins. These proteins show heterogeneity in displaying diverse biological functions owing to their specific carbohydrate-binding property (Goldstein and Hayes 1978). Though the term ‘lectin’ initially introduced describing the property of some proteins having selective carbohydrate binding and the ability to agglutinate erythrocytes (Peumans and Van Damme 1995), studies have added more information on the earlier definition of lectins. Interestingly some plant enzymes have fused carbohydrate binding and catalytic domain and reveal similar properties as lectins have (Collinge et al. 1993). A few type II RIP’s also known as polynucleotide: adenine glycosidase consists of two chains i.e., toxic chain (A) and carbohydrate-binding chain (B) (Barbieri et al. 1993). Some proteins have also been identified with only one carbohydrate-binding site and unable to precipitate glycoconjugates (Van Damme et al. 1994). Additionally, other proteins have also been related to lectins in plants but devoid of any carbohydrate-binding property. Based on these observations, lectins are defined as ‘Any storage proteins possessing at least one non-catalytic domain which binds reversibly to specific mono or oligosaccharides’ (Peumans and Van Damme 1995).

Lectins are ubiquitously distributed glycoproteins characterized for their carbohydrate-binding properties. Lectins have been identified from animals, plants, and microorganisms (Sharon and Lis 2001; Chandra et al. 2006). Numerous lectins have been isolated from plants and in-depth investigated for biochemical and functional characterization. Lectins are distributed in different plant tissues and their amount depends on developmental stage and pathological state. Their highest amount is reported from seeds; therefore they are mainly characterized as storage proteins. In seeds, they mainly accumulate either in vacuoles and may comprise 1% to up to 10 % of total seed proteins (Laija et al. 2010). However, sometimes they constitute about 50% of the total storage proteins (Van Damme et al. 2008). In seeds, lectins are synthesized as precursor molecule and sequestered in protein bodies during seed development and broken down during seed germination for providing essential amino acids. Apart from seeds, lectins have also been identified from vegetative tissues in low concentration. Additionally, plants also express minute amounts of lectins in response to abiotic and biotic stresses. In absence of stress, inducible lectins are not synthesized at detectable levels. The synthesis of these lectins is regulated by the cross talk of different plant hormones (Baboshia 2008). The most investigated plant lectins belong to the family Leguminosae and most of them have been purified from mature seeds. Legume lectins have broad specificity in
binding with carbohydrate moieties and glycoconjugates. Among various legume lectins, PHA and ConA are the most investigated legume lectins (Loris et al. 1998).

Plant lectins have been classified based on their carbohydrate-binding specificity, molecular structure, abundance, and subcellular localization into different groups. Merolectins have a single carbohydrate-binding domain and don’t have agglutination activity. Hololectins have two or more identical carbohydrate-binding domains, which bind either same or structurally similar sugars. Hololectins are di- or multivalent in structure and have agglutination activity. Chimerolectins are fusion proteins for having carbohydrate-binding domain fused with other catalytically active domain. Superlectins are a special type of chimerolectins containing two or more fused carbohydrate-binding domains (Van Damme et al. 2011).

Based on their carbohydrate-binding specificity lectins have been classified as (i) Mannose/glucose binding; (ii) Galactose/N-acetyl-D-galactosamine binding; (iii) N-acetyl-D-glucosamine binding; (iv) L-Fucose binding lectin; (v) Sialic acid binding (Goldstein and Poretz 1986; Van Damme et al. 1998). However, this classification doesn’t give the whole picture of carbohydrate specificity of lectins as some lectins recognize and bind with complex glycan structures. Moreover, some monosaccharides-specific lectins have also been identified with specificity to bind with oligosaccharides. Besides binding with carbohydrates, plant lectins are also able to bind with non-carbohydrate ligands such as 8-anilinonaphthalene-1-sulfonate (ANS) (Maliarik and Goldstein 1988), porphyrins (Pandey et al. 2009), and adenine (Shetty et al. 2013). Binding with non-carbohydrate molecules contributes to the diverse biological functions of plant lectins.

Plant lectins classification based on the ability to recognize and bind specific sugars does not give any information on evolutionary relationships. Based on comprehensive genome/ transcriptome analysis, plant lectins have been classified into 12 distinct families which are Agaricus bisporus agglutinin, Amaranthin, Chitinase-related lectins, Cyanovirin, Euonymus europaeus agglutinin, Galanthus nivalis lectin, Hevein, Jacalin, Legume lectins, LysM domain lectins, Nicotiana tabacum agglutinin (Nictaba) and Ricin B (Macedo et al. 2015) and each family is named after the highly investigated lectin.

Plant lectins have also been classified based on their expression pattern and subcellular localization. One group is classical lectins which are present in seeds and synthesizes constitutively from their inactive precursors with a signal sequence on RER and become active only after post-translational processing. After their biosynthesis, they are either stored in the vacuole or sorted to various extracellular compartments. These lectins have been reported to play crucial roles in plant developmental processes (De Hoff et al. 2009; Lannoo and Van Damme 2010; Nonomura et al. 2020) as well as in plant defense (Vandenborre et al. 2011; De Schutter and Van Damme 2015; Van Holle and Van Damme 2018). Another group includes inducible lectins, which are synthesized without signal peptide on free ribosomes and accumulate in the nucleus and cytoplasm (Van Holle et al. 2017; Lambin et al. 2020). Inducible lectins are present in lower amounts in normal conditions but their synthesis is induced after exposure to biotic and abiotic stress (Lannoo and Van Damme 2010; Vandenborre et al. 2011; Van Holle and Van Damme 2018).

Lectins are an important component of plant’s innate immune system. Lectins recognize PAMP’s (Pathogen-associated molecular patterns) and DAMP’s (Damage-associated molecular patterns). PAMP’s are pathogen-derived elicitors [(Bacterial and fungal exopolysaccharides, peptidoglycan lipopolysaccharides and fungal cell wall fragments (β-glucans, chitin, and chitosan)] whereas DAMP’s are host-derived elicitors [cell wall fragments, short and long oligogalacturonides (degradation products of pectin), arabinoxylan and small carbohydrate molecules (sucrose, trehalose, raffinose, and glucose)] (Van Holle and Van Damme 2018). At the cell surface, lectin domains (LecPs, LecRLKs, and LecRLPs), constitute a crucial component of the plant’s innate immune system (Bellande et al. 2017). After binding with PAMP’s and DAMP’s with lectin domains, a downstream signaling cascade is triggered which includes Ca^{2+} influx, ROS production, activation of MAP kinase pathway (Mitogen-Activated Protein Kinase Pathway) modulation of hormone biosynthesis and modulation of expression of defense-related genes, and synthesis of defense molecules (Lannoo and Van Damme 2014; De Schutter and Van Damme 2015).

Nucleocytoplasmic lectins interact with various intracellular effectors and play a crucial role in plant defense via activating effector-triggered immunity. Some nucleocytoplasmic lectins alter transcriptional programming by chromatin remodeling during plant defense (Van Holle and Van Damme 2018). Recently, Sahid et al. (2020) reported that Osr40c1, a nucleocytoplasmic lectin from rice also interacts with OsSAM2 protein (S-adenosine methyltransferase}
enzyme) and induces polyamine biosynthesis to impart drought tolerance.

Despite playing a crucial role in plant defense, a few nucleocytoplasmic plant lectins have been investigated in detail (Van Holle and Van Damme 2018). Therefore, comprehensive efforts are required to generate more information on their endogenous ligands and their contribution to intracellular signaling during plant defense and development. The information available in the reviews (Van Damme et al. 2004; Lannoo and Van Damme 2010; Tsaneva and Van Damme 2020) will be helpful in conducting future research on nucleocytoplasmic plant lectins. The model showing lectin-mediated signalling in plant defense is presented as figure 1.

