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Lectins: Proteins with Diverse Applications

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ABSTRACT

Lectins are proteins that bind to carbohydrates and sugar containing substances in a specific and reversible way or precipitate glycoconjugates. These heterogeneous class of carbohydrate-binding proteins or glycoproteins of non-immune origin are capable of specific recognition of, and reversible binding to, carbohydrates without altering their covalent structure. Lectins are found in a diversity of organisms and possess the ability to agglutinate erythrocytes with known carbohydrate specificity since they have at least one non-catalytic domain that binds reversibly to specific monosaccharides or oligosaccharides. This review aims to highlight the applications of lectins in various fields of biology. Lectins are isolated from their natural sources by chromatographic procedures with various modulations to increase their production. The yields of animal lectins are usually low compared with the yields of plant lectins such as legume lectins, which form a major source of these proteins. Lectins manifest a diversity of activities including anti-insect activities, antitumor, immunomodulatory, antimicrobial and HIV-1 reverse transcriptase inhibitory, which may find applications in many therapeutic areas. A small number of lectins demonstrate anti-parasitic activities.

INTRODUCTION

"Lectin" has been derived from the Latin word "legere", which means "to select", by William Boyd (Boyd and Shapleigh, 1954). This term was generalized to embrace all sugar-specific agglutinins of nonimmune origin, irrespective of source and blood type specificity (Sharon and Lis, 1972). Lectins have the ability to bind carbohydrates and the name "hemagglutinins" is used when the sugar specificity is unknown. Lectins are proteins/glycoproteins, which have at least one non-catalytic domain that exhibits reversible binding to specific monosaccharides or oligosaccharides (Peumans and Van – Damme, 1995 b). They can bind to the carbohydrate moieties on the surface of erythrocytes and agglutinate the erythrocytes, without altering the properties of the carbohydrates. Lectins with specific carbohydrate specificity have been purified from various plant tissues and other organisms. They can be classified on the basis of their carbohydrate specificity. They can also be categorized according to the overall structures into merolectins, holoectins, chimerolectins and superlectins, or be grouped into different families (legume lectins, type II ribosome-inactivating proteins, monocot mannose-binding lectins, and other lectins). The amount of lectin varies in different organisms. The high yields of lectins from different sources may facilitate mass production. Application of lectins is possible depending on their properties. The antimicrobial and anti-insect activities of lectins can be made use of in the control of pathogens. The production of anti-tumor and anti-viral drugs based on lectins may also have a significant utility in therapeutic industry.

History of lectins

Lectins were first described in 1888 by Stillmark, who observed that crude extracts of castor beans (*Ricinus communis*) contained a toxic substance named ricin that agglutinated human and some animal red blood cells. However, the modern age of lectinology started nearly 100 years later (Bies et al., 2004; Sharon and Lis, 2004).

Lectins were initially found and described in plants, but in subsequent years multiple lectins were isolated from microorganisms and also from animals (Sharon and Lis, 2004). The lectin-induced agglutination of cells has originally served as the most common assay to detect and quantify lectin activity in a variety of organisms (Vlodavsky and Sachs, 1975; Doyle and Keller, 1984; Goldhar, 1995).

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Despite their broad applicability as a method for the detection of lectin activity, agglutination assays have considerable limitations because only multivalent lectins can agglutinate. Monovalent lectins, with only one binding site for carbohydrates, are usually not detectable by agglutination assays. Therefore, agglutination assays are mostly applied for lectins that are know to have more than one carbohydrate-binding site. Advances in biophysical and molecular biology techniques as well as the availability of synthetic oligosaccharides have contributed to the identification of many lectins. Most lectins have been purified by affinity chromatography (Agrawal and Goldstein, 1967). For the isolation and characterization of a vast number of lectins, sugar-based polymers like Sephadex (glucose), Sepharose (galactose) or Chitin (N-acetyl-glucosamine) have been used. Glycoprotein-linked matrices are applied to the purification of lectins that recognize more complex saccharides (Goldstein, 2002). Many lectins have, in addition to the carbohydrate-binding domain, another domain with distinct activity. Proteins that carry lectin domain(s) and other domains with quite different properties have been better studied in animals than in plants (Gabius, 1994).

PRODUCTION OF LECTINS

Lectins are found in nature. A large number of lectins or hemagglutinins have been purified from different organisms.

Natural lectins

Animal lectins

Lectins are found in different animals. However, the yields are usually extremely low (Table 1). Mass purification of animal lectins necessitates bulk quantities of raw materials which make it not feasible.

Mushroom lectins

Yields of lectins from fresh mushrooms are low, e.g., 2.6 mg from 100 g of fresh fruiting bodies of Pleurocybella porrigens (Suzuki et al. 2009). In fact, the water content in fresh mushrooms is very high. Dried fruiting bodies of the mushrooms Russula lepida, Pholiota adiposa, and Inocybe umbrinella yielded 39, 70, and 15 mg lectin per 100 g fruiting bodies, respectively (Zhang et al. 2010, 2009; Zhao et al. 2009). Therefore, production from fresh mushroom is also unpractical.

