J. Crop Sci. Biotech. 2018 (September) 21 (3) : 217 ~ 227
DOI No. 10.1007/s12892-018-0002-0

RESEARCH ARTICLE

Current Scenario of Legume Lectins and Their Practical Applications

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Received: January 06, 2018 / Revised: April 27, 2018 / Accepted: May 25, 2018

Abstract

Lectins are diverse group of carbohydrate binding proteins distributed ubiquitously in plant species. Lectins are the subject of intense investigation. Therefore, in the past few years studies on legume lectins with respect to their biochemical and pharmacological properties have been extensively carried out. Legume lectins are reported to contain antifungal, mitogenic, immunomodulatory, and antitumor properties. Some of the lectin also display anti-HIV-1 reverse transcriptase and antineoplastic activities. Plant lectins are expected to open new vistas for the design and development of drugs to be used against different serious diseases. This article aims to review up-to-date advances of legume lectins *vis-à-vis* structure, biological properties, and their practical applications.

Key words : Lectin, antimicrobial, antitumor, mitogenic, anti-HIV-I reverse transcriptase

Introduction

Plants commonly synthesize some antinutrients as a part of their protection against their predators and/or as a means to survive under adverse growing conditions; lectins being one of such plant products. Lectins belong to a complex group of proteins/glycoproteins and are present in almost all biological systems including viruses, bacteria, fungi, unicellular organisms, animals and plants (Peumans and Van Damme 1995). Lectins are defined in terms of proteins which agglutinate the red blood cells with sugar specificity. In some cases however, sugar specificity is unknown and hence referred as hemagglutinins (Lam and Ng 2011). Many plant family members have been screened for lectins by determining their abilities to agglutinate erythrocytes with specifically reversible binding to monosaccharides, oligosaccharides, and glycoconjugates which are reported to chemically act in accordance to lock and key models (Kennedy et al. 1995). Lectins contain one non-catalytic domain for binding specific carbohydrates (Sharon and Lis 1989). Boyd and Shapleigh (1954) for the first time coined the term 'lectin' which originates from the Latin word "legere", it means to select. The plant lectin was discovered for the first time by Herrmann Stillmark (1888), who described the agglutination properties of ricin from castor bean (*Ricinus communis*) paving the way for accelerated research on lectin. It has been reported that modern age lectinology started about 100 years ago (Bies et al. 2004; Sharon and Lis 2004). Recently, the lectins from plants have attracted much attention because of their enormous biomedical potential with anti-tumor properties, resulting from their ability to reduce the growth and progression of cancer cells (Fu et al. 2011; Liu et al. 2010).

Two approaches for lectin classification are familiar. The primary basis of classification of lectins is beset on their carbohydrate specificity. Another basis of classification of lectins is their overall structures such as merolectin, hololectin, chimerolectin, and superlectin. The lectins may be grouped into different families such as legume lectins, type II ribosome-inactivating proteins, and monocot mannose-binding lectins. Plant lectins have been classified into four major groups by Van Damme et al. (1998) on the basis of their structures and biochemical properties. Four major types of lectins are merolectin, hololectin, chimerolectin, and superlectin which

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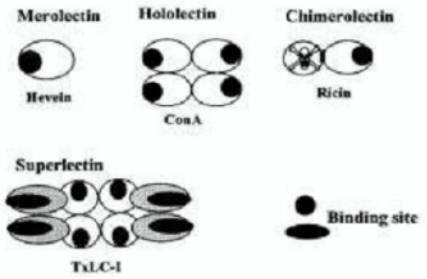

Fig. 1. Class of plant lectins representing binding domain (Peumans and Van Damme 1995).

contain a carbohydrate-binding domain out of which chimerolectin is abundantly found in plants (Fig. 1). Based on the structural features, lectins have been classified into four groups:

- Merolectins: These lectin have single carbohydrate-binding domain, unable to agglutinate cells.
- Hololectins: These lectins possess two similar domains for carbohydrate binding.
- Chimerolectins: This class of lectin display catalytic activity by one chain and biological activity by another chain.
- Superlectins: These are built of at least two carbohydrate-binding domains that are not identical. Thus, superlectins recognize structurally different sugar moieties (Teixeira et al. 2012).

The largest and best characterized plant family is *Leguminosae*. The yield of legume lectins is usually high compared to other plant and animal lectins. Lectins are known for their diverse biochemical and biophysical characteristics in terms of their molecular characteristics. This includes number of sugar binding sites, molecular weight, and sub-unit structure, etc. In legumes, most of the reports are constrained to the biochemical analysis of lectins. Only some members have been studied their biomedical significance (Une et al. 2018).