3. Biological implications of legume lectins

Lectins recognize diverse sugar structures and have been shown to possess important biological activities due to which lectins are the focus of intense research.

3.1 Agglutination

Hemagglutination assay distinguishes lectin from the mixture of proteins thereby is the easiest method to detect lectins in biological sources. In agglutination reaction, lectin binds with erythrocytes and forms multiple cross-bridges between them. Agglutination inhibition with sugars confirms the detection of lectin indicated by agglutination assay (Moreira et al. 1991). The difference between the binding of lectins and other carbohydrate-binding proteins is that they will never change their carbohydrate-binding properties. Since lectins can easily bind with foreign glycans they are considered an important tool in glycobiology.

Antimicrobial lectins interact with the glycocomponents present on the cell surface of microorganisms, thereby interferes with their growth, multiplication, and spread. The antimicrobial actions of legume lectins are reviewed under subheads 3.2, 3.3 and 3.4.

3.2 Antibacterial activity

Antibacterial activity of lectins mainly attributed to their binding with carbohydrate components of the bacterial cell wall or extracellular glycans. Antibacterial lectins strongly interact with N-acetyl-D-acetylglucosamine (NAG), N-acetyl-D-muramic acid (NAM), and tetrapeptide components of cell wall of gram-positive bacteria and with lipopolysaccharides (LPS) of gram-negative bacteria (Bourne et al. 1994; Ayoub et al. 1994; Qadir et al. 2013; Lagarda-Diaz et al. 2017). This interaction not only restricts the interaction of bacteria between the membrane and carbohydrate-binding proteins but also prevents penetration of the host cytoplasm (Mishra et al. 2019). Plant lectins cannot alter membrane structure and/or its permeability or disturb the metabolism of bacteria (Peumans and Van Damme 1995). Lectins from legumes Bauhinia variegata L., Dolichos lablab L., Trigonella foenum-graecum, Trifolium alexandrium L. and Delonix regia have shown antibacterial activity against some bacterial pathogens such as Mycobacterium rhodochrous, Bacillus cereus, Bacillus megaterium, Bacillus sphaericus, E. coli, Corynebacterium xerosis, Serratia marcescens and Staphylococcus aureus (Sammour and El-Shanshoury 1992). Gautam et al. (2018a) reported antibacterial activity of chickpea lectin against against E. coli, B. subtilis, S. marcescens and P. aeruginosa. El-Araby et al. (2020) reported the antibacterial activity of fava bean lectin, lentil lectin, and pea lectin against Klebsiella pneumonia, Staphylococcus aureus, Streptococcus mutants and Pseudomonas aeruginosa bacteria. Legume lectins have also been shown to inhibit bacterial biofilm formation (Islam and Khan 2012) and could be a potential candidate for the development of a non-antibiotic control measure of biofilm formation.

3.3 Antifungal activity

Plant lectins cannot bind with glycoconjugates present on fungal membranes or invade the cytoplasm of fungal cells due to the thick and rigid cell wall. However, indirect effects of lectin binding with cell wall components could affect fungal survival or other activities. For example, the binding of lectins with hyphae inhibits the growth of fungi, reduces nutrient absorption, and interferes with the spore germination process. The binding of lectins to the fungal cell wall also leads to swollen hyphae, vacuolization of cell content, and lysis of the hyphal cell wall. Chitin-binding lectins seem to play important role in plant defense against pathogenic fungi. In vitro studies have demonstrated that WGA (Wheat germ agglutinin) a chitin-binding lectin, inhibited the germination of fungal spore and hyphal growth of Trichoderma viride that confirms the antifungal action of chitin-binding lectins (Schlumbaum et al. 2018). 2004; Lannoo and Van Damme 2010; Tsaneva and Van Damme 2020) will be helpful in conducting future research on nucleocytoplasmic plant lectins. The model showing lectin-mediated signalling in plant defense is presented as figure 1.

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Although, this finding reported the antifungal activity of plant lectins, more definitive proof came from the study of Broekaert et al. (1989) who demonstrated the antifungal role of chitinase-free lectin from stinging nettle (Urtica dioica) against Botrytis cinerea, Trichoderma hamatum, and Phycomyces blakesleeanus. Till date, antifungal activity of various legume lectins has been well documented (Ye et al. 2001; Yan et al. 2005; Chen et al. 2009; Boleti et al. 2007; Sitohy et al. 2007; Qadir et al. 2013; Ang et al. 2014; Kumar et al. 2014; Gautam et al. 2018a; Elaraby et al. 2020).

### 3.4 Antiviral activity

The envelope of retroviruses and many other enveloped animal viruses is covered with glycoproteins. Antiviral activity of lectins depends on their ability to bind with complex glycans added as a result of post-translational modifications on viral envelope proteins which prevent interactions with host cells (Botos and Wlodawer 2003; Barton et al. 2014; Akkouh et al. 2015). Muller et al. (1988) for the first time reported that D-mannose specific lectin from Gerardia savaglia blocks HIV infection in H9 cells by preventing syncytium
formation in HTLVIIIB/H9-Jurkat cell system and HIV-1/human lymphocyte system. Several lectins from legumes such as Canavalia ensiformis (ConA), Lens culinaris (LCA), Vicia faba (VFA), Pisum sativum (PSA), Glycine max (SBA) and Phaseolus vulgaris (PHA-E) have also been found effective in inhibiting the interaction of the HIV virus with CD^4^ cells through binding with glycoprotein gp-120 present on virus envelope (Lagarda-Diaz et al. 2017).

Lectins specificity to bind with mannose/glucose/N-Acetyl glucosamine sugars has also been identified as a potent antiviral agent against coronaviruses (Keyaerts et al. 2007; Nascimento da Silva et al. 2020). SARS-coronavirus spike proteins is heavily glycosylated and contain many N-glycosylation sites (Krokhin et al. 2003), therefore lectins having specificity to bind with glycans linked with spike protein may inhibit the growth of coronaviruses. Keyaerts et al. (2007) identified two targets for antiviral action of lectin against SARS-CoV. The first target was located early in the replication cycle, most probably viral attachment, and the second target was located at the end of the infectious virus cycle. They concluded that lectins probably interfere with the glycans on the spike protein during virus entry in the host cells and virus release, thus have inhibitory activity against coronaviruses.

In the last 14 to 15 months, we have witnessed the loss of thousands of lives worldwide due to the dissemination of a new type of coronavirus (SARS-CoV-2, Covid-19). The first case of this novel coronavirus was reported from Wuhan, China in December, 2019. Since then, the virus has now been detected in different countries across the globe. The Covid-19 disease virus (SARS-CoV-2) is an enveloped virus covered with heavily glycosylated glycoproteins such as Spike protein (S-protein), Membrane protein (M-protein), Envelope protein (E-protein), and Nucleocapsid protein (N-protein) (Ahmed et al. 2020; Srivastava et al. 2021). These proteins have been identified to play a crucial role in SARS-CoV-2 virus pathogenesis in the host cells (Stemberg and Naujokat 2020; Verma et al. 2020). S-protein mediates virus entry in host cell through binding with human angiotensin-converting enzyme 2 (hACE2) and also interacts with host immune system (Ou et al. 2020; Vankadari and Wilce 2020; Walls et al. 2020; Luan et al. 2020). Besides structural proteins, glycosylated nonstructural proteins (3a protein), also determines the virulence of SARS-CoV-2 (Fung and Liu 2018; Issa et al. 2020). Interaction of these glycoproteins of the SARS-CoV-2 virus with lectins should be in-depth investigated for their antiviral action against this deadly virus (Sohrab et al. 2020; Capell et al. 2020).