Plant lectins

The lectin contents in some parts of plants are higher, e.g., 390 and 75 mg of the purified lectin was recovered from 100 g Remusatia vivipara tubers (Bhat et al. 2010) and Astragalus mongholicus roots (Yan et al. 2005), respectively. Lectins are also found in seeds. The lectin content in non legume plants is low, e.g., 3.3 mg lectin from 100 g Hibiscus mutabilis seeds (Lam and Ng 2009). Lectins are found in abundance in legume seeds. Phaseolus vulgaris is an herbaceous annual plant grown worldwide for its edible beans, popular in both dry and green bean forms. The commercial production of beans is well distributed worldwide. There are different varieties, including anasazi bean, black beans, cranberry bean, borlotti beans, pink beans, pinto beans, kidney beans, shell beans, white beans, yellow beans and French beans, etc. Lectins or hemagglutinins have been purified from different varieties of P. vulgaris. The lectin contents are low in some varieties and high in other varieties (Table 2).

Purification of lectins or hemagglutinins

Isolation of lectins generally begins with a saline (or buffer) extraction of the finely ground seed meal. Pre – extraction with acids (e.g., acetic acid used by Naeem et al. 2007), organic solvents (for example, methanol, diethyl ether or acetone used by Medeiros et al. 2010) is often employed to remove lipid or other interfering substances (Sumner and Howell, 1936).

Ammonium sulfate or alcohol fractionation, centrifugation and dissolution of the precipitate yield supernatant liquor containing the lectin(s). Plant lectins or agglutinins may be isolated from saline extracts by conventional protein purification techniques, affinity chromatography or a combination there of. Virtually all the lectin purification schemes employ affinity chromatography that exploits the specific sugar binding capacity of the lectin (Sharon et al., 1974). Knowledge of the sugar specificity of a lectin which can be obtained from inhibition experiments using simple sugars and crude lectin preparations, permits the design of a suitable purification procedure. Simply stated, a carbohydrate ligand with which the lectin interacts, is insolubilized, the lectin is adsorbed as the extract is percolated slowly over the adsorbent, and displacement of bound lectin is accomplished by elution, either with a sugar that competes for lectin sites with the specific adsorbent or by altering the nature of the eluent (by lowering the pH, increasing the ionic strength, or adding denaturants). The lectin from *Datura stramonium* by affinity chromatography on Sepharose fetuin (Kilpatrick and Yeoman, 1978). Datta and Basu (1983) purified a human erythrocyte specific lectin from the seeds of *Erythrina variegata Linn. var. orientalis Linn.* (Leguminosae) by affinity chromatography on acid treated sepharose 4B. An alternative approach involves insolubilized glycoproteins. Felsted *et al.,* 1975 isolated a lectin from saline extracts of red kidney beans (*Phaseolus vulgaris*) by affinity absorption on porcine thyroglobulin-Sepharose. Matsuda *et al.,* 1989 isolated a lectin from winged bean (*Psophocarpus tetragonolobus*) seed extracts by affinity chromatography on Sepharose-6-aminocaproyl-D-galactosamine.

Thus, an affinity system for the isolation of the lectin of red kidney beans (*Phaseolus vulgaris*) involved thyroglobulin – Sepharose (Felsted et al., 1975) and for the isolation of *Limulus polyphemus* lectin, bovine sub maxillary mucin - Sepharose. Fetuin - Sepharose has been employed for the isolation of the agglutinins from wheat germ, jack bean, potato, *Amaranthus hypochondriacus* seeds and several other sources (Owens and Northcote, 1980; Ozeki et al., 1996). The lectin from *Datura stramonium* was isolated by affinity chromatography on Sepharose fetuin (Kilpatrick and Yeoman, 1978).

Table. 1: Yields of animal lectins obtained by chromatographic isolation from natural sources.

Natural source	Chromatography for purification	Lectin yield	Reference
Acropora millepora (coral) plasma fluid	Mannose affinity chromatography	0.7 mg/100 ml plasma	Kvennefors et al. 2008
Aristichthys nobilis (bighead carp) gills	DEAE-Sepharose, Sephacryl S-200 and Superdex 200	9.4 mg/100 g	Pan et al. 2010
Bubalus bubalis (Buffalo) heart tissue	Ammonium sulfate precipitation and Sephadex G50	0.97 mg/100 g	Ashraf et al. 2010
Holothuria scabra (sea cucumber) coelomic fluid	Ultrafiltration and Phenyl-Sepharose	1.6 mg/100 ml	Gowda et al. 2008
Macoma birmanica (marine bivalve) foot muscles	Ammonium sulfate precipitation and N-acetylglucosamine Sepharose 4B	4.5 mg/100 g	Adhya et al. 2009
Nemopilema nomurai (jellyfish)	SP-Sepharose and BSM-Toyopearl	0.35 µg/100 g	Imamichi and Yokoyama 2010

Table. 2: Yields of plant lectins obtained by chromatographic isolation from seeds of different Phaseolus cultivars.