Legume lectins

Legume seeds attribute significance in human and animal nutrition worldwide. However, further research is in progress on lectins isolated from the leguminosae family pertaining to its pharmacological properties (Gautam et al. 2018). In leguminous family, more than 600 species have been screened for lectin (Rudiger 1988) and many are currently under process for purification and characterization. The major sources of lectins include mature seeds which contain nearly 10% of the total protein along with carbohydrates, dietary fibers, minerals, and vitamins. In addition to these nutritional components, some antinutritional compounds are also found in biologically significant amounts in raw seeds such as enzyme inhibitors, tannins, phytates, flavonoids, and lectins (Liener 1982). The major storage protein of the seeds happens to be the bulk of lectin available in cotyledons called the protein body. Among various naturally occurring chemical compounds found in the food legumes, lectins have now attracted considerable research interest because of their diverse biological significance both deleterious and beneficial (Fenwick et al. 1991).

The carbohydrate specificity of most of the plant lectins have been studied. Lectin concentration in legume seeds is varied with their protein content, e.g. *Phaseolus vulgaris* (2.4-5.0%), *Glycine max* (0.8%), and *Pisum sativum* (0.6%) (Rudiger and Gabius 2001; Ye and Ng 2001a; Ye et al. 2000). Phytohemagglutinin and Concanavalin-A are the best studied in legume lectin (Loris et al. 1998). According to Gatehouse et al. (1995), legume lectin is involved in plant-microbe interaction by binding to the cell surface of microbes, e.g. Concanavalin A and other lectins protect the plants against the *Callosobruchus maculatus* beetle. The plant-microbes interaction is an important mechanism which participates in the biological control of plant pathogens.

Distribution of lectins

The legume family is the richest source of lectin-containing species in plants. The content and composition of lectin varies in different taxa. Leguminous lectins are especially concentrated in the seeds as one of the components of seed storage proteins (Etzler et al. 1987). It is mainly present in the cotyledons of seeds and appears during the maturation of seed. Therefore, seeds are mainly used as a source material for lectin isolation and purification. In contrast to seeds, vegetative organs such as roots, leaves, rhizomes, bulbs, tubers, stem, bark, flowers, and even the nectar of plants contain lectin (Peumans and Van Damme 1995). Differentiation of tissues at the developmental stage leads to lectin variation. The legume seeds contain lectins large amounts. The quantity of lectins purified from different legume varieties of the same species differed greatly, including also *P. vulgaris* also (Lam and Ng 2011).

Structure of Lectins

Legume lectins within themselves exhibit remarkable sequence homologies and structural similarities despite differences in sugar specificities and quaternary structures. The primary structure of legume lectin is generally made up of a single subunit with one polypeptide chain of about 300 amino acid residues with average molecular mass of 30 kDa (Wales et al. 1991). The subunits of legume lectins are most often made up of single polypeptide chains of ~250 amino acids exhibiting the legume lectin fold. The fold primarily consists of three β-sheets, a 'flat' six-membered 'back' β-sheet, a small 'top' β-sheet and a curved, seven-stranded 'front' β-sheet and a number of loops interconnecting the sheets as well as the strands in them (Fig. 2) (Banerjee et al. 1996), e.g. Con-A and peanut agglutinin (PNA) (Banerjee et al. 1996; Chandra et al. 2001; Srinivasan et al. 1996).

Despite the diversity in carbohydrate-binding specificity, the folding patterns of secondary and tertiary structures of legume lectins are superimposable (Rudiger and Gabius 2001). At the primary, secondary, and tertiary structural monomeric

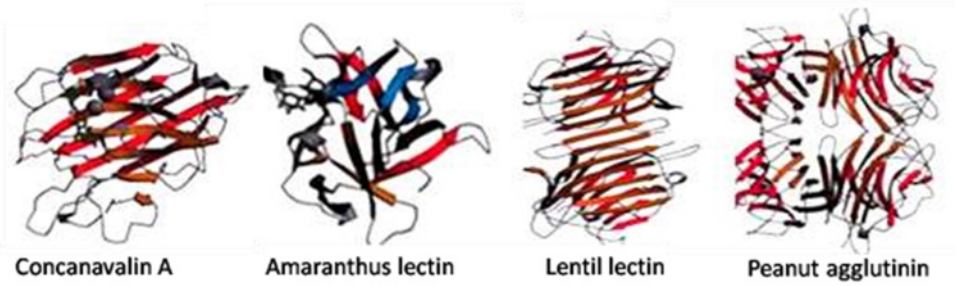

Fig. 2. 3-Dimentional structure of legume lectins.