Recently, a glucose/mannose lectin from hyacinth bean (Lablab purpureus) [Flt3 receptor-interacting lectin (FRIL)], also known as DLL-I, was purified and investigated for its antiviral action against the SARS-CoV-2 virus (strain hCoV-19/Taiwan/NTU04/2020) (Liu et al. 2020). The study revealed that FRIL at concentrations higher or equal to 6.25 μg/ml inhibited the cytopathic effect of the SARS-CoV-2 virus. Moreover, FRIL was able to bind with the N-glycosylated S-protein of the SARS-CoV-2 virus. FRIL also had antiviral activity against the influenza virus. The authors concluded that FRIL could have potential application in the treatment/prevention of Covid-19 and influenza disease (Liu et al. 2020). The encouraging results from the study, lectins from different sources should be investigated for their antiviral action against SARS-CoV-2 and other enveloped viruses (Nascimento da Silva et al. 2020).

3.5 Anti-cancer activity

The research interests in exploiting the potential of lectins as an anticancer molecule have increased in recent times (Gautam et al. 2020). The carbohydrate-mediated cell recognition; communication and adhesion are essential processes for tumor progression and metastasis in cancer. One of the important characteristics of cancer cells is that they display altered glycan structures on cell surfaces and can be explored to develop lectin-based tools for diagnostic and therapeutic research on cancer. Due to the carbohydrate-binding specificity of lectin, lectins have become an important tool to study carbohydrate expression profiles of cancer cells, metastatic distribution patterns, and prognosis of lymphatic invasion (Brooks and Carter 2001; Konno et al. 2002). Fucosylation of proteins and lipids in tumor cells has been explored for the diagnosis of cancer (Miyoshi et al. 2012). Legume lectins exert anticancer activity by inducing caspase-independent, and caspases and mitochondrial-dependent apoptosis pathways in cancer cells. Upon binding with glycoconjugates expressed on cancer cells, lectins increase the production of ROS (Reactive Oxygen Species) in cancer cells and result in their autophagic and apoptotic cell death (Mukhopadhyay et al. 2014; Panda et al. 2014). Moreover, the increased level of ROS in cancer cells also induces caspases and SEK/JNK pathway and leads to programmed death of cancer.
cells (Polito et al. 2009). Lectin binding also increases the expression of tumor suppressor proteins (p38 ad p53) in cancer cells (Bantel et al. 1999; Lyu et al. 2002; Hostanska et al. 2003). Moreover, lectin binding also alters the signaling pathways involved in the expression of Fas, Bax, Bcl-XL and Bcl-2 proteins disrupts the mitochondrial membrane potential and leads to apoptosis through ROS induced p38-p53 pathway in mitochondria (Liu et al. 2009; Lam and Ng 2010).

Amin et al. (2007) reported that ConA mediates p73-dependent apoptosis in p53-null cells by inhibiting the Akt survival signaling and activating Foxo-Bim signaling. Lectin induced ER stress and UPR (Unfolded Protein Response) in cancer cells leads to up-regulation of IRE-1α, CHOP and activation of caspase 12 (Chan et al. 2012). Besides apoptosis, legume lectins also exert anticancer activity through autophagy (Bhutia et al. 2019). Chang et al. (2007) reported ConA mediated autophagy in hepatoma cells through activation of BNIP3-mitochondrial pathway in which BNIP3 depolarizes mitochondria, and increases ConA permeability to the mitochondrial surface, and initiates autophagy. Con A also induces autophagy in cancer cells by mediating PI3K/Akt/mTOR and MEK/ERK pathway (Roy et al. 2014). In addition to this, a proinflammatory cytokine, macrophage migration inhibitory factor (MIF), has been reported to play important role in ConA mediated autophagy (Lai et al. 2015). The anticancer activity of lectins from legumes such as Phaseolus vulgaris (Lam and Ng 2010; Fang et al. 2010, 2011; Chan et al. 2012, 2016; Ang et al. 2014; Wang et al. 2021), Phaseolus lunatus (Wu et al. 2016), Cicer arietinum (Kumar et al. 2014; Gautam et al. 2018b), Abrus precatorius (Rammnath et al. 2009), Astragalus membranaceus (Huang et al. 2012), Astragalus mongholicus (Yan et al. 2009), Dioclea lasiocarpa (Gondim et al. 2017), Glycine max (Ye and Ng 2011; Panda et al. 2014), Sophora flavescens (Liu et al. 2008; Shi et al. 2014), Vicia faba (Jordinson et al. 1999), Lotus corniculatus (Rafiq et al. 2013), Bauhinia forficata (Silva et al. 2014), Bauhinia ungulata (Silva et al. 2013; de Sousa et al. 2016), Cratylia mollis (de Oliveira et al. 2017), Calliandra surinamensis (Procópio et al. 2017b), and Entada rheedii (Naik and Kumar 2020) have been well documented.

3.6 Legume lectins and immune homeostasis

Immune homeostasis is defined as the equilibrium state is maintained by a network of components of immune and adaptive system that continually monitor their environment, actively distinguishing between self and non-self, establishing cell-to-cell communication to protect from diseases (Crimeen-Irwin et al. 2005). The components of immune and adaptive system with specific functions and ability to produce and release molecules and exerts immuno-modulatory response. In addition to these components, different naturally occurring compounds can generate immuno-modulatory responses. Studies have revealed that lectins have immune-modulatory activity, which include activation of Th1, Th2 or Th17 responses (Coelho et al. 2017). Lectins induce mitogenic effect by stimulating the proliferation of T-cells (Kilpatrick 1999). Mitogenic activity of lectins depends on their interaction with specific carbohydrates on T-cell surface receptors (TCR). Binding of lectins with TCR receptors releases secondary messengers and start downward signaling pathways such as increase in cytosolic Ca^2+ levels, cytokines release, leading to immunomodulatory reaction. Lectins stimulate the synthesis of multiples clones of T cells, therefore considered as polyclonal mitogens. Interactions between lectins and T cells have been proved useful for analysis of biochemical events in T-cell activation mechanism and its regulation (Sharon and Lis 2004). Upon mitogenic activation, T-cell produces high amount of cytokines, IL-2, IFN-γ and TNF-α. Lectin binding with surface receptors on T-cells triggered transmembrane signals which induce mitogenic effects on lymphocytes through increasing cytosolic Ca^2+ concentration and ROS (Reactive Oxygen Species) production (de Melo et al. 2010) and TCR-dependent mechanism (de Melo et al. 2011) and lead to the proliferation of lymphocytes. PHA is the first mitogenic lectin (Teixeira et al. 2012). Cramoll and ConA lectins also showed high mitogenic activity in mice splenocytes in vivo (de Melo et al. 2011). Both PHA and ConA lectins have been used extensively for in vitro cell proliferation experiments. de Oliveira et al. (2011b, a) demonstrated immunomodulatory action of ConBr, a lectin isolated from Canavalia brasiliensis seeds. ConBr was able to induce in vitro proliferation of splenocytes with minimal damage to the cellular structure. Furthermore, ConBr increased in the production of cytokines such as IL-2, IL-6 and IFN-γ production and decreased IL-10. These findings indicate potential immunomodulatory effect of this lectin in conjunction with intrinsic role of carbohydrates in intercellular communication related to the inflammatory process.
Due to the carbohydrate-binding specificity, many plant lectins have shown insectistatic and insecticidal activities. Artificial insect feeding assay with plant lectins has shown adverse effects on feeding behavior, fecundity, and growth and development of insects (Vandenborre et al. 2011). The extent and type of

| Lectin type     | Structure | Example                                      | PDBID     | Reference               |
|-----------------|-----------|----------------------------------------------|-----------|-------------------------|
| Merolectin      | ![Merolectin Diagram](image1) | ![Merolectin Example](image2) | 1Q9B      | (Hevein Protein)        | Reyes-Lopez et al. (2004) |
| Hololectin      | ![Hololectin Diagram](image3) | ![Hololectin Example](image4) | 2PEL      | (Peanut Lectin)         | Banerjee et al. (1996)    |
| Chimerolectin   | ![Chimerolectin Diagram](image5) | ![Chimerolectin Example](image6) | 3IWR      | (Class I chitinase protein from Oryza sativa L. japonica) | Kezuka et al. (2010) |
| Superlectin     | ![Superlectin Diagram](image7) | ![Superlectin Example](image8) | TxLC-I lectin (Tulip bulbs) | - | - |

Table 1. Domain structure-based classes of lectin

Lectin classification based on molecular structure. The circle and hexagonal shape represents lectin domain and carbohydrate binding site, respectively. The rectangle and triangle shapes represent additional protein and metal binding domain, respectively.
Entomotoxic effects of lectin are dependent on various factors such as glycosylation pattern, insect species, and stage of development (Michiels et al. 2010). In the last few decades, insecticidal and insecticidal activities of plant lectins have been extensively investigated against agriculturally important insects.