Phaseolus cultivar	Chromatography for purification	Yield(mg/100 g seed)	Sugar specificity	Reference
Anasazi bean	Affi-gel blue gel, Mono S and Superdex 200	13	Not found	Sharma et al. 2009
Dark red kidney bean	DEAE-cellulose and Affi-gel blue gel	107	Not found	Xia and Ng 2006
Escumite bean	Affinity chromatography (glutaraldehyzed membranes from blood group O erythrocytes)	163(total of 4 isoforms	N-acetyllactosamine type glycans	Castillo Villanueva et al. 2007
Extralong autumn purple bean	Blue-Sepharose, Q-Sepharose, Mono Q and Superdex 75	35	Galactose	Fang et al. 2010
French bean 12	SP-Sepharose, Affi-gel blue, Q-Sepharose, and Superdex 200	4.8	Not found	Leung et al. 2008
French bean	Blue-Sepharose, Q-Sepharose and Superdex 75	1100	Not found	Lam and Ng 2010b
Red kidney bean	Affi-gel blue gel and CM-Sepharose	27.5	Lactoferrin, ovalbumin, thyroglobulin	Ye et al. 2001

Table. 3: Anti-insect activity of lectins.

Natural source of lectin	Insect affected	Anti-insect effect	Sugar specificity	Reference
Allium sativum (garlic) bulbs	*Acyrthosiphon pisum*	Increased mortality	Mannose	Fitches et al. 2008
Arisaema intermedium and *Arisaema wallichianum* (Araceae)	*Bactrocera cucurbitae*	1. Prolonged period of development 2. Inhibited pupation and emergence	Not found	Kaur et al., 2009
Gracilaria cornea (red alga)	*Boophilus microplus*	Reduced 1. body weight of female after oviposition period, 2. egg mass weight, and 3. hatching period	Fetuin, porcine stomach, mucin	Lima et al. 2005
Gracilaria ornate (red alga)	*Callosobruchus maculatus*	Delayed development	Fetuin, porcine stomach, mucin	Leite et al. 2005
Myracrodruon urundeuva (aroeira preta) bark	*Aedes aegypti*	Increased mortality	N-acetyl-Dglucosamine	Sá et al. 2009
Xerocomus chrysenteron fruiting bodies	*Myzus persicae*	Increased mortality	Fetuin, porcine stomach mucin	Jaber et al. 2008
Xerocomus chrysenteron fruiting bodies	*Myzus persicae*	1. Increased mortality 2. Reduction of body weight, duration of development and fecund	Fetuin, porcine stomach mucin	Jaber et al. 2007

Table. 4: Plant lectins with antimicrobial activity.

Plant (tissue)	Lectin specificity	Antimicrobial activity
Araucaria angustifolia (seed)	GlcNAc	*Clavibacter michiganensis, Xanthomonas axonopodis* pv. *Passiflorae*
Artocarpus incisa (seed)	GlcNAc	*Fusarium moniliforme, Saccharomyces cerevisiae*
Artocarpus integrifolia (seed)	GlcNAc	*F. moniliforme, S. cerevisiae*
Astragalus mongholicus (root)	Lactose/D-Gal	*Botrytis cincerea, Fusarium oxysporum, Colletorichum sp., Drechslera turcia*
Eugenia uniflora (seeds)	Carbohydrate complex	*Bacillus subtilis, Corynebacterium bovis, Escherichia coli, Klebsiella* sp., *Pseudomonas aeruginosa, Streptococcus sp., Staphylococcus aureus*
Gastrodia data (corms)	α-Man/ GlcNAc	*B. cinerea, Ganoderma lucidum, Gibberella zeae, Rhizoctonia solani, Valsa ambiens*
Hevea brasiliensis (latex)	Chitotriose	*B. cinerea, Fusarium culmorum, F. oxysporum* f. sp. *pisi, Phycomyces blakesIeeanus, Pyrenophora triticirepentis, Pyricularia oryzae, Septoria nodorum, Trichoderma hamatum*
Myracrodruon urundeuva (heartwood)	GlcNAc	*B. subtilis, Corynebacterium callunae, E. coli, Klebsiella pneumoniae, P. aeruginosa, S. aureus, Streptococcus faecalis. Fusarium solani, F. oxysporum, F. moniliforme, Fusarium decemcellulare, Fusarium lateritium, Fusarium fusarioides, Fusarium verticiloides*
Ophiopogonjaponicus(rhizome)	Man	*Gibberella saubinetii, R. solani*
Opuntia ficus indica (cladodes)	Glc/Man	*Colletrotrichum gloesporioides, Candida albicans, F. oxysporum, F. solani*
Phaseolus coccineus (seeds)	Sialic acid	*Helminthosporium maydis, Gibberalla sanbinetti, R. solani, Sclerotinia sclerotiorum*
Phthirusa pyrifolia (leaf)	Fru-1,6-P2	*B. subtilis, K. pneumoniae, Staphylococcus epidermidis, S. faecalis F. lateritium, R. solani*
Pisum sativum (seed)	Man	*Aspergillus flavus, F. oxysporum, Trichoderma viride*
Sebastiania jacobinensis (bark)	Carbohydrate complex	*F. moniliforme, F. oxysporum*
Talisia esculenta (seeds)	Man	*Colletotrichum lindemuthianum, F. oxysporum, S. cerevisiae*
Triticum vulgaris (seeds)	GlcNAc	*Fusarium graminearum, F. oxysporum*
Urtica dioica (rhizome)	GlcNAc	*B. cinerea, C. lindemuthianum, Phoma betae,Phycomyces blakesleeanus, Septoria nodorum, Trichoderma hamatum, T. viride*