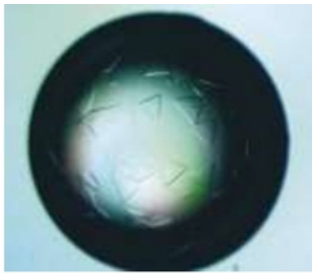

Fig. 3. Crystals of *C. arietinum* lectin (CAL) using the hanging-drop vapour-diffusion method.

levels, legume lectins exhibit considerable variation in their quatenary structure; small differences in the amino acid sequences at the monomer-monomer interfaces and the presence/absence of glycosylation affects the monomer's association modes. The monomer structures appear like a jellyroll motif, which contains a carbohydrate recognition domain (CRD) and metal binding sites for divalent cations (Ca^{2+} and Mn^{2+}) (Ambrosi et al. 2005). The β-sheet of legume lectin also contains highly conserved *Asp* and *Asn* amino acids attached to calcium and manganese ions (Van Eijsden et al. 1992). These two amino acids play an important role in carbohydrate recognition (Sharma and Surolia 1997). Effect of such variation provides the specificity in the binding of multivalent glycan. Most legume lectins appear to assemble as homodimers or homo-tetramers (dimers of dimers), the stability of which is attributed to hydrophobic cooperation, hydrogen bonds, and salt links (Diaz et al. 2017). The amino acid variation leads to structural polymorphism that makes legume lectin an excellent model for molecular interactions studies.

Our previous studies reported crystallization and preliminary X-ray characterization of lectin from chickpea (*Cicer arietinum* L.) (Katre et al. 2005). Our studies with circular dichroism (CD) experiments have shown that the secondary-structural components for *Cicer arietinum* lectin (CAL) were 34% helix, 28% β-sheet, and 38% random coil. The results also demonstrated that the structure of CAL differ from the characteristic antiparallel β-sheet structure of legume lectins (Chandra et al. 2001). Unlike other legume lectins, CAL lacks specificity for simple sugars or sugar derivatives (Reeke and Becker 1998). The *Cicer arietinum* L. crystals diffract to a resolution of 2.3Å and belong to the rhombohedral space group R3, with unit-cell parameters a = b = 81.2, c = 69.4 Å (Fig. 3).

Detection of Lectin

Presence of lectins can be achieved by the agglutination of erythrocytes known as the heamagglutination. The first of all, the methods of heamggglutination used to determine the presence of lectin in castor beans extract was reported by Stillmark (1888) in his doctoral thesis. Therefore, coagulation of red blood cells called hemagglutination is the most suitable and reliable method to confirm the presence of lectin/ hemagglutinin. The lectins bind to the carbohydrate moieties present on the surface of erythrocytes and agglutinate them without altering the properties of carbohydrates. Lectins however undergo few conformational changes upon binding to sugar. In no case, have global changes in protein structure been observed instead small movements are restricted to the immediate vicinity of the sugar (Weis and Drickamer 1996). Hemagglutination assay is carried out in 96 well (U/V shape) microtitre plate and the results are recorded as hemagglutination titer unit, i.e. HAU. The unit of hemagglutination activity (U) termed as titer was expressed as the reciprocal of the highest dilution of the lectin that showed complete agglutination. Further, the specific activity of the lectin is defined as the titer of hemagglutination per mg of protein (Wang et al. 1995). Chickpea is the second most important legume in the world after dry bean and pea (Parthasarathy et al. 2010). In our previous studies, hemagglutinating activity of 50 chickpea extracts for lectin was determined (Bhagyawant et al. 2015).

Boyd and Shapleigh (1954) found that some lectins are blood type specific. The assay can be performed using human and rabbit erythrocytes. Different erythrocytes react in a different ways with plant lectin. Reports of chickpea producing a certain amount of agglutinating activity with cow erythrocytes are reported. Ynalvez et al. (2015) isolated and characterized lectin activity in Texas Live Oak (*Quercus fusiformis*). Some of the plant lectins are non-blood group specific that includes *Quercus fusiformis* and *Erythrina speciosa* displaying lectin activity. Its lectin activity was examined in the human blood ABO system and animal blood groups of rabbit, mouse, sheep, etc. (Konozy et al. 2003).