Entomotoxic lectins are stable in a wide range of pH and able to resist proteolytic degradation in the insect gut. Insect feeding on plants releases lectin from disrupted plant structures and bind with different glycoconjugates and other structures in the insect midgut. Since the epithelial cell lining of the insect gut is directly exposed to lectins, therefore is the import target site of insecticidal lectins. The epithelial cells form peritrophic membrane covered with a grid-like network of glycoproteins and glycoprotein receptors containing glycan structures (Hegedus et al. 2009). The presence of glycan structures makes the peritrophic membrane a potential binding site for insecticidal lectins.

Interaction of lectins with glycan structures leads to disruption of epithelial cells lining in the insect gut, elongation of striated border microvilli, swelling of epithelial cells and increase the membrane permeability for harmful substances in hemolymph and affect the growth and development of insects (Majumder et al. 2005; Lagarda-Diaz et al. 2009; Vandenborre et al. 2011; Sprawka et al. 2015). Some lectins can pass through midgut epithelium and accumulate in fat body cells, hemolymph, ovarioles, and malpighian tubules (Powell et al. 1998a, b; Macedo et al. 2015). Lectin binding with secreted glycoproteins such as ferritin (Sadeghi et al. 2008) results in the formation of large complexes, therefore cannot diffuse back through the peritrophic membrane for being recycled in the digestive system. This results in leakage of digestive enzymes in the insect gut (Vandenborre et al. 2011). Several enzymes such as membrane-bound amino-peptidases, α-amylases, α- and β-glucosidases, β-subunit ATP synthase, clathrin heavy chain, HSP70, NADH quinone oxidoreductase, sarcoplasmic reticulum type calcium ATPase, sucrase, trypsin-like enzymes and vacuolar ATPase, are the other potential binding sites of lectins in insects (Macedo et al. 2015). Lectins also exert entomotoxic effects via induction of caspase-dependent apoptotic pathway in the insect gut (Sprawka et al. 2013, 2015; Tang et al. 2020).

Insect glycan structures are mainly high mannose and paucimannose-type, thus mannose/glucose binding lectins have a great interest as insectstatic and insecticidal lectins. A small number of complex glycan structures have also been identified in insect gut (Michiels et al. 2010). The effect of lectins on the feeding behavior of insects is related to their binding with taste and olfactory receptors (Glycosylated integral membrane-spanning proteins), and interfere with their functioning or even initiates false signals to the nervous system (Michiels et al. 2010).

The entomotoxic nature of legume lectins was first reported for *Phaseolus vulgaris* lectin (PHA-E) by Janzen et al. (1976). They reported inability of bruchid beetle (*Callosobruchus maculatus*) to feed on black bean seeds (*Phaseolus vulgaris* L.). Artificial feeding assay with purified lectin showed inability of insects to survive at 5% and even at 0.10% concentrations. They reported inability of bruchid beetle (*Callosobruchus maculatus*) to feed on black bean seeds (*Phaseolus vulgaris* L.). Gatehouse et al. (1984) also reported insecticidal property *Phaseolus vulgaris* lectin (PHA). Numerous legume lectins have been investigated for entomotoxic activity against different insects (table 2).

It has been observed that some plant lectins exhibit entomotoxic activity against a particular insect while other posses broad insecticidal action against insect belong to different orders. Since different insects have very low pH (strongly acidic) to a very pH (alkaline) in midgut, therefore entomotoxic lectins must have capacity to resist the hostile environment in insect midgut (Vandenborre et al. 2011). Another important factor associated with the variable entonotoxic action of lectins is their ability to resist proteolytic degradation in insect midgut (Zhu-salzman et al. 1998). Insects have their own proteolytic machinery and for exerting entomotoxic effect, lectins must be able to resist proteolytic degradation in insect midgut (Felton 2005). It is a well-known fact that the lectins have specificity in binding with carbohydrate moieties, therefore different lectins will interact differentially to target sites in the insect midgut. This can be understand by the action of wheat germ agglutinin (WGA) which is not toxic to pea aphid (*Acyrthosiphon pisum*) which lacks a functional peritrophic membrane, while GNA and ConA lectins exert entomotoxic activity against this insect (Rabbe et al. 1995). Since glycosylation patterns in insect midgut change depending on the development stage or other factors, the binding of lectin may differ in insect gut (Aoki et al. 2007; Michiels et al. 2010; Vandenborre et al. 2011). Some plant lectins have entomotoxic effects at larval stage and some of them have at adult stage (Vandenborre et al. 2011). For example, *Pisum sativum agglutinin* has shown entomotoxic effects only on larvae of pollen beetle, not on adults (Melander et al. 2003).
4. Carbohydrate specificities of legume lectins

One of the important features of legume lectins is that they are storage proteins synthesized as inactive precursor proteins with a signal peptide. Their biosynthesis starts on membrane-bound ribosomes or polyribosomes in the cytosol. Targeting of these proteins to the endoplasmic reticulum is mediated by the signal sequence present at the N-terminus of the growing polypeptide chain. As the polypeptide chain elongates, the signal peptide is removed co-translationally by the signal peptidase enzyme. The polypeptide chain releases into ER lumen. Glycosylation is an important post-translational modification that ensures proper folding and functioning of proteins. N-linked glycosylation occurs at consensus sequences (Asn-X-Ser/Thr) where X is any amino acid except proline. The extent of glycosylation confers stability to proteins. Most of the legume lectins are glycosylated with mannose type and complex-type glycans. Differences in glycosylation patterns result in the formation of different glycoforms (Van Damme et al. 1998).

After glycosylation, they accumulate in protein storage bodies in seeds (De Hoff et al. 2009) where some proteolytic events occur such as removal of C-terminal propeptide (Vitale et al. 1984) and generation of β-chain (N-terminus) and α-chain (C-terminus) (Lioi et al. 2006). The association of these chains forms dimers; they are then proteolytically processed to form tetramers containing two separate α and β-chains. The trimming of the C-terminal of the polypeptide is a common event in legume lectin biosynthesis and also responsible for the generation of lectin isoforms (Rabijns et al. 2001; Loris et al. 2003). Besides fulfilling the role of storage proteins, seed lectins also have a crucial role to play during plant defense (Chrispeels and Raikhel 1991). Lectins are also localized to vegetative tissues such as roots, nodules, bud, and bark in smaller amounts (De Hoff et al. 2009). They show considerable sequence variation...
similarity with seed lectins. For example, DB58 lectin from Dolichos biflorus stem and leaf lectin share sequence similarity with D. biflorus seed lectin (Schnell and Etzler 1988).