Wheat germ agglutinin was also isolated by using insolubilized ovomucoid (Avrameas and Guilbert, 1971). Erythrocytes treated with formaldehyde and glutaraldehyde, have been used as adsorbents for lectin isolation (Avrameas and Guilbert, 1971). Whenever possible commercially available adsorbents are also employed. An increase in the number of purification steps usually results in a lower recovery. In order to produce a large quantity of lectins, the first criterion is a high lectin content in the starting material. The second criterion is the use of a simple purification protocol. Tetrameric escumite lectin was purified by affinity chromatography on a column containing glutaraldehyde membranes from blood group O erythrocytes. Four isoforms were separated on Mono-S (cation exchanger) (Castillo-Villanueva et al., 2007). Dark red kidney bean hemagglutinin was unadsorbed on DEAE-cellulose but adsorbed on Affi-gel blue gel (Xia and Ng, 2006). French bean 35 hemagglutinin with high purity was isolated by chromatography on Blue-Sepharose and Q-Sepharose (Lam and Ng, 2010b).

APPLICATIONS

Lectins have become the focus of intense interest for biologists and in particular for the research and applications in agriculture and medicine (Movafagh et al., 2013). These proteins with unique characteristics have found use in diverse fields of biology and as more lectins are being isolated and their role in nature elucidated, they continue to occupy an important place in agricultural and therapeutic areas of research.

Anti-insect activity of lectins

One of the interesting roles of lectins is in host defence against pathogens and predators (Fitches et al., 2010: Hakim et al., 2010; Kaur et al., 2009, 2006a, b). As there is a need to replace conventional insect control measures which cause pollution and disturb the food chain, several alternative measures have been attempted including use of plant lectins. The anti-insect activity of plant lectins against a wide array of insect species have been well documented and represents a potential of using plant lectins as naturally occurring insecticidal agents against pests, which restrain increased crop production (Fitches et al., 2010; Hogervorst et al., 2006). *Bactrocera cucurbitae* is a major pest of cucurbitaceous vegetables and fruits in many parts of the world (Kumar et al., 2006). The pest has so far defied almost all conventional control measures and the damage caused to the standing crop has been reported to be 100% in some cases (Singh et al., 2009).