Carbohydrate specificity

The protein-carbohydrate interactions confirm the specificity of lectins. Legume lectins represent diversity in carbohydrate specificity as evident from published reports (Diaz et al. 2017). Legume lectins with distinguished carbohydrate affinity are nowadays recognized as a marker in plant defense against insects and/or pests. Carbohydrate-lectin interactions are significant in medical, pharmacological, and other biological applications. The lectins are mainly involved in cell-cell recognition, where the carbohydrate protein interactions appear to be important. Normally, lectins possess shallow carbohydrate-binding sites. Lectin has unique properties different from many other proteins in their specificity to bind simple or complex carbohydrates. Lectin interacts with carbohydrates through a network of several non-covalent interactions such as hydrogen bonds, hydrophobic interactions, Van der Waals interactions, and metal ion coordinations (Sharon and Lis 1990).

The lectins with particular carbohydrate specificity have been purified from different legume seeds and its plant parts. Carbohydrate specificity also constitutes one of the basis for lectin classification (Goldstein and Poretz 1986). Plant lectins are divided into the following groups: namely mannose, N-acetylglucosamine, galactose, N-acetylgalactosamine, fucose, sialic acid, and a group with complex sugar specificity. Popular methods for classifying plant lectin employ their monosaccharide specificity. However, monosaccharide specificity does not tell the complete story as in some cases lectins exclusively recognize complex glycans. Also, lectins with the same monosaccharide specificity may recognize different oligosaccharides. For instance, monocot mannose binding lectin from *Galanthus nivalis*, *Narcissus peseudonarcissus,* and *Listera ovate* bind mannose but differ in their fine sugar specificity. *Galanthus nivalis* agglutinin prefers terminal Man α 1-3 Man (Shibuya et al. 1988), whereas *Narcissus pseudonarcissus* agglutinin and the *Listera ovate* agglutinin have the highest affinity for Man α 1-6 Man and Man α 1-3 Man α 1-3, respectively (Kaku et al. 1990; Saito et al. 1993).

Some of the plant lectins display blood group specificity. For example, *Sophora japonica* and *Dolichos biflorus* show specificity with A and B blood groups while *Erythrina velutina* demonstrate specificity with A, B, and O blood groups (Etzler and Kabat 1970; Stojanovic et al. 1983). Most lectins have high affinity for oligosaccharides compared to simple sugars. The specificity of lectins to carbohydrates is examined by hapten inhibition techniques in which sugars are tested for their hemagglutination or precipitation by the lectins. The alternative methods to confirm the lectin specificity include spectrophotometry, fluorimetry, and equilibrium dialysis (Sharon and Lis 1989).

Overview of lectin purification

Using affinity chromatography, purification of lectin is usually carried out since they bind to specific sugars. However, for complex sugar binding lectins/hemagglutinins, a wide range of strategies can be employed for lectin purification, as shown in Table 1. Initially lectin extracts are precipitated by ammonium sulfate fractionation, followed by using various chromatographic approaches (He et al. 2013). Most widely and suitable methods for lectin purification techniques used by different workers are gel filtration, ion exchange, and affinity chromatography. However, affinity chromatography has been widely used in laboratory practice if the sugar specificity of lectin is known.

In order to obtain a high yield of lectin, the source material should contain high lectin so that simple purification procedures can be employed (Lam and Ng 2011). By and large, purifying lectin effectively with its natural properties and careful selection of affinity resin can be done, if sugar specificity is known.

The applications of recombinant technique in fermentation process enhances lectin yield significantly. One of the major limitations of recombinant technique is the high cost of experimentation and low yield. In the fermentation process, *Escherichia coli* is widely used as an expression system while other strains, e.g.,] BL21 (DE3) RIL and Nova Blue (DE3) are also used for expression of different recombinant lectins. In this technique, generally *E. coli* is transformed with expression vector which is grown in sterilized BMGY and Luria-Bertani (LB) medium in fermenter along with antibiotics, e.g. ampicillin to reduce the chance of contamination. Sonication is one of the methods of lectin isolation subjecting the cells to homogenization in an appropriate lysis buffer. The purification of protein to the electrophoretic homogeneity involves different chromatography techniques including HPLC and/or affinity column chromatography (Tateno et al. 2004; Upadhyay et al. 2010). Isolation of lectins from legume seed begins with the soaking of seeds overnight

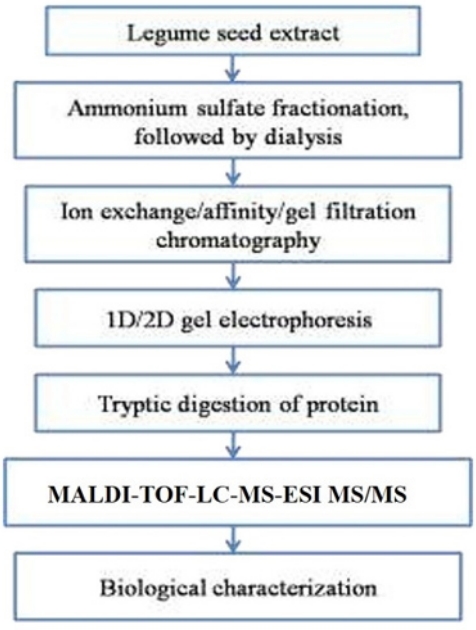

Fig. 4. A flow chart entailing purification and characterization of legume lectin.