Typically, the primary structure of legume lectins are protomers made up of 250 to 300 amino acid residues (~25 to 30kDa) and show evolutionary conservedness (Wales et al. 1991). Most of the legume lectin promoters can give rise to single-chain lectins which don’t have cleavable sites (PHA, ConA, SBA). In some instances, the protomers are proteolytically processed and produce two chains, β-(N-terminal, large) and α-(C-terminal, short), thereby usually referred to as two chain lectins (Vicia faba lectin and Pisum sativum lectin). Most, but not all, are glycosylated and carry up to three asparagine-linked oligosaccharides per subunit (Van Damme et al. 1998). The conserved amino acids include several of those that participate in hydrogen bonding or hydrophobic interactions with the monosaccharide held in the combining site and almost all residues that coordinate the metal ions. Primary structure analysis of legume lectin also reveals high conservedness in the ligand-binding sites. The analysis of primary sequences of legume lectins is the best way to investigate evolutionary relatedness, to predict their processing pathway, to study folding patterns, and to investigate carbohydrate-binding specificity of lectins.

The dominance of β-strands is an important characteristic of the secondary structure of legume lectins. Legume lectins have higher proportion of β-sheets, β-turns, and negligible amount of α-helix in their secondary structure (Swamy et al. 1985), thus considered as β-sheet proteins. The structural components of the secondary structure have implications in the analysis of the 3D structure of legume lectins. ConA was the first lectin for which a high resolution crystallographic structure was resolved (Edelman et al. 1972; Hardman and Ainsworth 1972). Since then 3D structures for different legume lectins have been also elucidated (table 3).

In general, the 3D structure of legume lectins consists of flat six-stranded anti-parallel β-sheets (Back face) and seven-stranded curved anti-parallel β-sheets (front face), interconnected by several loops (figure 2a). Nearly 50% of amino acid residues are present in loops. The negligible amount of α-helix is one of the important features of the structure of legume lectins. The folding patterns of secondary and tertiary structures of legume lectins are superimposable to each other. The dome-like structure represents the β-sandwich structure, structurally related to the ‘Jelly roll fold’ (Stirk et al. 1992) also known as lectin fold (Srinivasan et al. 1996) with two hydrophobic cavities, formed between the front and back β-sheets and between curled loop and front β-sheets. The concavity in front β-sheets and a second hydrophobic core formed carbohydrate-binding domain is well suited to be bind with carbohydrates. Legume lectins require divalent cations particularly Ca\(^{2+}\) and Mn\(^{2+}\) for their activity as they are essential for maintaining the stability of the carbohydrate-binding site. Amino acids involved in the formation of the metal-binding site namely glutamic acid, aspartic acid, and histidine in legume lectins are conserved (Rini 1995).

The carbohydrate and metal-binding sites are localized in close vicinity at the top of the front sheet in the 3D structure (Cumming et al. 2017). In legume lectins structure, four loops, i.e., A, B, C, and D are responsible for the formation of CRD (Carbohydrate Recognition Domain) (Sharma and Surolia 1997; Benevides et al. 2012). The four conserved amino acids in loops are essential for binding with carbohydrates (figure 2b). Aspartic acid residue in loop A forms hydrogen bonds between its side chain and carbohydrate ligand. The binding of two metal ions is stabilized by four water molecules (Adar et al. 1998). Isomerization of trans peptide bond to the cis orientation between alanine and aspartic acid residues is necessary for proper orientation of asparagine and arginine residues in carbohydrate bonding site that further stabilized the carbohydrate-binding site. The formation cis peptide bond is driven by the binding of metal ions. In loop C, asparagine via amide group forms a hydrogen bond with the hydroxyl group of the binding sugar (Cummins et al. 2017). Some legume lectins also have a hydrophobic cavity, which is responsible for their non-covalent interactions with non-carbohydrate ligands. Binding with non-carbohydrate ligands don’t have any influence on the carbohydrate-binding specificity of lectins and also leads to their diverse biological functions (Srinivas et al. 2000). Various legume lectins have been identified to be specific to galactose, N-acetyl-D-galactosamine, mannose, glucose, N-acetyl-D-glucosamine, fucose, and more complex carbohydrate structures. Variability in the conformation and size of C and D loops determines carbohydrate-binding specificity of lectins (Sharma and Surolia 1997; Rao et al. 1998). A complex network of hydrogen bonding, hydrophobic interactions, Vander Waal’s forces, and metal ion co-ordination bonding determines the carbohydrate-binding specificity of lectins.
The quaternary structure of legume lectins is characterized by an oligomeric structure in which lectin monomers are assembled as homodimers (Canonical legume lectin dimer) or homotetrameric structure (dimmers of dimers) (Lagarda-Diaz et al. 2017). Moreover, heterotetrameric structures have also been observed. Hydrophobic interactions, hydrogen bonds, disulfide, and salt linkages are the main forces maintaining the structure of legume lectins (Sharma and Surolia 1997; Manoj and Suguna 2001). Typically different types of quaternary structures are known for legume lectins [Canonical, ECorL-type, GS4-type, DBL-type, ConA-type, PNA-type, GS1-type, and DB58-type and Arcelin-5-type (monomeric) structures]. The difference between the protomers of legume lectins lies in β-chain structure corresponds to C-terminal in which 12 amino acid residues become truncated. The presence of the α-helix at the C-terminal is responsible for the joining of two protomers and stabilization of the structure.

The interaction of proteins with carbohydrates has always been an interesting area of research for biologists for having a deep understanding of myriad of biological processes such as cell-cell recognition and disease resistance (Van Holle et al. 2017). Legume lectins owing to their specific carbohydrate binding have provided a model system for glycobiologists understanding molecular basis of these biological processes. They have also been used for the purification and characterization of complex carbohydrates and glycoconjugates. The carbohydrate specificity of some legume lectins to different carbohydrates is presented in table 3.

Studies have revealed that the interaction of hydroxyl groups of sugars to the amino acid side chains via hydrogen bonding and hydrophobic forces is required for lectins binding with carbohydrates. Interactions with these hydroxyl groups serve function of orienting sugar molecules in binding site (Drickamer 1997). The tertiary structures of lectins bound with their bound carbohydrates are also presented in table 3.
sugar ligands and mutational studies revealed conserved triad of amino acids residues (Asp, Gly/Arg, Asn) responsible for carbohydrate binding. All of them bind the monosaccharide through main chain amides and not through their side chain residues. The substitution of either Aspartic acid or Asparagine in several legume lectins resulted in loss of sugar binding activity (Adar and Sharon 1996). In addition to this a conserved aromatic residue (Phenyl alanine/Tryptophane /Tyrosine) in primary binding site is involved in sugar stacking interactions. In legume lectins, specific to D-galactose or D-N-acetyl glucosamine oxygen in the side chains of aspartic acid residue are hydrogen bonded to the C3-OH and C4-OH group of monosaccharide while amide chain of glycine make hydrogen bond only with C3-OH group (Sharon and Lis 2002). Further, an amino acid triad is required for the stacking of the hydrophobic face of the sugar. Aspartic acid and amide of asparagine coordinate with Ca$^{2+}$ present in all legume lectins, which helps to position these residues in the correct place at the sugar binding site (Lis and Sharon 1998). Ca$^{2+}$ and Mn$^{2+}$ ions present in all legume lectins are coordinated via the carboxylic group of the two conserved Aspartic acid residues. Binding of the two metal ions is further stabilized by four water molecules. The presence of a rare cis-peptide bond between the conserved Aspartic acid of the triad and the preceding amino acid, which is almost always alanine is an added characteristic (Sharon and Lis 2002). The cis-peptide bond is required for the proper orientation of Asp in the combining site. The structure of metal binding region plays a major role in determining sugar specificity of lectins (Yamamoto et al. 2000). Differentiation between galactose and mannose by legume lectins is due to the differential orientation of the ligand.