Lectins have been suggested as one of the promising agents against insect pests and have been engineered successfully into a variety of crops including wheat, rice, tobacco, and potatoes. This approach could be used as a part of integrated pest management strategies and caveat pest attack. In general, it seems that large-scale implementation of transgenic insecticidal and herbicide-tolerant plants does not display considerable negative effects on the environment. Moreover, at least some transgenic plants can improve the corresponding environments and human health because their production considerably reduces the load of chemical insecticides and herbicides (Velkov et al., 2005). Lectins demonstrate anti-insect activity. They increase the mortality or delay the development of insect (Table 3). When incorporated in an artificial diet, *Arisaema jacquemontii* lectin adversely affected the development of *Bactrocera cucurbitae* larvae (Kaur et al., 2006a). Arisaema helleborifolium lectin exhibited anti-insect activity towards the second instar larvae of B. cucurbitae (Kaur et al., 2006b). The insecticidal property of lectins may be due to orchestration of enzymatic activity of larvae. After treatment with different lectins, the activity of esterases in larvae was increased whereas the activity of acid phosphatase and alkaline phosphatase decreased. Galectin-1 treatment of *Plutella xylostella* larvae brought about disruption of the microvilli and induced abnormalities in these epithelial cells (Chen et al. 2009b). *Dioscorea batatas* lectin inhibited the emergence of Helicoverpa armigera larvae into adults by avidly binding to larval brush border and peritrophic membrane (Ohizumi et al., 2009). *Arum maculatum* tuber lectin caused *Lipaphis erysimi* and *Aphis craccivora* to succumb, by binding to the gut brush border membrane vesicle proteins (Majumder et al., 2005). *Olneya tesota* lectin bound to midgut glycoconjugates and microvillae of *Zabrotes subfasciatus* larvae. Diminished oviposition and a failure of emergence of adult beetles were observed (Lagarda-Diaz et al., 2009). *Annona coriacea* lectin displayed toxicity in *Anagasta kuehniella* which apparently resulted from a change in the gut membrane environment and consequent disruption of digestive enzyme recycling mechanisms by binding to midgut proteins (Coelho et al., 2007). Bauhinia monandra leaf lectin produced mortality in *Zabrotes subfaciatus* and *Callosobruchus maculatus* when incorporated into an artificial diet. *B. monandra* leaf lectin produced a 40% decrement in weight of *A. kuehniella* larvae. *B. monandra* leaf lectin bound to midgut proteins of the insect *C. maculatus* (Macedo et al., 2007). The detached leaves from transgenic tobacco plants expressing Allium sativum lectins reduced the weight gain and development and the metamorphosis of Spodoptera littoralis larvae. Furthermore, the larvae were detrimental to the pupal stage resulting in weight reduction and lethal abnormalities (Sadeghi et al., 2008). Production of *Rhopalosiphum maidis* nymphs was significantly reduced on *Galanthus nivalis* agglutinin-expressing plants (Wang et al., 2005). *G. nivalis* agglutinin was also found bound to glycoproteins that can be found in the guts of larvae of *Adalia bipunctata*, *Chrysoperla carnea*, and *Coccinella septempunctata* (Hogervorst et al., 2006). A lectin from *Colocasia esculenta* (L.) Schott corms was shown to have anti-insect potential towards *Bactrocera cucurbitae* (Coquilett) (Thakur et al., 2012) The lectin was found to be specific towards N-acetyl-D-lactosamine (LacNac), a disaccharide and asialofetuin, a desialylated serum glycoprotein. The lectin significantly decreased the percent pupation and emergence with respect to control. Effect on various enzymes was studied by employing LC50 (51.6 µg ml-1) CEA in the artificial diet bioassay of second instar larvae. All the enzymes tested namely esterases, phosphatases (acid and alkaline), superoxide

dismutases, catalase and glutathione-S-transferase showed a significant ($p<0.01$, $p<0.05$) increase in their enzyme and specific activities. These results showed that CEA affected normal growth and development and presented stress to the larvae, activating their detoxification and anti-oxidant systems. Thus, the lectin seems to be a useful candidate for the control measures of *Bactrocera cucurbitae*. The lectin gene presents a useful candidate for the integrated pest management. The value of this candidate gene is weighed by the fact that it expresses an edible protein and hence is not expected to pose any serious health threats on human health, if expressed in a transgenic plant.

Antimicrobial Activity

Many human pathogens utilize cell surface glycans as either receptors or ligands to initiate adhesion and infection (Sharon and Lis, 1989; Sharon and Lis, 2003; Zem et al., 2006; Hyun et al., 2007; Oppenheimer et al., 2008; Magalhaes et al., 2009; Mukhopadhyay et al., 2009). *Escherichia coli* (*E. coli*), for example, binds to host mannosides, while influenza virus binds to host sialic acids (Mukhopadhyay et al., 2009). Other strains of *E. coli* have been discovered that demonstrate specificities towards other host cell surface carbohydrate moieties such as galabiose (Gal-α-4-Gal) and NeuAc-α-2,3-Gal-β-3-GalNAc (Khan et al., 2000; Buts et al., 2003). The genital pathogen *Neisseria gonorrhea* specifically binds N-acetyllactosamine (Gal-β-4-GlcNAc, LacNAc), and *Streptococcus pneumonia* specifically binds the pentasaccharide NeuAc-α-3-Gal-β-4-GlcNAc-β-3-Gal-β-4-Glc as well as the internal tetra- and trisaccharides Gal-β-4-GlcNAc-β-3-Gal-β-4-Glc and GlcNAc-β-3-Gal-β-4-Glc respectively. *Pseudomonas aeruginosa* specifically binds fucose (L-Fuc) (Barthelson et al., 1998). Bacteria can discriminate between two identical glycans that differ in only one hydroxyl group (Sharon, 2006). Such host–pathogen interactions are multivalent, and therefore the binding events are of high affinity and suited for host invasion (Nimrichter et al., 2004; Mukhopadhyay et al., 2009).

