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Annick Barre, Yves Bourne, Els J. M. van Damme, Pierre Rougé. Overview of the Structure–Function Relationships of Mannose-Specific Lectins from Plants, Algae and Fungi. *International Journal of Molecular Sciences*, 2019, Protein–Carbohydrate Interactions: Structure–Function Relationships, 20 (2), pp.254. 10.3390/ijms20020254 . hal-02388775

HAL Id: hal-02388775

<https://amu.hal.science/hal-02388775v1>

Submitted on 21 Jan 2020

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Review

Overview of the Structure–Function Relationships of Mannose-Specific Lectins from Plants, Algae and Fungi

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Received: 11 December 2018; Accepted: 31 December 2018; Published: 10 January 2019



Abstract: To date, a number of mannose-binding lectins have been isolated and characterized from plants and fungi. These proteins are composed of different structural scaffold structures which harbor a single or multiple carbohydrate-binding sites involved in the specific recognition of mannose-containing glycans. Generally, the mannose-binding site consists of a small, central, carbohydrate-binding pocket responsible for the “broad sugar-binding specificity” toward a single mannose molecule, surrounded by a more extended binding area responsible for the specific recognition of larger mannose-containing *N*-glycan chains. Accordingly, the mannose-binding specificity of the so-called mannose-binding lectins towards complex mannose-containing *N*-glycans depends largely on the topography of their mannose-binding site(s). This structure–function relationship introduces a high degree of specificity in the apparently homogeneous group of mannose-binding lectins, with respect to the specific recognition of high-mannose and complex *N*-glycans. Because of the high specificity towards mannose these lectins are valuable tools for deciphering and characterizing the complex mannose-containing glycans that decorate both normal and transformed cells, e.g., the altered high-mannose *N*-glycans that often occur at the surface of various cancer cells.

Keywords: lectin; plant; fungi; mannose-binding specificity; structure; function; use as tools

1. Introduction

Protein-carbohydrate interactions are part of the most efficient signaling pathways occurring inside living organisms or between living organisms and their environment. Lectins or Carbohydrate-Binding Agents (CBAs) are proteins that have specialized in the specific recognition of carbohydrates during the evolution of all living organisms. The large family of carbohydrate-binding proteins contains a large variety of carbohydrate-binding domains (CBDs), each with one or more carbohydrate-binding sites (CBSs) which specifically recognize simple or more complex sugars. Depending on the lectin, the carbohydrate-binding domains belong to distinct structural scaffolds usually organized in homo- or hetero-dimeric or tetrameric structures [1]. According to the nature and the organization of their domains, plant and fungal lectins have been classified in two groups of lectins, (1) lectins exclusively composed of carbohydrate-binding domains and (2) chimerlectins composed of a carbohydrate-binding domain linked to another domain(s) devoid of any carbohydrate-binding

properties [1]. With respect to their binding properties, plant and fungal lectins can be subdivided in different groups, such as for example Man-specific lectins, Gal/GalNAc-specific lectins, and Fuc-specific lectins [2]. However, the binding of lectins towards simple sugars is probably not really relevant. It is more realistic to assume that lectins will interact with the more complex *N*-glycan chains that decorate the cell surface of all living organisms [3]. In addition, the idea has progressively emerged that, besides lectins which are abundantly distributed in storage tissues like seeds and bulbs and play a defensive/protective role, other less abundant lectins participate in more discrete carbohydrate recognition processes equally necessary for the proper functioning of the living organisms [4]. In this respect, the discovery of Nictaba, a lectin localized in the nucleus of tobacco (*Nicotiana tabacum*) cells, represents a milestone in our vision of the function devoted to plant and fungal lectins in vivo [5].

Owing to the huge amount of structural and functional data that have been accumulated for several decades these carbohydrate-binding proteins from plants and fungi have become a tool to decipher the structure–function relationships inherently associated to protein macromolecules. In this respect, lectins involved in the specific recognition of mannosyl residues, the so-called mannose-binding lectins, represent an important group of functional proteins taking into account the widespread distribution of mannose-containing *N*-glycans of the *N*-acetylglucosamine type and high-mannose type. The present review aims to present an exhaustive overview that summarizes all published informations related to the structure–function relationships of mannose-specific lectins from plants and fungi, and their possible applications as analytical and therapeutic tools for biomedical research.

2. Diversity of Mannose-Binding Lectins in Higher Plants

To date, lectins with a mannosyl-binding specificity have been identified in many different plant families, including monocotyledonous as well as dicotyledonous species (Table 1). Among the monocot families, research has focused on the Liliaceae and Amaryllidaceae [6], whereas the Fabaceae family occupies a predominant position in the dicot group [6]. Following to the pioneering work of Agrawal & Goldstein [7], who reported that concanavalin A (Con A), the lectin from Jack bean (*Canavalia ensiformis*) seeds, was easily retained by simple filtration through a column containing cross-linked dextran gel (Sephadex, Pharmacia) and subsequent desorption by the addition of glucose or mannose to the eluting buffer, both Con A and many other mannose-specific lectins (Table 1) were easily purified using a single affinity chromatography step. Mannose-specific lectins were also successfully isolated from different algae, mushrooms and lower plant species [8]. Moreover, some mannose-specific lectins from red algae specifically recognize the core (α 1-6)-fucosylated *N*-glycans of cancer cells and can be used as biomarkers for the detection of cancer glycoforms [9]. In this respect, they resemble LcA from *Lens culinaris*, PsA from *Pisum sativum* and LoL-I from *Lathyrus ochrus*, which show strong binding to core-fucosylated mono- and bi-antennary *N*-glycans [10,11].

Table 1. Overview of plant, algae and fungi lectins with a mannosyl-binding specificity (β -sandwich: β s, β -prism: β p, n.d.: not determined).