Table 1. Purification methods, biophysical properties and applications of some plant lectins.

S.N.	Name of plant lectin	Molecular weight (kDa)	Purification methods	Applications	References
1	*Vigna sesquipedalis*	60 kDa	FPLC-Superdex 75 column	It inhibited HIV-reverse transcriptase, stimulated the mitogenic response of mouse splenocytes	Wong and Ng 2003
2	*Cicer arietinum* L.	43 kDa	SP-Sephadex column	Crystallization and preliminary X-ray characterization	Katre et al. 2005
3	*Phaseolus vulgaris*	33 kDa	Affi-gel blue gel and CM-cellulose	Inhibit leukemia L1210 cells, antifungal protein against *Mycosphaerella arachidicola*	Xia and Ng 2006
4	*Phaseolus vulgaris* L. (Purple bean)	60 kDa	Q-Sepharose, Superdex 75 10/300 GL column	Anti-HIV-1 RT, Antitumor, Anticancer activity in nasopharyngeal carcinoma cells (CNE-1, CNE-2, HNE-2), breast cancer cells (MCF-7) and liver cancer cells (Hep G2)	Fang et al. 2010
5	*Phaseolus vulgaris* (French bean)	64 kDa	Column of Blue-Sepharose, Q-Sepharose and elfiltrationcolumnofSuperdex75	Antiproliferative against hepatoma HepG2 cells and breast cancer cells, antifungal, and anti-HIV-1 reverse transcriptase activities	Lam and Ng 2010
6	*Glycine max*	25 kDa	Q-Sepharose, SP-Sepharose, and Superdex 75	Antitumor for breast cancer and hepatoma cells, HIV-1 reverse transcriptase inhibitory activities	Ye and Ng 2011
7	*Phaseolus scutifolius* (White tepary Bean)	31 kDa	Size exclusion chromatography (SEC) on TSK 3000 SW size exclusion HPLC column	Cytotoxicity activity on mouse 3T3 fibroblast cell clones, Mitogenic activity	Valadez-Vega et al. 2011
8	*Spatholobus parviflorus*	29 and 31 (tetramer)	CM Sephadex C50, affinity chromatography with activated guar gum	Crystallization and preliminary X-ray characterization	Geethanandan et al. 2011
9	*Phaseolus vulgaris* (brown kidney bean)	32 kDa	Affi-gel blue gel, SuperdexG-75	Enhanced mRNA expression of the cytokines IL-2, TNF-a and IFN-c	Chan et al. 2012
10	Concanavalin A, *Lens culinarisis* agglutinin, peanut agglutinin -lectin		Commercially available	Virus growth inhibition	Uematsu et al. 2012
11	*Archidendron jiringa* Nielsen-lectin	35.7 kDa	Purified by aqueous extraction, 90% ammonium sulphate precipitation and concanavalinA-Sepharose 4B affinity chromatography	Antifungal activity against *C. cassiicola, F. oxysporum* and *E. turicicum*	Virounbounyapat et al. 2012
12	*Indigo feraheterantha* (Indigo bush)	70 kDa	DEAE-cellulose followed by gel filtration chromatography on Sephadex G 100	Antibacterial activity against the pathogenic bacteria	Qadir et al. 2013
13	*Glycine max* (soybean)	120 kDa	Lactamyl Sephadex-G-100 affinity column	Induces autophagy and apoptosis as well as DNA damage via ROS-mediated pathway	Panda et al. 2014
14	*Phaseolus acutifolius var. acutifolius* A. Gray (tepary bean)	28 kDa	G-75 Sephadex gel filtration column and then Zorbax GF-250 HPLC column	Differential cytotoxicity on colon cancer cells	Arteaga et al. 2016
15	*C. bonariensis*	25.5 kDa	Sephadex G-50 matrix	Potential anticancer molecules capable of inducing cell death, mainly by apoptotic and autophagic mechanisms	Cavada et al. 2017
16	*Vatairea guianensis*	120 kDa	DEAE-Sephacel column & affinity chromatography (guar gum)	Elicites edematogenic activity, involving prostaglandins, IL-1b and CRD.	Marques et al. 2017
17	*Canavalia gladiate*	30 kDa	Maltamyl-Sepharose 4B	Cancer chemopreventive agent	Une et al. 2018
18	*Cicer arietinum L.*	35 kDa	DEAE cellulose and SP-sephadex chromatography	Antifungal, antibacterial and anticancerous	Gautam et al. 2018