Cytotoxic effects of lectins may be revealed by antitumoral and antiviral activities and also by deleterious effect on microorganisms (Table 4); lectins of different carbohydrate specificities are able to promote growth inhibition or death of fungi and bacteria. Table 4 shows proposed applications of lectins for detection, typing, and control of bacteria and fungi that cause damage to plants and humans. Antibacterial activity on Gram-positive and Gram-negative bacteria occurs through the interaction of lectin with components of the bacterial cell wall including teichoic and teichuronic acids, peptidoglycans and lipopolysaccharides; study revealed that the isolectin I from *Lathyrus ochrus* seeds bind to muramic acid and muramyl dipeptide through hydrogen bonds between ring hydroxyl oxygen atoms of sugar and carbohydrate binding site of lectin and hydrophobic interactions with the side chains of residues Tyr100 and Trp128 of isolectin I (Bourne et al., 1994). Despite the large numbers of lectins and hemagglutinins that have been purified, only a few of them manifested antifungal activity. The inhibition of fungi growth can occur through lectin binding to hyphas resulting in poor absorption of nutrients as well as by interference on spore germination process (Lis and Sharon, 1981). The polysaccharide chitin is constituent of fungi cell wall and chitin-binding lectins showed antifungal activity; impairment of synthesis and/or deposition of chitin in cell wall may be the reasons of antifungal action (Selitrennikoff, 2001). Probably the carbohydrate-binding property of lectin is involved in the antifungal mechanisms and lectins of different specificities can promote distinct effects. Plant agglutinins are believed to play a role in plant defense mechanism against microorganism phytopathogens (Sa et al., 2009a).

The expression of *Gastrodia elata* lectins in the vascular cells of roots and stems was strongly induced by the fungus *Trichoderma viride*, indicating that lectin is an important defense protein in plants (Sá et al., 2009b). Following insertion of the precursor gene of stinging nettle isolectin I into tobacco, the germination of spores of *Botrytis cinerea*, *Colletotrichum lindemuthianum*, and *T. viride* was significantly reduced (Does et al., 1999). Thus, lectins may be introduced into plants to protect them from fungal attack. Plant lectins can neither bind to glycoconjugates on the fungal membranes nor penetrate the cytoplasm owing to the cell wall barrier. It is not likely lectins directly inhibit fungal growth by modifying fungal membrane structure and/or permeability. However, there may be indirect effects produced by the binding of lectins to carbohydrates on the fungal cell wall surface. Chitinase-free chitin-binding stinging nettle (*Urtica dioica* lectin) impeded fungal growth. Cell wall synthesis was interrupted because of attenuated chitin synthesis and/or deposition (Van Parijs et al., 1991). The effects of nettle lectin on fungal cell wall and hyphal morphology suggest that the nettle lectin regulates endomycorrhizal colonization of the rhizomes. Severa1 other plant lectins inhibit fungal growth. The first group includes small chitin-binding merolectins with one chitin-binding domain, e.g., hevein from rubber tree latex (Van Parijs et al., 1991) and chitin-binding polypeptide from *Amaranthus caudatus* seeds (Broekaert et al., 1992). The only plant lectins that can be considered as fungicidal proteins are the chimerolectins belonging to the class I chitinases. However, the antifungal activity of these proteins is ascribed to their catalytic domain.

Antitumor activity

Owing to their fine specificity, lectins have various applications in biomedical sciences including cancer research. It is well documented that lectins have an antitumor effect. Plant lectins represent a well-defined and a novel non-traditional source of anticancer compounds. A number of plant lectins (predominantly galactoside and galNAc specific) have been in pre-clinical and clinical trials as potential drugs for treatment of cancer (Ernst et al., 2003). Within the past few years, lectins have become a well-established means for understanding varied aspects of cancer and metastasis. Evidence is now emerging that lectins are dynamic contributors to tumor cell recognition (surface markers), cell

adhesion and localization, signal transduction across membranes, mitogenic stimulation, augmentation of host immune defense, cytotoxicity, and apoptosis. To advance understanding of these lectin-dependent processes, attempts are being made to discover new lectins that have one or more of these functions and to develop lectin- (or glycoconjugate-) based tools that could be used to home in on tumor cells. Legume lectins are one of the most extensively studied plant lectin families for their molecular basis of the protein–carbohydrate interactions for several decades (Damodaran et al., 2008). In recent years, the main interests in this lectin family lay in their potential application as anti-tumour agents that could bind specific cancer cell surface glycoconjugates. 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*. Recent study has showed that ConA induces apoptosis in human melanoma A375 cells in a caspase-dependent pathway. Subsequently, ConA caused mitochondrial transmembrane potential (MMP) collapse, cytochrome *c* release, activation of caspases and eventually triggering a mitochondria-mediated apoptosis (Liu et al., 2009).