Plant, Alga, Mushroom Family	Plant, Alga, Mushroom Species	Lectin	Structural Scaffold	Oligomer	Ref.
Pteridophyta	<i>Phlebodium aureum</i>	PAL	β barrel	2	[12]
Gymnosperms	<i>Araucaria brasiliensis</i>	Lectin I	n.d.	10	[13]
		Lectin 2	n.d.	6	
	<i>Ginkgo biloba</i>	Gnk2	α β	1	[14]
	<i>Cycas revoluta</i>	CRLI	β -prism	2	[15,16]
Fabaceae	<i>Bowringia mildbraedii</i>	BMA	β -sandwich	2/4	[17]
	<i>Cajanus cajan</i>	CcL	β s	2	[18]
	<i>Camptosema pedicellatum</i>	CPL	β s	4	[19]
	<i>Canavalia boliviana</i>	ConBo	β s	4	[20]
	<i>Canavalia bonariensis</i>	CaBo	β s	4	[21]
	<i>Canavalia brasiliensis</i>	ConBr	β s	4	[22]
	<i>Canavalia ensiformis</i>	ConA	β s	4	[23]
	<i>Canavalia gladiata</i>	CGL	β s	4	[24]
	<i>Canavalia grandiflora</i>	ConGF	β s	4	[25]
	<i>Canavalia maritima</i>	ConM	β s	4	[26]
	<i>Canavalia virosa</i>	ConV	β s	4	[27]
	<i>Centrolobium microchaete</i>	CML	β s	4	[28]
	<i>Centrolobium tomentosum</i>	CTL	β s	4	[29]
	<i>Cladrastis lutea</i>	CLAI,II	β s	4	[30]
	<i>Cratylia floribunda</i>	CFL	β s	2/4	[31]
	<i>Cratylia mollis</i>	CRAMOLL	β s	2/4	[32]
	<i>Cymbosema roseum</i>	CRLI	β s	4	[33]
	<i>Dioclea grandiflora</i>	DGL	β s	4	[34,35]
	<i>Dioclea guianensis</i>	Dguia	β s	4	[36]
	<i>Dioclea lasiocarpa</i>	DLL	β s	4	[37]
	<i>Dioclea lasiophylla</i>	DlyL	β s	4	[38]
	<i>Dioclea reflexa</i>	DrfL	β s	4	[39]
	<i>Dioclea rostrata</i>	DRL	β s	4	[40]
	<i>Dioclea sclerocarpa</i>	DSL	β s	4	[41]
	<i>Dioclea violacea</i>	DVL	β s	4	[42]
	<i>Dioclea virgata</i>	DvirL	β s	4	[43]
	<i>Dioclea wilsonii</i>	DwL	β s	4	[44]
	<i>Lathyrus aphaca</i>	LaphL	β s	2	[45]
	<i>Lathyrus articulatus</i>	LarL	β s	2	[45]

Table 1. Cont.

Plant, Alga, Mushroom Family	Plant, Alga, Mushroom Species	Lectin	Structural Scaffold	Oligomer	Ref.
	<i>Lathyrus cicera</i>	LcL	β s	2	[45]
	<i>Lathyrus hirsutus</i>	LhL	β s	2	[46]
	<i>Lathyrus nissolia</i>	LnL	β s	1	[47]
	<i>Lathyrus ochrus</i>	LoL	β s	2	[48]
	<i>Lathyrus odoratus</i>	LodL	β s	2	[49]
	<i>Lathyrus sativus</i>	LsL	β s	2	[50]
	<i>Lathyrus sphaericus</i>	LsphL	β s	1	[51]
	<i>Lathyrus sylvestris</i>	LsiL	β s	2	[52]
	<i>Lathyrus tingitanus</i>	LtL	β s	2	[46]
	<i>Lens culinaris</i>	LcA	β s	2	[53]
	<i>Millettia dielsiana</i>	MDL	β s	2	[54]
	<i>Onobrychis viciifolia</i>		β s	n.d.	[55]
	<i>Pisum arvense</i>	PAL	β s	2	[56]
	<i>Pisum sativum</i>	PsA	β s	2	[57]
	<i>Pterocarpus angolensis</i>	PAL	β s	2	[58]
	<i>Sophora flavescens</i>	SFL	β s	2	[59]
	<i>Trigonella foenumgraecum</i>		β s	n.d.	[60]
	<i>Vicia cracca</i>		β s	2	[61]
	<i>Vicia ervilia</i>		β s	4	[62]
	<i>Vicia faba</i>	VfA	β s	2	[63]
	<i>Vicia sativa</i>		β s	2	[64]
Mimosaceae	<i>Parkia biglobosa</i>	PBL	β s	2	[65]
	<i>Parkia platycephala</i>	PPL	β s	2	[66]
Dalbergieae	<i>Platypodium elegans</i>	nPELa	β s	2	[67]
	<i>Platymiscium floribundum</i>	PFL	β s	2	[68]
Fagaceae	<i>Castanea crenata</i>	CCA	β s	6/8	[69]
Moraceae	<i>Artocarpus heterophyllus</i>	ArtinM	β -prism	4	[70,71]
	<i>Artocarpus incisa</i>	Frutapin	β p	4	[72]
	<i>Artocarpus integer</i>	CMB	β p	4	[73,74]
	<i>Artocarpus integrifolia</i>	artocarpin	β p	4	[75,76]
		jacalin	β p	4	[77,78]
	<i>Artocarpus lakoocha</i>	artocarpin	β p	4	[79]
	<i>Morus nigra</i>	Moniga-M	β p	4	[80]

Table 1. Cont.