and to make their crude extract by using different extraction solutions in buffers such as Tris-HCl buffer (pH-7.2) and phosphate buffer (pH-7.4) (Katre et al. 2005).

The purification of lectins commonly employs the use of different chromatography resins. For example, *Vigna sesquipedalis* lectin was purified using Superdex 75 column through FPLC (Wong and Ng 2003), *Cicer arietinum* lectin was purified by using ion-exchange chromatography through DEAE-cellulose (Katre et al. 2005), and gel filtration chromatography through Superose-12 (Wakankar et al. 2013), Dark red kidney bean on Affi-gel blue gel (Xia and Ng, 2006) chromatography. The published reports indicate that the production of lectins often relies on the use of a chromatography procedure. A brief scheme of commonly used procedures for lectin purification is demonstrated in Fig. 4.

Chickpea is one of the protein-rich legumes grown under varied conditions worldwide. In our previous study, lectin from desi chickpea (*Cicer arietinum* L.) cultivar BDN 9-3

was purified and crystalized (Katre et al. 2005). *Cicer arietinum* L. lectin, i.e. CAL possessed complex-sugar specificity. The molecular weight of the native protein as determined by gel filtration using HPLC was 43 000 Da. It has been identified as a homodimer of subunit molecular weight 21 500 Da by SDS-PAGE both in the presence and in the absence of β-mercaptoethanol. The evidence for the complex specificity of CAL comes from the observation that the hemagglutination activity of 1 mg lectin inhibited using about 10 μg desialated fetuin.

Primary sequences of legume lectin

The amino acid sequences of legume lectins have now been time-honored chemically or by molecular genetic techniques. The NH_2-terminal amino acid sequences of one chain of lectins were followed by the α-chain. A BLAST search (Marchler-Bauer et al. 2003) based on the partial sequence against a non-redundant database discloses a match at 90% identity with the N-terminal sequence of a major seed albumin (PA-2) from *Pisum sativum* (Sharma et al. 2015).

Plant lectins and their applications

The widespread distribution of lectins in the plant kingdom suggests that these molecules are of physiological importance to plants. Lectins have been reported to be associated to diverse functions concerning the defense mechanisms of plants (Sá et al. 2009). It has been proposed that lectins may protect plants against bacterial (Charungchitrak et al. 2011), fungal (Ye and Ng 2002), and viral (Sato et al. 2012) pathogens during seed imbibition, germination, and early growth of the seedlings. The noteworthy contributions of legume lectins are discussed below.

Lectin as storage and defense proteins

Lectins are typically found in storage vacuoles, extracellular compartments, cytoplasm, and the nucleus. They are abundant especially in legume seeds. Hence, it may play a role as storage protein (Nakamura et al. 2004). Lectins are useful in insect resistance for various agricultural crops. Some of the legumes representing different cultivars of the same species demonstrate variation in biological activities (Chan et al. 2016). For example, the antiproliferative activity is given by French bean No. 35 cultivar while French bean No. 1 cultivar expresses mitogenic activity; the Indian cultivar exhibited none of these activities belonging to *P. vulgaris* (Chan et al. 2016). Recently, the introduction of the coding sequence of *Allium sativum* leaf agglutinin in a rice cultivar to obtain sustainable protection from attack of sap-sucking plant hoppers has been achieved (Sengupta et al. 2010).

Nitrogen fixation capability of lectins

There exists a symbiotic relationship between leguminous plants and nitrogen-fixing bacteria. Wheat germ agglutinin can bind to the agglutinin binding receptor on the cell membrane of *Azospirillum lipoferum*, which is then stimulated to elevate transcription of the nitrogenase enzyme. As a result, the signaling cascade is triggered and nitrogen fixation capability is increased (Karpati et al. 1999). Literature perusal revealed that the lectins may possibly be involved in rhizobial symbiosis enhancing crop productivity. Lectins may be involved in sugar transport, binding of symbiotic rhizobia to form root nodules, as well as symbiotic and pathogenic interactions between some microorganisms and hosts (Sreevidya et al. 2005).