Furthermore, other recent reports have demonstrated that a legume lectin named *S. flavescens* lectin (SFL) can induce tumour cell death through a caspase-dependent apoptotic pathway, and its apoptotic mechanisms is speculated to be the death-receptor pathway (Liu et al., 2008). And, another typical legume lectin with specificity towards sialic acid purified from *Phaseolus coccineus* L. (*Phaseolus. multiflorus* wild) seeds possesses a remarkable anti-proliferative activity. This lectin induced the caspase dependent apoptosis in murine fibrosarcoma L929 cells. Besides, its antineoplastic activity was decreased abruptly when the sialic acid-specific activity was completely inhibited, which indicates that this sugar-binding specificity might be the main reason sparking off the antineoplastic activity and apoptosis (Chen et al., 2009). *Flammulina velutipes* hemagglutinin-inhibited proliferation of leukemia L1210 cells (Ng et al., 2006). *Haliclona crater* lectin displayed a cytotoxic effect on HeLa and FemX cells (Pajic et al., 2002). Dark red kidney bean hemagglutinin exerted an antiproliferative activity toward leukemia L1210 cells (Xia and Ng, 2006). Small glossy black soybean (*Glycine max*) lectin impeded proliferation of breast cancer MCF7 cells and hepatoma HepG2 cells (Lin et al., 2008). Del Monte banana lectin retarded proliferation of (L1210) cells and hepatoma (HepG2) cells (Cheung et al., 2009). Extra long autumn purple bean lectin inhibited the proliferation of hepatoma HepG2 cells by inducing the production of apoptotic bodies (Fang et al. 2010). Mistletoe lectin can be used in cancer patients to improve the quality of life (Semiglazov et al., 2006). In order to widen the application of anti-tumor lectins, the mechanism of action was elucidated. Lectins elicit apoptosis in different cancer cell lines. Examples include Korean mistletoe lectin-treated B16-BL6 melanoma cells (Park et al., 2001), Korean mistletoe lectin-treated human A253 cancer cells (Choi et al., 2004), *Agrocybe aegerita* lectin-treated HeLa cells (Zhao et al., 2009), Abrus agglutinin-treated Dalton's lymphoma cells (Bhutia et al. 2008a) and HeLa cells (Bhutia et al., 2008b), *Sophora flavescens* lectin-treated HeLa cells (Liu et al., 2008), *Polygonatum odoratum* lectin treated murine fibrosarcoma L929 cells (Liu et al., 2009b), *Polygonatum cyrtonema* lectin-treated human melanoma A375 cells (Liu et al., 2009a), *Pseudomonas aeruginosa* hemagglutinin-treated breast cancer cells (MDA-MB-468, and MDA-MB-231HM cells; Liu et al., 2009c), French bean hemagglutinin-treated breast cancer MCF-7 cells (Lam and Ng ,2010a), and recombinant protease-resistant galectin-9- treated myeloma cells (Kobayashi et al., 2010). Although the apoptotic pathways look different, activation of different caspases is usually involved. Caspase-3 plays a central role in apoptosis. It interacts with caspase-8 and caspase-9. Therefore, caspase-3 is usually investigated in apoptotic pathways, except in the case of a caspase-3- deficient cell line (e.g., MCF-7 cells) which was used in the study of French bean hemagglutinin (Lam and Ng, 2010a). Caspase-8 and -9 are also activated (Liu et al., 2009a; Liu et al., 2009b, c; Kobayashi et al., 2010; Lam and Ng, 2010a). Apoptosis can be mediated by death receptors initated by lectins. FAS receptor is the receptor with which lectins often interact (Liu et al., 2009b, c; Lam and Ng, 2010a). The interaction is probably by protein–protein interaction. The Bcl family members (anti-apoptotic factors) were down-regulated (Bhutia et al., 2008a, b; Liu et al. 2009a; Lam and Ng, 2010a). The sequestration of cytochrome c in mitochondria was interrupted and cytochrome c release was observed (Bhutia et al. 2008a, b; Liu et al., 2009a, b; Lam and Ng, 2010a). Finally, mitochondrial membrane depolarization was detected (Liu et al., 2009a, b; Lam and Ng, 2010a) and G_0/G_1 arrest was frequently observed (Bhutia et al. 2008a, b; Liu et al. 2009c; Lam and Ng 2010a) which seems to be the characteristic of lectin-induced apoptosis although sub G_1 arrest (Park et al., 2001) and G_2/M arrest (Lam and Ng, 2010a) were found in some cases. Investigations of the anti-tumor effect of lectin in vivo have been reported. *Pleurotus citrinopileatus* lectin (Li et al. 2008) and *R. lepida* lectin (Zhang et al., 2010) exerted potent antitumor activity in white Kunming mice bearing sarcoma 180, and caused inhibition of tumor growth when administered intraperitoneally. Lectins have received a lot of attention from cancer biologists due to their remarkable anti-tumor properties. Lectins ConA, ConBr, and CFL are all structurally related and induce apoptosis in the MCF-7 cell line. They have been shown to reduce both proliferation and viability of leukemic cells ConA and ConBr lectins have cytotoxic effects in leukemic cells. Lectins (Con A and Con Br) have been shown to induce internucleosomal DNA fragmentation and alter mitochondrial transmembrane potential in leukemic cells. ConA and ConBr induce apoptosis in leukemic cells by triggering an intrinsic mitochondrial pathway and also increase ROS (Reactve Oxygen Species) (Faheina et al., 2011). The aqueous extract of European mistletoe (*Viscum album*, L.) has been applied in cancer therapy (Lyu et al., 2004). However, in order to make lectin useful practically in the clinical setting, a delivery system is required to lower toxicity, extend exposition, and improve efficacy. Wheat