Plant, Alga, Mushroom Family	Plant, Alga, Mushroom Species	Lectin	Structural Scaffold	Oligomer	Ref.
Asteraceae	<i>Helianthus tuberosus</i>	Heltuba	β p	8	[81]
Brassicaceae	<i>Arabidopsis thaliana</i>	PP2-A1	β p	n.d.	[82]
Ranunculaceae	<i>Clematis montana</i>	CML	β p	2	[83]
Aloaeae	<i>Aloe arborescens</i>	ALOE	β p	4	[84]
Araceae	<i>Arisaema lobatum</i>	ALA	n.d.	2+2	[85]
	<i>Arisaema heterophyllum</i>	AHA	β p	n.d.	[86]
	<i>Arum maculatum</i>	AMA	β p	2+2	[87]
	<i>Colocasia esculenta</i>	CEA, tarin	β p	2+2	[88]
	<i>Dieffenbachia sequina</i>		β p	2+2	[87]
	<i>Lysichiton camtschatcensis</i>		β p	2+2	[89]
	<i>Pinellia ternata</i>	PTA	β p	2+2	[90]
	<i>Remusatia vivipara</i>	RVL	β p	2+2	[91]
	<i>Typhonium divaricatum</i>	TDL	β p	2+2	[92]
	<i>Xanthosoma sagittifolium</i>	XSL	β p	2+2	[93]
	<i>Zantedeschia aethiopica</i>	ZAA	β p	n.d.	[94]
Asparagaceae	<i>Ophiopogon japonicus</i>	OJL	β p	n.d.	[95]
	<i>Polygonatum cyrtonema</i>	PCL	β p	4	[96]
	<i>Polygonatum multiflorum</i>	PMA	β p	4	[97]
Convolvulaceae	<i>Polygonatum odoratum</i>	POL	β p	4	[98]
	<i>Calystegia sepium</i>	Calsepa	β p	2	[99]
	<i>Ipomoea batatas</i>	ipomoelin	β p	4	[100]
Alliaceae	<i>Allium altaicum</i>	AALTA	β p	2	[101]
	<i>Allium ascalonicum</i>	AAA	β p	2	[102]
	<i>Allium cepa</i>	ACA	β p	2	[103]
	<i>Allium porrum</i>	APA	β p	2	[103]
	<i>Allium sativum</i>	ASA-I/II	β p	2	[104]
	<i>Allium tuberosum</i>	ATA	β p	2	[105]
	<i>Allium ursinum</i>	AUA-I/II	β p	2	[106]

Table 1. Cont.

Plant, Alga, Mushroom Family	Plant, Alga, Mushroom Species	Lectin	Structural Scaffold	Oligomer	Ref.
Amaryllidaceae	<i>Amaryllis vittata</i>	AVA	β p	n.d.	[107]
	<i>Clivia miniata</i>	CMA	β s	2	[108]
	<i>Crinum asiaticum</i>	CAA	β p	n.d.	[109]
	<i>Galanthus nivalis</i>	GNA	β p	4	[110]
	<i>Hippeastrum hybrid</i>	HHA	β p	2	[111]
	<i>Leucojum vernum</i>	LVL	β p	n.d.	[112]
	<i>Zephyranthes candida</i>	ZCA	β p	4	[113]
	<i>Zephyranthes grandiflora</i>	ZGA	β p	4	[114]
	<i>Lycoris aurea</i>	LAA	β p	2	[115]
	<i>Lycoris radiata</i>	LRA	β p	2	[116]
Dioscoreaceae	<i>Dioscorea batatas</i>	DB1	β p	1	[117]
	<i>Dioscorea bulbifera</i>	DBL	β p	1	[118]
Iridaceae	<i>Crocus sativus</i>	CSL	β p	n.d.	[119,120]
	<i>Crocus vernus</i>	CVA	β p	4	[121]
Liliaceae	<i>Aspidistra elatior</i>	AEL	n.d.	2	[122]
	<i>Narcissus pseudonarcissus</i>	NPA	β p	2,4	[111]
	<i>Narcissus tazetta</i>	NTL	β p	2	[123]
	<i>Narcissus tortifolius</i>	NTA	β p	n.d.	[124]
	<i>Tulipa hybrid</i>	TxLCI TL-MII	β p β p	4 2	[125]
Smilacaceae	<i>Smilax glabra</i>	SGM2	β p	3	[126]
Hyacintheae	<i>Scilla campanulata</i>	SCAman	β p	2	[127]
Musaceae	<i>Musa acuminata</i>	BanLec	β p	2	[128]
	<i>Musa paradisiaca</i>		β p	2	[129]
Pandanaceae	<i>Pandanus amaryllifolius</i>	pandanin	β p	n.d.	[130]
Orchidaceae	<i>Cymbidium hybridum</i>	CHA	β p	2	[131]
	<i>Dendrobium officinale</i>	DOA2	β p	n.d.	[132]
	<i>Epipactis helleborine</i>	EHMBP	β p	2	[131]
	<i>Gastrodia elata</i>	gastrodianine	β p	2	[133]
	<i>Liparis noversa</i>	LNL	β p	2	[95]
	<i>Listera ovata</i>	LNL	β p	2	[131]

Table 1. Cont.