In mannose/glucose lectins like ConA (Derewenda et al. 1989), LOL-I (Lathyrus ochrus Isolectin) (Bourne et al. 1990) and lentil lectin (Loris et al. 1994), galactose and mannose are oriented in a way such that the carboxyl oxygens of Asp are H-bonded to 6-OH and 4-OH of the sugars and amide of the asparagine side chain is hydrogen bonded to the 4-OH. In addition, the main chain amide of glycine, forms H-bonds with 3-OH. In contrast, in galactose specific lectins like ECorL (Adar and Sharon 1996), SBA (Dessen et al 1995), and PNA (Banerjee et al. 1996), Aspartic acid oxygens form hydrogen bonds with 4-OH and 3-OH and amide of Asparagine and Glycine to 3-OH. Therefore, legume lectins, conserved amino acid triad, stabilized and positioned by metal ions or water molecules, responsible for binding of diverse monosaccharides (Sharon and Lis 2002). Using Ligplot analysis, the carbohydrate binding specificity analysis of rice bean lectin (RbL) revealed that C3-OH and C4-OH groups of galactose sugar were hydrogen bonded to oxygen groups of aspartic acid$^{112}$ residue (OD1 and OD2) with 2.56 Å and 2.84 Å bond length while
glycine$^{130}$ via NH group was hydrogen bonded to C3-OH with 2.84 Å bond length (Katoch 2020). The presence of Tyrosine$^{154}$ amino acid residue fulfilled the function of stacking of hydrophobic face of the sugar. In addition, leucine $^{241, 242}$ via their amino group were hydrogen bonded to the C6-OH group with 3.04 Å and 2.84 Å bond lengths. N-acetyl-D-glucosamine sugar interacted with rice bean lectin via two hydrogen bonds between with the oxygen’s of aspartic acid side chains and C6-OH and C4-OH groups of the sugar. The amide side chains of asparagine$^{156}$ and glycine$^{130}$ residues were involved in hydrogen bonding with C4-OH and C3-OH group of the sugar (Katoch 2020). Lectins exhibit higher affinity towards oligosaccharides suggesting occurrence of additional interactions with parts of the ligand located outside monosaccharide binding site (Loris et al. 1998). Higher affinity of ECorL for lactose is attributed to hydrogen binding between amide group of Glutamine$^{210}$ and 3-OH of glucose moiety of disaccharide along with interaction of Galactose with conserved amino acid triad in primary binding site. Mutagenesis of Gln219 of ECorL (Adar and Sharon 1996) and refined 3D structure of ECorL-Lac complex revealed the importance of hydrogen bonding between a glutamine residue and 3-OH of the sugar (Katoch 2020). The presence of intronless nature of a novel gene related to legume lectins, binding site for Ca$^{2+}$ ion formed by side chains of Glu$^{150}$, Asp$^{152}$, Asp$^{160}$, His$^{165}$ amino acid residues have also been predicted for rice bean lectin in our laboratory using GalaxySite Web server.

Legume lectins are closely related proteins and share high sequence similarity that denotes their conserved nature during evolution (Lioi et al. 2006; Gautam et al. 2018a) to preserve their biological functions (Pinto et al. 2008). Therefore, they have been stressed as a useful tool to study evolutionary and phylogenetic relationships. Sometimes, the presence of isoforms of legume lectins due to microheterogeneity in amino acid sequences has been reported which indicates their probable encoding by the family of tandemly linked genes (Peumans et al. 2001; Pinto et al. 2008). In some tetrameric lectins (Phytohemagglutination from Phaseolus vulgaris), the polypeptide chains are encoded by two tandemly linked genes and share about 90% similarity (Chrispeels and Raikhel 1991). In soyabean, more than one lectin genes have been detected among which only a single gene produces a single functional polypeptide. The other lectin genes may be pseudo-genes originating from the process of gene duplication (Galasso et al. 2004). In some other legumes such as Griffonia simplicifolia, two or more seed lectins with different carbohydrate specificities and amino acid sequences are encoded by different genes or small families of genes. There are some examples of legumes in which seed and vegetative lectins are encoded by different genes (Van Damme et al. 1995).

Although the presence of intronless genes is a characteristic feature of prokaryotic cells, several intronless genes have been identified in eukaryotes. The presence of intronless genes in eukaryotes, provide tools to make comparison among different genomes and evolutionary relationships. Most of the characterized legume lectin genes are devoid of intervening sequences, including Canavalia ensiformis lectin (Carrington et al. 1985; Min et al. 1992) and Canavalia gladiata lectin genes (Yamauchi and MinamiKawa 1990). Filho et al. (2017) analyzed 35 legume lectin gene sequences and revealed that all sequences are composed of a single exon and have no introns. Vodkin et al. (1983) also reported that Le1 from soyabean encodes almost 1kb long mRNA and contains no introns. Similarly, Hua et al. (2015) also reported the intronless nature of a novel gene related to legume lectins from Salvia miltiorrhiza Bunge. D’Onofrio...
et al. (1991) suggested that the presence of an intronless gene might be a structural feature that is maintained because it provides a selective advantage by rapidly encoding turning over transcripts to respond without significant delay to various exogenous signals. Since splicing is not required, very little time would elapse between transcription and accumulation of mature mRNA in the cell. The intronless nature of the legume lectins gene may be one of the reasons for their high concentrations in seeds.

5. Technological advances involving legume lectins

5.1 Lectin blotting

Glycosylation is essential for maintaining the structural and functional integrity of proteins. It also plays a crucial role in many essential biological processes for example cell-cell interactions and protein targeting (Cao et al. 2013). Studies have revealed that the alteration in glycosylation pattern or glycan profile is an important characteristic of the pathophysiological state of cells. Thus, decoding information in glycosylation pattern is essential for the diagnosis and treatment of diseases. Lectins are considered an important glycan deciphering molecule due to their carbohydrate specificity. Lectin blotting is an effective technique for lectin-mediated characterization of glycans linked with proteins and lipids. The working principle of the lectin blotting technique is similar to western blotting in which probed or labeled lectins are used in place of labeled antibodies (Shan et al. 2001; Hashim et al. 2017). The steps in lectin blotting include electrophoretic separation of glycoproteins, transfer of proteins to the nitrocellulose membrane, membrane incubation with biotinylated lectins, and detection with the streptavidin–enzyme conjugate. Lectin blotting is an effective tool in glycan analysis (Norton et al. 2016; Vainauskas et al. 2016).

5.2 Legume lectins-based biosensors

Interaction between protein and carbohydrates plays a crucial in different biological processes such as cell-cell interactions, cell signaling as well as host-pathogen interaction. Legume lectins, owing to their vast diversity in carbohydrate-binding specificity, are potential candidates to develop optical and electrochemical biosensors Klukova et al. 2016). Moreover, legume lectin-based biosensors could be a fast and cost-effective alternative to antibodies and nucleic acids based biosensors (Luna et al. 2014).

Among legume lectins, the specificity of ConA lectin with glucose/mannose sugars has been explored in the development of biosensors for different applications such as detection of virus and bacteria as well as profiling of serum glycoproteins and cell surfaces glycoproteins. An electrochemical biosensor based on ConA lectin has also been developed for the non-enzymatic recognition of glucose (Li et al. 2011). An electrochemical biosensor based on ConA and gold nanoparticles-modified electrode has been developed to recognize serum glycoproteins from patients infected by norovirus (Hong et al. 2015) and dengue virus, zika virus, chikungunya virus and yellow fever virus (Simao et al. 2020). Ma et al. (2015) developed a label-free lectin biosensor for the quantitative measurement of the interaction between lipopolysaccharide (LPS) on Gramnegative bacteria and immobilized ConA. Yaghoubi et al. (2020) developed ConA coupled silicon-based biosensor for the detection of bacteria. Biosensors based on Cramoll lectin and BmoLL lectin have been developed for dengue virus serotypes detection (Oliveira et al. 2011a, b; Andrade et al. 2011; Avelino et al. 2014). The glycan-binding specificity of lectins could also be used to develop biosensors for fast detection of coronavirus including SARS-CoV-2 (Nascimento da Silva et al. 2020).