Cytotoxicity

Concerning lectin affinity, it can bind to cancer cell membranes or their receptors and thus induce cytotoxicity (Liu et al. 2015). Previous reports on *Phaseolus vulgaris* lectins inhibited the prolification of human tumor cells that could elicit production of nitric oxide (NO) through up-regulation of inducible NO synthase (iNOS) which is anticarcinogenic to produce apoptotic bodies (Fang et al. 2011). The lectin-dependent cytotoxicity explained the interaction of lectins with T-lymphocytes that require specific recognition by the effected cells mediated by lectin (Parker and Martz 1980). Thus, the lectins not only recognize specific cell types, but also affect cell physiology. The mitogenic lectins promoted the closeness between effected and target cells which resulted in the cytotoxicity of the affected cells (Greene et al. 1981; Parker and Martz 1980). Lectin from wheat germ (Kurisu et al. 1980), *Griffonia simplicifolia* (Maddox et al. 1982), possess the ability to bind carbohydrate moiety of mouse macrophage tumor cells and encourage the killing of tumor cells (Eckhardt et al. 1982).

Lectins as anti-HIV agents

Lectins have been reported to have promising biological and medical applications. The legume lectins have been shown to be involved in causing inhibition of viral progression in humans and animals (Balzarini et al. 1991). The first anti-viral lectin reported as D-mannose specific lectin from *Gerardia savaglia* stopped infection of H9 cells with human immunodeficiency virus type 1 (HIV-1). The exact mechanism behind this is the formation of cluster due to multivalent interaction of the three sugar-binding pockets with three high-mannose type glycans of HIV envelop gp120. Some legume lectins like concanavalin-A, *Lens culinaris* agglutinin, *Pisum sativum, Vicia faba,* and many other lectins were found to bind with HIV envelop gp120, which inhibit fusion of HIV-infected cells with $CD4^+$ cells by interacting with carbohydrate of HIV-infected cells (Hansen et al. 1989). The lectins derived from *Phaseolus vulgaris* have been found to inhibit the activity of HIV-1 reverse transcriptase (Ye and Ng 2001b).

Lectins as insecticides

Lectins derived from a variety of crops including wheat, rice, tobacco, etc., have been recommended as chemical agents acting against many insect pests. These days, lectins

are being exploited as a part of the integrated pest management approaches. Lectins bind to insect gut glycan receptors which is essential site for the survival and growth of insect pests and exhibit anti-insecticidal activity. Legume lectins derived from *Amburana cearenis, Anaden anthera, Dioclea megacarpa,* and *Piptadenia* are the prospective sources of lectins with larvicidal activities against the mosquito species of *Aedes aegypti*. Lectins protect the seeds from being damaged by beetle *Callosobruchus maculatus,* e.g. *Canavalia brasiliensis, Dioclea grandiflora, Cratylia floribunda,* etc. (Gatehouse et al. 1995). There are many purified plant-based lectins reported to possess significant insecticidal properties. For example, *Dioscorea batatas* lectin inhibited the *Helicoverpa armigera* larvae in the adult stage. The *Dioscorea batatas* lectins act in a similar manner to kill *Helicoverpa armigera* larvae (Ohizumi et al. 2009). The *Arum maculatum* tuber lectins bind with the brush border membrane vesicle proteins of the gut to cause deleterious effects on the *Lipaphis erysimi* and *Aphis craccivora* (Majumder and Mondal 2005).

Lectins as antibacterial agents

The major role of lectins involved in plant defense mechanisms is to prevent the entry of microorganisms into the cytoplasm. Lectins can indirectly interact with carbohydrate moieties of the bacterial cell wall (Peumans and Van Damme 1995) and block the movement of motile bacteria at the air-water interface (Broekaert and Peumans 1986). Recent studies have revealed that strong binding of plant lectins with muramic acid, N-acetylmuramic acid, and muramyl dipeptide of bacterial cell walls protects the plants against microbes (Ayouba et al. 1994). Recently, lectin obtained from *Indigo feraheterantha* (Indigo bush) have been shown to be effectively inhibit against several pathogenic bacteria such as *Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli,* and *Bacillus subtilis* (Qadir et al. 2013).