Plant, Alga, Mushroom Family	Plant, Alga, Mushroom Species	Lectin	Structural Scaffold	Oligomer	Ref.
Poaceae	<i>Oryza sativa</i>	Orysata	β p	2	[134]
Red algae	<i>Bryothamnion seaforthii</i>	BSL	n.d.	1	[135]
	<i>Bryothamnion triquetrum</i>	BTL	n.d.	1,2	[136]
	<i>Euchemia denticulatum</i>	EDA	n.d.	1	[137]
	<i>Euchemia serra</i>	ESA	n.d.	1	[138]
	<i>Griffithsia</i> sp.	griffithsin	n.d.	2	[139,140]
	<i>Hypnea cervicornis</i>	HCA	n.d.	1	[141]
	<i>Hypnea japonica</i>	HJA	n.d.	1	[9]
	<i>Hypnea musciformis</i>	HMA	n.d.	1	[142]
	<i>Kappaphycus alvarezii</i>	KAA-2	n.d.	1	[143]
	<i>Kappaphycus striatum</i>	KSA	n.d.	1	[144]
Green algae	<i>Boodlea coacta</i>	BCA	β -prism	1	[145]
	<i>Halimeda renschii</i>	HRL40-1/2	n.d.	4	[146]
Hydnangiaceae	<i>Laccaria bicolor</i>	tectonin 2	β -propeller	n.d.	[147,148]
Trichocomaceae	<i>Penicillium chrysogenum</i>	PeCL	n.d.	n.d.	[149]
Saccharomycetaceae	<i>Saccharomyces cerevisiae</i>	Flo5A	β -sandwich	2	[150]
	<i>Saccharomyces pasteurianus</i>	Flo1p	β s	4	[151]
Schizosaccharo-mycetaceae	<i>Schizosaccharomyces pombe</i>	glucosidase	β s	2	[152]
Hygrophoraceae	<i>Hygrophorus russula</i>	HRL	n.d.	4	[153]
Marasmiaceae	<i>Marasmius oreades</i>	MOA	β -prism	2	[154]
Pteridaceae	<i>Ceratopteris richardii</i>	cyanovirin	CVN-fold	1	[155]
Sordariaceae	<i>Neurospora crassa</i>	cyanovirin	CVN-fold	1	[155]
Tuberaceae	<i>Tuber borchii</i>	cyanovirin	CVN-fold	1	[155]

3. Structural Organization of the Plant, Algal and Fungal Mannose-Binding Lectins

3.1. Structure of Mannose-Specific Plant Lectins

Mannose-specific lectins from plants essentially belong to three distinct structural scaffolds that assemble in different ways to generate more complex oligomeric structures:

3.1.1. The β -Sandwich Fold

The jelly roll scaffold occurring in legume lectins (Fabaceae) consists of either a single or two polypeptide chains. In two-chain lectins, the light (α) and heavy (β) chains made of six and seven strands of antiparallel β -sheet, respectively, non-covalently associate in a β -sandwich protomer (Figure 1A). Protomers associate by non covalent bonds to give the homodimeric lectins of the Viciae tribe, e.g., pea lectin (*Pisum sativum* agglutinin PsA) [57], lentil lectin (*Lens culinaris* agglutinin LcA) [156], yellow vetch lectin (*Lathyrus ochrus* lectin Lol) [48] (Figure 1B), and the faba bean lectin (*Vicia faba* agglutinin VfA or favin) [63] (Figure 1B). In contrast, the Man-specific lectin from *Lathyrus sphaericus* consists of an uncleaved single chain protomer [51]. The single-chain protomers associate into homotetramers. Examples are the mannose-binding lectins characterized in the tribes Baphieae (*Bowringia mildbraedii* agglutinin BMA) [17], Dalbergieae (*Centrolobium tomentosum* lectin CTL [29], *Pterocarpus angolensis* lectin PAL [58]), Diocleae (Con A [23,157] (Figure 1C), *Cymbosema roseum* CRL [33], *Dioclea grandiflora* lectin Con GF [25], and other *Dioclea* sp. lectins). Dimeric lectins such as PsA, possess two identical mannose-binding sites whereas tetrameric lectins like Con A, exhibit four mannose-binding sites. Gal/GalNAc-specific lectins from other legume tribes such as the soybean agglutinin SBA (*Glycine max*) from the Glycinae tribe (PDB code 1SBF) [158], the peanut agglutinin PNA (*Arachis hypogaea*) from the Aeschynomeneae (PDB code 2PEL) [159], the coral tree lectin EcorL (*Erythrina corallodendron*) from the Erythrinae tribe (PDB code 1AXY) [160], and the kidney bean leucoagglutinin PHA-L (PDB code 1FAT) [161] and erythroagglutinin PHA-E (PDB code 3WCR) [162], (*Phaseolus vulgaris*) belonging to the Phaseolae tribe, all strikingly resemble Con A and other Diocleae lectins but differ in the topological organization for the single-chain protomers that constitute the lectin.

3.1.2. The β -Prism I Fold

The β -prism I scaffold serves as a building block for the mannose-binding lectins in seeds of the Moraceae such as artocarpin, the lectin from the Jackfruit (*Artocarpus integrifolia*) seeds which serves as a prototype for this group [163]. The β -prism I scaffold consists of three bundles of four antiparallel β -strands forming three Greek keys 1, 2 and 3, arranged into a β -prism structure along a longitudinal axis (Figure 1D). Depending on the lectins, a posttranslational proteolytic cleavage between the β -strands β 1 and β 2 of Greek key 1 occurs during seed ripening, to liberate the light α -chain with a terminal Gly1 residue exhibiting a free H₂N- group, and the heavy β -chain comprising the rest of the β -prism structure. This proteolytic cleavage occurs in the Gal/GalNAc-specific homotetrameric lectins of Moraceae, such as jacalin (Figure 1E) (PDB code 1JAC) [164], the MPA lectin from Osage orange (*Maclura pomifera*) seeds (PDB code 1JOT) [165], and the Gal/GalNAc-specific lectin Morniga-G from the bark of blackberry (*Morus nigra*) [80]. However, the Man-specific lectins from the Moraceae family, e.g., artocarpin from Jackfruit [163] and Morniga-M from blackberry [166], consist of an uncleaved single-chain β -prism polypeptide chain. Similarly, Heltuba, the lectin from the Jerusalem artichoke (*Helianthus tuberosus*), also consists of a single-chain β -prism polypeptide chain made of 8 β -prisms non-covalently associated around a central axis to form a flattened star-shaped architecture comprising 8 identical carbohydrate-binding sites (Figure 1F) [81].