5.3 Legume lectins-based drug delivery system

Lectins have been used as a medium for targeted delivery of drugs. The basis of lectin-mediated drug targeting is that most of the cell surface proteins and many membrane lipids are attached with glycans and serve as binding ligands for lectins. Different cells alter their glycan profile or express different glycan profiles in response to pathological states. Lectins owing to their specific carbohydrate-binding provide a great means to target drugs specifically to various cells and tissues that are in a pathological state (Gavrovic-Jankulovic and Prodanovic 2011). Moreover, the internalization via receptor-mediated endocytosis in cells promotes drug uptake actively by the cells. Cai and Zhang (2005) evaluated the cytotoxicity of PNA lectin with 5-fluorouracil (5-Fu) derivative on LoVo cells. Jain and Jangdey (2009) used ConA lectin-mediated delivery system of drug clarithromycin for effective treatment of colonization of Helicobacter pylori. Ikeymoto et al. (2016) evaluated liposomes covered with Bauhinia purpurea agglutinin as a drug delivery
system to treat human prostate cancer. The study reported that binding of the delivery system with DU145-cells in mice resulted in and suppression of the growth of the cells.

5.4 Lectin affinity chromatography

Lectin affinity chromatography is an important method for glycoconjugates purification (Hashim et al. 2017). This chromatography based on fact that carbohydrate moieties present on glycoconjugates interact with immobilized lectin on matrix via hydrogen bonding, hydrophobic, electrostatic and van der Waals interactions (Monzo et al. 2007). Various legume lectins are frequently used for affinity chromatography of glycoconjugates (Monzo et al. 2007). Sumi et al. (1999) differentiated carcinoma and prostatic hyperplasia through differences in the carbohydrate structures of the prostate-specific antigen (PSAg) using lectin affinity chromatography. They used a consecutive series of columns with immobilized ConA, PSA, WGA, phytohemagglutinin E4 (PhHA-E4) and phytohemagglutinin L4 (PhHA-L4). Durham and Regnier (2006) used the combination of ConA (specific to mannose) and Artocarpus altillis lectin (specific to GalNAc in O-glycosylated and Man-containing sites of N-glycans) to isolate O-glycosylated peptides while investigating O-glycosylation sites of human serum proteins. This chromatographic technique has potential for analyzing and identifying site-specific glycosylation of many proteins in combination with mass spectroscopy (Mishra et al. 2019).

5.5 Lectin arrays

In the last few decades, methods based on mass spectrometry have been used extensively in glycome research (Satomaa et al. 2009). Although widely used, there are some concerns regarding the utilization of MS (Mass Spectroscopy) based methods in glycome research, such as the release of glycans from glycoconjugates which brings error in profiling of glycans (Dell and Morris 2001). Moreover, MS-based glycan profiling methods require complex sample preparation. For linkage analysis of glycans, NMR spectroscopy has been proved a powerful tool but has the limitation of availability of substantial quantities of homogeneous samples. Lectin arrays have provided a good alternative to MS-based methods of glycan profiling. This technology involves the utilization of densely immobilized lectins on a solid support for the profiling of glycoconjugates (Dang et al. 2020). Lectin array is a simple, rapid, and sensitive technique in comparison to MS-based methods. Unlike to MS-based methods, removal of glycan from glycol conjugates is not required in the lectin array technique, therefore lectin arrays is an efficient technique to analyze and differentiate the glycomic profile of samples. Lectin arrays technique has been used for glycophenotyping of different bacteria, profiling of biomarkers of different diseases, and expression pattern analysis of glycogenes (glycosyltransferases, sulfotransferases, and sugar-nucleotide transporters) (Katrlik et al. 2010).

5.6 Legume lectins histochemistry

Generally, lectin histochemistry uses labeled lectins as potential markers for altered glycans moieties on tissue and cells, which are in a pathological state. Direct and indirect methods have been used to generate conjugate lectins. In the direct method, lectins are covalently linked to fluorophores, enzymes (Horseradish peroxidase), colloidal gold, or ferritin (Sobral et al. 2010; Leal et al. 2012; Hashim et al. 2017). In the indirect method, lectin is labeled with biotin, which is recognized by enzyme-linked streptavidin. Lectin histochemistry has become an efficient approach to study alteration in the glycosylation pattern of normal and cancer cells (Marafioti et al. 1994; Nishimura et al. 2000; Beltraão et al. 1998; Beltrão et al. 2003; Sobral et al. 2010; Coelho et al. 2017). Sobral et al. (2010) reported that ConA and UEA-I lectins have been found useful to differentiate different histological grades of mucoepidermoid carcinoma. ConA lectin was able to stain all grades of mucoepidermoid carcinoma tissues, while UEA-I lectin staining revealed a direct correlation between the intensity of staining and malignancy. Leal et al. (2012) visualized Aspergillus structures in brain and lung tissue samples using HRP-conjugated WGA and ConA. LCA and WFA have been used as an FDA authorized glycan deciphering lectins in cancer diagnosis (Gautam et al. 2020).

5.7 ELLA (enzyme-linked lectin assay)

The working principle of ELLA is similar to Enzyme-Linked Immunosorbent Assay (ELISA) but the difference is in the utilization of capturing as well as detecting reagent. In the case of ELLA, enzyme-conjugated plant lectins are used to detect specific glycans
on cell surfaces (Hashim et al. 2017). A direct enzyme-linked PNA lectin assay was used for pancreatic cancer diagnosis (Ching and Rhodes 1989). Reddi et al. (2000) used enzyme-linked PNA assay to estimate the levels of Thomsen-Friendenreich antigen (T-Ag) in serum of patients with squamous cell carcinoma of the uterine cervix. Bronzoni et al. (2005) detected bronchitis virus and its specific antibodies with ConA-based sandwich ELISA. Leriche et al. (2000) used ConA based ELISA for colorimetric detection of D-glucose and D-mannose produced by the biofilms of 10 bacteria strains. Strathmann et al. (2002) also used ConA based ELLSA to characterize extracellular carbohydrates in Pseudomonas aeruginosa biofilms. ELLA technique has high throughput potential and other advantages, as it is easy to perform, very cost-effective, and requires a minimal amount of sample (Mishra et al. 2019).

6. Potential applications of legume lectins

6.1 In plant protection

Presently, concerns are increasing agriculturists across the globe regarding the attainment of food and nutritional security to millions of people. Emerging evidences have suggested that crop infestation with insects and pathogens is one of the crucial factors jeopardizing global agriculture production and their impacts are likely to be increased in future because of rising food demands and changing climatic conditions (Lehmann et al. 2020). Though chemical based pest management strategies has brought significant improvement in crop production, their bad effects on environment and human health have outweighed the benefits associated with their use. Due to changing climatic scenario and sluggish agriculture production, the adoption of environmentally friendly and effective pest management strategies is imperative. The use of plant inhibitory proteins is an effective approach for insect pest management. Lectins have been well documented as potential bio-pesticides (Gatehouse et al. 1995; Powell 2001; Carlini and Grossi-de-Sa 2002) and considered as a potential candidate for generating resistance in susceptible crops. Genes encoding legume lectins have the potential for providing resistance to susceptible crops. Use of lectin genes for transferring insect-pest resistance in plants has an added advantage that the encoding proteins are correctly processed inside the host.