germ agglutinin and *Ulex europaeus* agglutinin displayed strong interaction with human urinary carcinoma 5,637 cells, which enabled them to target to bladder cancer cells (Plattner et al., 2008). The encapsulation of *Cratylia mollis* lectin with liposomes lowered its tissue toxicity in the liver and kidney, and improved its antitumor activity in Swiss mice inoculated with sarcoma 180 (Andrade et al., 2004). Mistletoe lectin was stabilized with alginate/chitosan microcapsules coated by a biodegradable polymer wall which can be used to protect the lectin from acidic pH in the stomach (Lyu et al., 2004). Immunofluorescence and/or immunohistochemical studies using lectins can reveal the early premalignant stage of prostate carcinogenesis. Expression of glycoconjugates is often altered in tumor cells. Abundant N-acetylglucosamine (α1,3) Nacetylglucosamine/ galactose and galactose (β1,4) Nacetylglucosamine (α,2) mannose (α1,6) residues were observed in dysplastic epithelium tumor cells as evidenced by labeling by the N-acetylgalactosamine-specific and complex type oligosaccharide-specific lectins. The binding of these lectins to androgen-independent rat prostatic carcinoma was revealed, indicating that these sugar residues are common in some dysplastic and neoplastic prostatic cells (Chan et al., 2001).

Generally speaking, the above-mentioned discoveries of the lectins suggest that they might possess some similar biological activities and anti-tumour mechanisms that are closely correlated with their corresponding molecular structures. Thus, these results would provide new clues for further exploring the anti-tumour mechanisms of the lectins.

Antiviral Activity

A lectin (D-mannose–specific) from *Gerardia savaglia* was for the first time reported to prevent infection of H9 cells with human immunodeficiency virus (HIV)-1. Furthermore, the 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 gp120 envelop molecule (high-mannose oligosaccharides; Muller et al., 1988). A year later, the lectins concanavalin A, wheat germ agglutinin, *Lens culinaris* agglutinin, *Vicia faba* agglutinin, *Pisum sativum* agglutinin and phytohaem (erythro) agglutinin were found to bind to gp120. They were able to inhibit fusion of HIV-infected cells with CD4 cells by a carbohydrate-specific interaction with the HIV-infected cells (Hansen et al., 1989). Plant lectins displayed anti-coronaviral activity, especially mannose-binding lectins, in severe acute respiratory syndrome coronavirus. They interfered with viral attachment in early stage of replication cycle and suppressed the growth by interacting at the end of the infectious virus cycle (Keyaerts et al., 2007). Banana (*Musa acuminata*) lectin has been shown to inhibit HIV replication (Swanson et al. 2010). The treatment of AIDS with lectins is being investigated in many studies. Different lectins have different anti-HIV mechanisms. More recently, lectin from the polychaete marine worm *Chaetopterus variopedatus* inhibited cytopathic effect induced by HIV-1 and the production of viral p24 antigen (Wang et al., 2005). The sea worm (*Serpula vermicularis*) lectin suppressed the production of viral p24 antigen and cytopathic effect induced by HIV-1 (Molchanova et al., 2007). *P. cyrtonema Hua* lectin inhibited HIV-I- and HIV-II-induced cytopathicity in MT-4 and CEM cells (An et al., 2006). Banana lectin directly bound the HIV-1 envelope protein (gp120) and blocked entry of the virus into the cell, and decreased the levels of the strong-stop product of early reverse transcription (Swanson et al., 2010). Extra long autumn purple bean lectin (Fang et al., 2010) and mushroom *Russula delica* lectin (Zhao et al., 2009) were able to inhibit HIV-1 reverse transcriptase. Hence, lectins are potential drugs for treatment of AIDS. Besides the aforementioned practical applications of lectins, there have been isolated reports of the antibacterial (Ngai and Ng, 2007) and anti-nematode (Wang et al., 2005) activities of lectin.

CONCLUSION

Lectins are a subject with immense potential and of intense investigations. As more lectins are isolated and further studies are conducted on the biological activities and mechanisms of action of lectins, the production of lectins can be improved and new applications of lectins can be found and explored for significant contributions in various fields of biology.

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