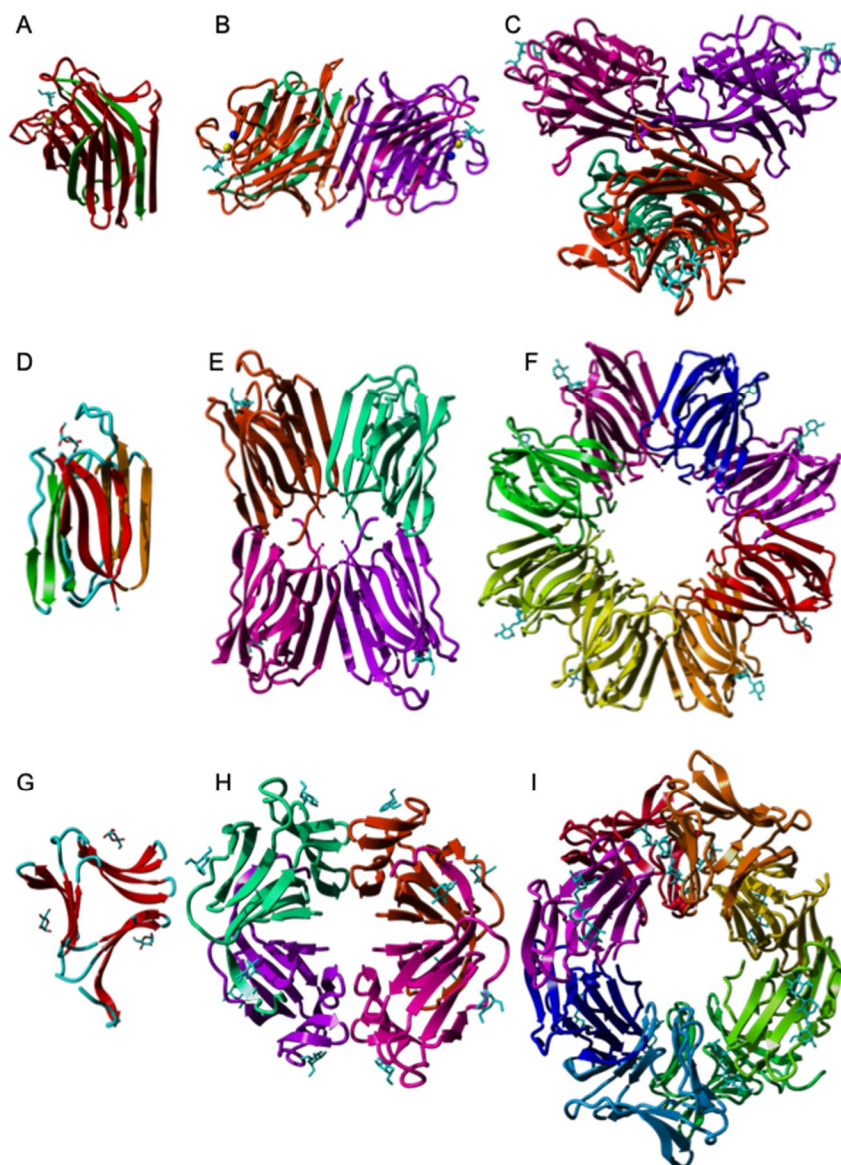


Figure 1. Structural diversity of the mannose-binding lectins. (A). Two-chain lectin protomer of *Lathyrus ochrus* (PDB code 1LOE [48]). Light chain and heavy chains are colored green and red, respectively. (B). Homodimeric organization of the *L. ochrus* isolectin-I (1LOE). The light and heavy chains of the dimer are colored differently. (C). Homotetrameric organization of Con A (PDB code 3CNA). The four single-chain protomers are shown in different colors. (D). The β -prism organization of the artocarpin protomer from *Artocarpus integrifolia* (PDB code 1J4S). The three bundles of β -strands forming the β -prism are colored green, red and orange, respectively. (E). Homotetrameric organization of artocarpin from *A. integrifolia* (1J4U). The β -prism protomers are colored differently. (F). Homooctameric organization of Heltuba from *Helianthus tuberosus* (1C3M) [81]. The β -prism protomers are colored differently. (G). The β -prism II organization of the protomer of GNA from *Galanthus nivalis* (PDB code 1MSA). (H). Organization of the β -prism II protomers in the GNA tetramer (PDB code 1MSA). (I). Hexameric structure of the tarin lectin from *Colocasia esculenta* (PDB code 5T20). The six β -prism-folded protomers are colored differently.

3.1.3. The β -Prism II Fold

The β -prism II scaffold was first identified in GNA, the mannose-specific lectin isolated from the bulbs of snowdrop (*Galanthus nivalis*), a plant species belonging to the monocot family Amaryllidaceae [110]. The scaffold consists of three bundles of four β -strands arranged into a flattened

β -prism structure around a central pseudoaxis (Figure 1G). A carbohydrate-binding site occurs in a groove located at the center of the bundle of β -strands forming each β -sheet. The monocot-specific lectins result from the non-covalent association of four β -prism II scaffolds. Depending on the lectin, four identical β -prism II of 12 kDa form a homotetramer, e.g., in GNA (Figure 1H) [167], whereas other lectins consist of heterotetramers built up from the symmetrical association of two 12 kDa and two 14 kDa β -prism subunits, e.g., the Araceae lectins [6]. Usually, all three carbohydrate-binding sites occurring in each β -prism scaffold are readily functional but in a few lectins, one or two carbohydrate-binding sites are apparently inactive due to point mutation(s) in key residues involved in the H-bonding of mannose. Tarin from *Colocasia esculenta* assembles into homohexameric structures made of 6 β -prism scaffolds [168] (Figure 1I).

The β -trefoil scaffold, another β -prism II scaffold, has been primarily identified in type II Ribosome-Inactivating Proteins (RIP-II), in amaranthin, a T antigen-specific lectin from amaranth (*Amaranthus caudatus*) [169], and it also occurs in the stress inducible lectins composed of EUL (*Euonymus* lectin) domains, such as the lectins from rice (*Oryza sativa*) and *Arabidopsis* [170]. The β -trefoil scaffold consists of six β -hairpins arranged around an approximate three-fold symmetry axis, linked to extended loops that simulate the three lobes of a trefoil leaf (Figure 2). The Man-binding sites are located in the shallow depressions of the β -strands but, usually not all binding sites are functional.