Transgenic wheat plants expressing snowdrop lectin under the influence of constitutive and phloem specific promoters were generated and revealed retarded fecundity of English Grain Aphid (Sitobion avenae) (Stoger et al. 1999). Gatehouse et al. (1999) also reported that feeding of Laconobia oleracea (Tomato moth) on potato plants expressing ConA showed retarded development, decreased larval weight, and decreased fecundity. The pea lectin gene under the control of pollen specific promoter transferred in oil-seed rape (Brassica napus) and reduction in the growth of pollen beetles larvae (Melander et al. 2003). Transgenic tobacco plants expressing MbL protein (Moth bean lectin) showed a significant reduction in the larval weight gain of tobacco cutworm (Singh et al. 2012). Guo et al. (2013) expressed soybean lectin in tobacco plants and revealed resistance against Phytophthora nicotianae and reduced larval weight gain of beet armyworm (Spodoptera exigua). Singh et al. (2016a, b) conferred resistance to Brassica juncea plants against aphid (Lipaphis erysimi) by transferring Vigna radiata lectin gene. Rani et al. (2017) also transformed Brassica juncea plant with Lens culinaris lectin gene using cotyledons explants under the phloem specific promoter.

Numerous lectins are present in vegetables and crops that are routinely consumed by humans and animals. Since many of these plants are eaten raw, these plant lectins are considered non-toxic for humans and mammals in general. However, some legume lectins e.g. ConA and PHA have been known for exerting toxic effects in mammals (Vasconcelos and Oliveira 2004). This signifies the need of conducting toxicity studies concerning the safety issues associated with genetically engineered plants with lectin genes. The use of legume lectins genes for plant transformation could also be considered as a potential way of protection from virus infection (Saha et al. 2006). Fusion proteins containing plant lectins and fusion lectins have strong inhibitory effects on insect development than mixture of individual proteins (Zhu-Salzman et al. 2003; Hos-sain et al. 2006). Thus, lectin-encoding genes could be used in designing multigene transfer strategies for insect resistance in susceptible crops. Moreover, lectins can also act as a carrier protein to deliver toxic substance to insect haemolymph (Fitches et al. 2002).

6.2 In glycan analysis

Glycan research is a fundamental part of cell glycobiology to comprehensively elucidates the functions of glycans either found independently or conjugated to other non-carbohydrate biomolecules (Hirabayashi
et al. 2001). Lectins have been considered as an important tool to decipher information embedded in the glycode of cells. It has been shown that lectins can be used. Lectins have also been considered as a potential tool to study alteration in glycan profile during various stages of cell growth as well as during pathogenesis. Various lectins-based high throughput molecular tools have been developed to decode complex information stored in glycode. Plant lectin-based affinity chromatography has been used for the identification and purification of glycoproteins. Lectin arrays technique has been developed for high-throughput glycan analysis. Many of the lectins currently used as tools in glycobiology come from plants and the major proportion is constituted by legume lectins. Plant lectins with modified carbohydrate specificity can be useful tool for glycome research (Melnykova et al. 2013). ConA is the most widely used legume lectin for glycan analysis. Other lectins PHA-E and PHA-L, Lens culinaris lectin (LCA), Ulex europaeus agglutinin I, Maackia amurensis leukoagglutinin (MAL) and Griffonia simplicifolia agglutinin have also been used in glycomic research.

6.3 In plant growth and development

Typically, legume lectins behave as storage proteins and play vital functions during plant growth and development, which include storage and trafficking of carbohydrates, storage of hormones, and cell-cell interactions via binding with cell surface receptors. Apart from being storage proteins, they have also been reported to play a significant role in plant defense mechanisms. Legume seed lectins have also been reported to be involved in early events of legume-rhizobium symbiosis (De Hoff et al. 2009). Legume seed lectins bind with nod factor (Lipo-oligosaccharide molecules structurally organized as tri, tetra, or pentasaccharides of N-acetylglucosamine) on bacterial surface and assist in initial attachment of symbiotic bacteria to root epidermal cells (Diaz et al. 1989; Van Eijsden et al. 1995). Transgene studies revealed that the introduction of the legume lectins gene could change the nodulation specificity of plants. For example, introduction of soybean lectin gene Le1 into Lotus corniculatus, nodulated by Rhizobium loti developed nodules in response to Bradyrhizobium japonicum, which nodulates soybean not Lotus (Van Rhijn et al. 1998). Sreevidya et al. (2005) revealed that the introduction of legume lectin gene can induce colonization of symbiotic bacteria in monocots. In the study, the introduction of pea lectin gene resulted in colonization of root epidermal cell of rice plants (Oryza sativa L. cv. Murasaki) by Rhizobium leguminosarum, Bradyrhizobium japonicum and Rhizobium sp. NGR234). Moreover, transformed plants showed enhanced root growth and lateral root proliferation. The introduction of legume lectin genes can be a potential way of improving the growth of monocot plants (Melnykova et al. 2013). Exogenous application of legume lectins also improves legume-rhizobium symbiosis (Baimiev et al. 2009) that can relate to the ability of lectins to induce the metabolic changes in bacterial cells and adhesion of microorganisms to root surface. Exogenous application of lectins to seeds can also improve seed germination and plant growth (Kirichenko and Titova 2006). Chimeric lectins/ hybrid lectins, which combine the carbohydrate-binding properties of different lectins, can be introduced into legume plants to expand the range of symbiotic partners under particular soil and climatic conditions. This could lead to a higher nitrogen fixation and correspondingly high yield (Yamamoto et al. 2000; Baimiev et al. 2009; Melnykova et al. 2013).

6.4 In biomedical research

The ability to bind with carbohydrate moieties and glycoconjugates has allowed the use of lectins in biomedical research. They have been widely used in identification and profiling of glycans attached to cancer cells and pathogens (Xia and Ng 2006; Blonski et al. 2007; Sobral et al. 2010; Kabir et al. 2013; Silva et al. 2014). Lectins due to their ability to bind with viral glycoproteins inhibit virus entry in host cells, they are considered as alternative antiviral agents against enveloped viruses (Mitchell et al. 2017) and could be used to design devices for viral disease diagnosis via targeting viral glycoproteins or host glycoproteins. Legume lectins induce Th1 responce (de Oliveira et al. 2011b, a; Teixeira et al. 2012) and thus considered as potential vaccine adjuvants (Sander et al. 2019; Nascimento da Silva et al. 2020). Some legume lectins such as SBA, PNA, ConA and PHA interacts glycosylated TLR receptor on macrophage and/or dendritic cells thus can fulfill the role of vaccine adjuvants (Unitt and Hornigold 2011; Sander et al. 2019). The carbohydrate specificity of lectins has also been used to develop various devices for glycan analysis in disease research. The mannose/glucose binding specificity of GNA lectin has been used to modify plasmapheresis apparatus (lectin affinity plasmapheresis, LAP) to
remove HCV (Hepatitis C virus) (Tullis et al. 2009), Ebola virus (Buttner et al. 2014) and MERS-CoV and Marburg virus (Koch et al. 2018) from blood. Further research is warranted for the future use of lectin affinity plasmapheresis in disease treatment (Nascimento da Silva et al. 2020).

7. Conclusion and future perspective

The interactions between carbohydrate moieties and proteins have been recognized crucial for different biological processes such as extracellular and intracellular signaling and cell-to-cell recognition. The carbohydrate binding specificity of lectins makes them a valuable tool in the study of glycoconjugates and for understanding the mechanisms of many biological processes. Within the group of plant lectins, legume lectins are an extensively investigated homologous proteins with variability in their carbohydrate specificity and diverse biological functions. Legume lectins are important tools in glycobiology and are considered as the best model system to investigate protein-carbohydrate interactions. Role of legume lectins as plant defense protein and their utilization as potential antimicrobial agents for drug development and drug therapies has also been well documented. Considering the crucial role of legume lectins in plant defense, the lectin genes could be used for designing strategies for multigene transfer to generate resistance in susceptible crops. Lectins from legumes have been implicated in the development of different lectin-based high throughput molecular tools and have established as an important glycan deciphering tool in glycobiology. However, still there is a lot of scope for harnessing the potential of lectins for different biotechnological and biomedical applications. Moreover, the identification and characterization of novel legume lectins and in depth investigation on existing legume lectins will have profound effect on the further development of field of lectinology.

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