Lectins as antifungal agents

A large number of lectins have been reported however, only a small number have shown to exhibit antifungal properties. The chitin-binding lectins can play an important role in plant defense against fungi. The chimerolectins were found to be the only plant lectins with potential fungicidal proteins, which belong to class I chitinases. The mechanism against fungicidal activity involves the binding of lectin to the fungal cell membrane thereby inhibiting the fungal growth. Further, the binding of lectin to carbohydrates on the fungal cell wall surface interrupts the chitin synthesis (Van Parijs et al. 1991). The legume lectins demonstrating the fungicidal activity are documented in literature. This includes lectin from *Pisum sativum* which offers protection against *Fusarium oxysporum* (Sitohy et al. 2007); *Cicer arietinum* lectin protects against *Candida parapsilosis, Candida krusei* (Gautam et al. 2018), and *Candida tropicalis* (Kumar et al. 2014).

Lectins as antitumor agents

In recent years, the lectin family has attracted much attention due to their anti-tumor properties that could bind specific cancer cell surface glycoconjugates. Owing to a set of cell surface proteins and lipids, lectins can facilitate its binding and interact differentially with distinct cells. This makes them good antitumor agents. Concanavalin A (ConA), a typical legume lectin with a mannose/glucose-binding specificity, was reported to induce apoptosis in murine macrophage PU5-1.8 cells through clustering of mitochondria and release of cytochrome-c (Suen et al. 2000). An earlier study has shown that ConA induces apoptosis in human melanoma A375 cells in a caspase-dependent pathway (Liu et al. 2009). Subsequently, ConA caused mitochondrial transmembrane potential (MMP) collapse, cytochrome-c release, activation of caspases, and eventually triggering a mitochondria-mediated apoptosis. Another typical legume lectin with specificity towards sialic acid and purified from *Phaseolus coccineus* L. (*Phaseolus multiflorus* wild) seeds possesses a remarkable anti-proliferative activity. Gondim et al. (2017) investigated the potential of DLasiL lectin isolated from the seeds of *Dioclea lasiocarpa* as an anticancer agent. They investigated the potential of DLasiL lectin in A-2780 ovarian, A-549 lung, PC-3 prostate, and MCF-7 breast human cancer cell lines. Recently, Une et al. (2018) studied the lectin isolated from Japanese red sword beans as a potential cancer chemopreventive agent. This lectin has similarities to concanavalin A in amino acid composition and sequences as well.

Lectins as antiviral agents

The ability of lectins to inhibit the growth of viruses *in vitro* is documented in the literature. The D-mannose specific lectin from *Gerardia savaglia* was reported to prevent the spread of H9 cells with human immunodeficiency virus (HIV)-1 (Müller et al. 1988). This lectin inhibited syncytium formation in the HTLV-IIIB/H9-Jurkat cell system and HIV-1/human lymphocyte system by reacting with the oligosaccharide side chains of the HIV-1 envelop gp120 glycoprotein molecule. A year later, the lectins ConA, wheat germ agglutinin, *Lens culinaris* agglutinin, *Vicia faba* agglutinin, *Pisum sativum* agglutinin, and phytohaem (erythro) agglutinin were found to bind with gp120 (Hansen et al. 1989).

Mitogenic activity of lectins

Mitogenic stimulation by plant-based lectins was observed in the dormant stage of lymphocytes. The first mitogenic stimulation in such lymphocytes was found in the PHA of *Phaseolus vulgaris* (Nowell 1960). The mitogenic activity has also been reported to be present in *Phaseolus acutifolius* (Valadez-Vega et al. 2011) and *Vigna sesquipedalis* (Wong and Ng 2003).

Lectins as toxicants

Lectins become toxic to the mammalian cells when used in high concentrations (Liener et al. 1986). Some lectins

transported along with neuronal processes inactivate the ribosomes resulting in neuronal death. An example includes ricin and abrin (Wiley et al. 1982). The toxin lectin consists of two polypeptide chains inter-linked by disulfide bonds. The heavier (B) chain possesses the carbohydrate binding site, whereas the lighter (A) chain inhibits protein synthesis in the cells (Fulton et al. 1986; Olsnes and Pihl 1982).

Conclusion

Plant defense is the primary application of plant lectins. In addition, they exert non-preference predominantly to their predators like higher animals. Lectins also constitute a part of the seed storage organ in the form of carbohydrate-binding proteins which can be thus used as passive-defense protein. Since phytolectins possess an ability to make specific glyco-conjugates, they may be exploited towards the identification of different microbial strains and other infectious agents for diagnostic purposes. Several plant-derived components have been used from ancient times to treat/cure several human diseases. Applications displayed by plant lectins in pharmacological studies may generate new active principles in the near future.

Acknowledgements

The authors are thankful to the University Grants Commission (UGC), New Delhi for funding and specially Mr. Ajay Gautam, for providing research fellowship.

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