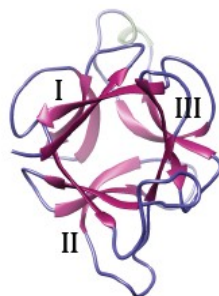


Figure 2. Three-dimensional models for the EUL domain of EUL-domains of rice lectin Oryzata, showing the β -trefoil organization made of three bundles of antiparallel β -sheets (I, II, III).

An unexpected four-bladed β -propeller structure was found to occur in a PA₂ albumin from chickpea (*Cicer arietinum*), which displays a well documented hemagglutinating activity most probably related to a lectin with an unusual hemopexin fold [171].

3.2. Structure of Mannose-Specific Algal Lectins

The mannose-specific lectin griffthsin from the red alga *Griffithsia* sp., consists of a domain-swapped dimer made of two protomer exhibiting the β -prism I fold, that closely resembles to the jacalin-related lectin organization (PDB code 2GTY) [140]. Swapping results from the participation of two β -strands of one molecule in the completion of the three four-stranded sheets forming the β -prism of the other molecule, and vice versa. As a result of this swapping, both molecules in the dimer consist of a complete β -prism organization (Figure 3).

In spite of a high number of cloned and sequenced lectins from different species of red and green algae, their three-dimensional organization(s) were poorly investigated and still remain unknown. Their amino acid sequences readily differ from that of griffithsin and, most probably, they also differ from griffithsin by their three-dimensional structure and monomer organization.

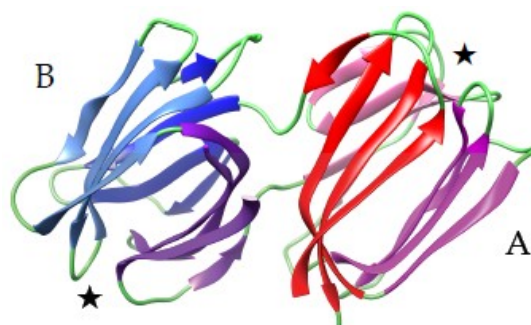


Figure 3. Three-dimensional model of griffithsin (PDB code 2GTY), showing the β -prism organization made of three four-stranded β -sheets in each monomer. The four stranded β -sheets are colored red, pink and magenta in monomer (A), and blue, light blue and purple in monomer (B), respectively. The stars indicate the localization of the carbohydrate-binding sites in each monomer.

3.3. Structure of Mannose-Specific Fungal Lectins

Mannose-specific lectins isolated from fungi result from the non-covalent association of different structural scaffolds resulting in more complex oligomeric structures:

An unusual six-bladed β -propeller organization built up from 4-stranded anti-parallel β -sheets was identified in tectonin 2, a lectin from the mushroom *Laccaria bicolor* AAL (PDB code 5FSC), that specifically recognizes O-methylated glycans [148] (Figure 4).

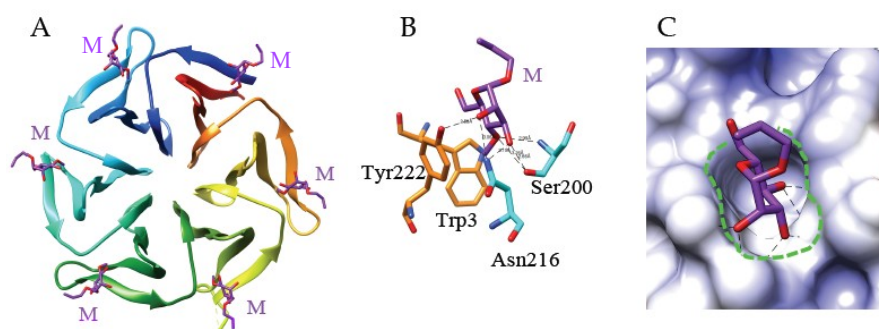


Figure 4. (A). Beta-propeller organization of tectonin 2 from the mushroom *Laccaria bicolor* in complex with allyl- α 4-methyl-mannoside. The lectin consists of 6 antiparallel strands of β -sheet (colored differently) organized in 6 blades around the axis of the β -propeller. The allyl-mannoside residues (M) anchored to the carbohydrate-binding sites of the lectin are colored purple (PDB code 5FSC) (B). Sixth mannose-binding site of tectonin 2 in complex with allyl- α 4-methyl-mannoside. Hydrogen bonds connecting the monosaccharides to the amino acid residues Ser200, Asn216 and Tyr222, forming the monosaccharide-binding site are represented by black dashed lines. Aromatic residues Trp3 and Tyr222, participating in stacking interactions with the sugar ring are colored orange. The molecular surface of the lectins is colored dark grey and their extended oligosaccharide-binding areas are delineated by white dashed lines. (C). The shallow depression corresponding to the monosaccharide-binding site that accommodates the allyl-mannoside residue (colored purple) at the molecular surface (colored according to the coulombic charges) of tectonin 2, is delineated by a green dashed line.

A similar 6-bladed β -propeller structure was observed in the fucose-binding lectins from the bacteria *Ralstonia solanacearum* [172], *Photorhabdus luminescens* [173], *Photorhabdus asymbiotica* [174], as well as in the tachylectin from the Japanese horseshoe crab *Tachypleus tridentatus* [175]. However, the β -propeller scaffold is not specific for the fucose-binding property since a β -propeller structure was shown to occur in other lectins with quite different sugar-binding specificities, e.g., the Neu5Ac- and GlcNAc-specific lectins from the mushrooms *Psathyrella velutina* [176] and *Psathyrella asperospora* [177],

and the lectin Bambl from the bacterium *Burkholderia ambifaria*, which specifically interacts with the lewis x antigen, the blood H type 1 and H type 2 tetrasaccharides and the blood group B epitope [178].

The β -sandwich scaffold is another structural scaffold found in the mannose-binding N-terminal domain of flocculins Flo1 and Flo5 from *Saccharomyces cerevisiae*, and Flo1 from *S. pasteurianus* [150,151]. These surface-adhesins possess a N-terminal domain that readily accommodates Man and α 1,2-mannobiose via a network of hydrogen bonds and stacking interactions with aromatic residues, very similar to those occurring in Man-specific lectins of higher plants (Figure 5). Most of the amino acid residues involved in the binding of mannose also serve as ligands for a Ca^{2+} ion located at the bottom of the mannose-binding site. The mannose-binding activity of Flo1 and Flo5 proteins plays a key role in the self-recognition processes occurring during the growth of the yeasts.

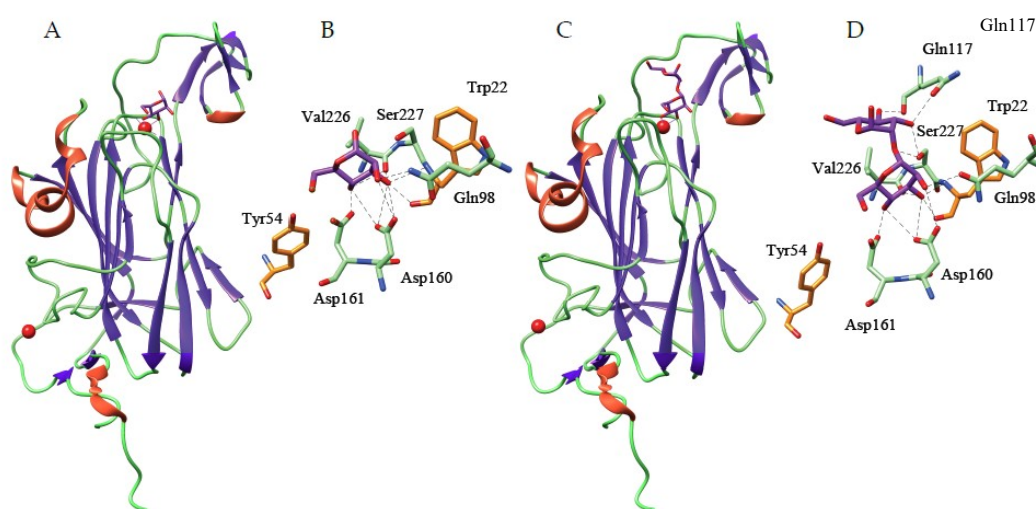


Figure 5. (A,C). Beta-sandwich organization of Flo5 from the yeast *Saccharomyces cerevisiae* in complex with mannose (A) (PDB code 2XJP) and α 1,2-mannobiose (C) (PDB code 2XJS). The mannose-binding N-terminal domain of Flo5 consists of two strands of β -sheet forming a β -sandwich structure. (B). Network of hydrogen bonds anchoring mannose (colored purple) to the amino acid residues forming the carbohydrate-binding site located at the top of the β -sandwich. Two stacking interactions of the pyranose ring of mannose with aromatic residues Tyr54 and Trp228 (colored orange), complete the interaction. (D). Network of hydrogen bonds anchoring α 1,2-mannobiose (colored purple) Flo5, showing additional hydrogen bonds anchoring α 1,2-mannobiose to Gln117 and Ser 227 residues. Residues Asp160, Asp161, Val226 and Trp228, also serve as ligands for a Ca^{2+} ion (colored red in A and C) located at the bottom of the mannose-binding pocket.

The cyanovirin-fold (CVN-fold) also occurs as a structural scaffold identified in the cyanovirin-N family of mannose-binding fungal lectins, including the ascomycetous fungi *Ceratopteris richardii* (CrCVNH), *Neurospora crassa* (NcCVNH) and *Tuber borchii* (TbCVNH) [155]. The NcCVNH lectin consists of a two swapped domains polypeptide chain of 111 amino acids, built up from a domain A of 56 residues (residues 1–42 and residues 100–111), and a domain B of 57 residues (residues 43–99). According to the swapping occurring between both domains, domain A comprises the triple-stranded β -sheet (β 1, β 2, β 3) associated to the β -hairpin (β 9, β 10), whereas domain B consists of the triple-stranded sheet (β 6, β 7, β 8) associated to the β -hairpin (β 4, β 5) (Figure 6A). Other CrCVNH and TbCVNH exhibit a very similar organization.

It is noteworthy that most of the Man-specific lectins identified in bacteria consist of the so-called CVN family fold (Table 2), which comprises cyanovirin, actinohivin, and microvirin occurring in cyanobacteria (ex blue-green algae) as a two swapped domains polypeptide chain, each domain built up from a β -sheet of three anti-parallel β -strands linked to a β -hairpin by a short α -helical turn [179] (Figure 6B).

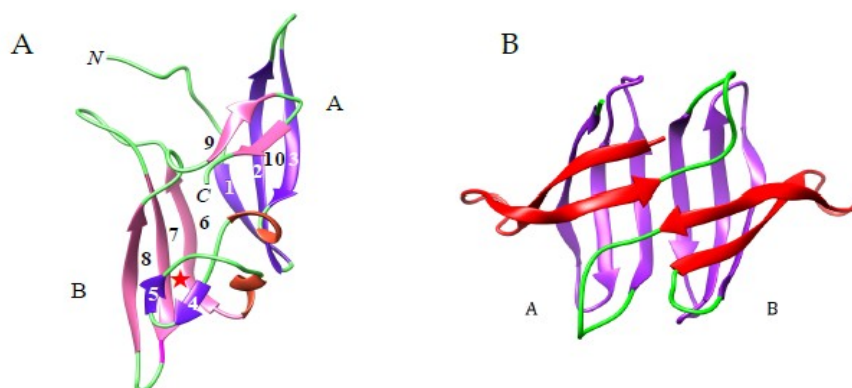


Figure 6. (A). Beta-sandwich organization of NcCVNH from *Neurospora crassa* (PDB code 2JZL), showing the two-swapped domains A (colored purple) and B (colored pink). Strands of β -sheet are numbered 1–10. N and C indicate the N-terminal and C-terminal extremities of the polypeptide chain, respectively. The mannose-binding site has been identified at the top of domain B (red star ★). (B). Ribbon diagram showing the structural organization of the two-domain (A and B) cyanobacterial microvirin from *Microcystis aeruginosa* (PDB code 2YHH) The β -strands, β -hairpins and turns, are colored purple, red and green, respectively.

Table 2. Overview of bacterial lectins of the CVN-fold with a mannose-binding specificity.

Bacteria Family	Species	Lec Lectin	Dstructural Scscaffold	Ref.
Actinomycetaceae	<i>Actinomycete</i> sp.	actinohivin	CVN-fold	[180]
Burkholderiaceae	<i>Burkholderia cenocepacia</i>	BcLA	id.	[181]
Cyanothecaceae	<i>Cyanothece</i> sp.	Cyt-CVNH	id.	[182]
Nectriaceae	<i>Gibberella zeae</i>	Gz-CVNH	id.	[183]
Oscillatoriaceae	<i>Oscillatoria agardhii</i>	OAA	id.	[184]
Microcystaceae	<i>Microcystis aeruginosa</i>	microvirin	id.	[179]
	<i>Microcystis viridis</i>	MVL	id.	[185]
Myxococcaceae	<i>Myxococcus xanthus</i>	cyanovirin-N	id.	[186]
Nostocaceae	<i>Nostoc ellipsosporum</i>		id.	[187]
Pseudomonadaceae	<i>Pseudomonas fluorescens</i>	PFL	id.	[186]
	<i>Pseudomonas putida</i>	LLP	id.	[188]
Scytonemataceae	<i>Scytonema varium</i>		id.	[189]
Thermotogaceae	<i>Thermotoga maritim</i>	Tmcbm27	β -sandwich	[190]

The mannose-binding properties of these lectins exhibiting the CVN-fold account for their anti-HIV-1 activity.

4. The Mannosyl-Binding Specificities of Mannose-Binding Lectins

The high-resolution X-ray structures for a series of complexes between the isolectins LoLI and LoLII from the Cyprus vetch (*Lathyrus ochrus*) and various N-oligosaccharides of increasing complexity including tri-, octa- and dodecasaccharides, accomplished a breakthrough by providing a new framework for understanding how plant lectins specifically accommodate sugar units of complex N-glycans [191–193]. Additional crystal structures of other Man-specific lectins in complex with N-oligosaccharides allowed to decipher the complexity of the carbohydrate-binding of complex glycans to plant and fungal lectins at the molecular level (Table 3).

Table 3. PDB codes of lectins from plants and fungi, complexed with simple sugars (m), oligomannosides (o), and complex (c) mannose-containing glycans.

Plant Species:	Lectin:	PDB Code:	Ref.
<i>Bowringia mildbraedii</i>	BMA	2FMD(o)	[194]
<i>Canavalia ensiformis</i>	ConA	1BXH(o), 1CVN(o), 1I3H(o), 1ONA(o), 1QDC(o), 1QDO(o), 1TEI(o), 1VAM(m), 5CNA(m), 5WEY(o)	[195–203]
<i>Canavalia gladiata</i>	CGL	2D7F(m), 2EF6(o), 2OVU(o)	[204,205]
<i>Canavalia maritima</i>	ConM	2OW4(o), 2P37(o)	[205]
<i>Canavalia virosa</i>	ConV	5F5Q(m)	[27]
<i>Centrobium tomentosum</i>	CTL	5EYX(o), 5EYY(o)	[29]
<i>Cymbosema roseum</i>	CRLI	4MYE(m)	
<i>Dioclea grandiflora</i>	DGL	1DGL(o)	[35]
<i>Dioclea lasiocarpa</i>	DLL	5UUY(m)	[37]
<i>Dioclea lasiophylla</i>	DlyL	6CJ9(m)	[38]
<i>Dioclea reflexa</i>	DrfL	5TG3(m)	[39]
<i>Dioclea rostrata</i>	DRL	2ZBJ	[40]
<i>Dioclea sclerocarpa</i>	DSL	4NOT(m)	[41]
<i>Dioclea virgata</i>	DvirL	3RS6(m)	[43]
<i>Lathyrus ochrus</i>	LoLI	1LOA(m), 1LOB(m), 1LOF(o), 1LOG(o)	[191,192,206]
	LoLII	1LGB(c), 1LGC(c)	[193]
<i>Pisum arvense</i>	PAL	5T7P(m)	[207]
<i>Pisum sativum</i>	PsA	1BQP(m), 1RIN(o)	[208,209]
<i>Pterocarpus angolensis</i>	PAL	1Q8O(o), 1Q8P(o), 1Q8Q(o), 1Q8S(o), 1Q8V(o), 1UKG(m), 2AR6(o), 2ARB(o), 2ARE(m), 2ARX(o), 2AUY(o), 2GN3(m), 2GN7(o), 2GMM(o), 2GMP(o), 2PHF(o), 2PHR(o), 2PHT(o), 2PHU(o), 2PHW(o), 2PHX(o)	[210–213]
<i>Parkia biglobosa</i>	PBL	4MQ0(m)	
<i>Artocarpus incisa</i>	frutapin	5M6O(m)	[72]
<i>Artocarpus integrifolia</i>	artocarpin	1J4U(m), 1VBO(o), 1VBP(o)	[163,214]
	jacalin	1KUJ(m), 1WS4(m), 1WS5(m)	[77,78]
<i>Morus nigra</i>	Morniga-M	1XXR(m)	[168]
<i>Helianthus tuberosus</i>	Heltuba	1C3M(o), 1C3N(o)	[81]
<i>Colocasia esculenta</i>	tarin	5D9Z(m), 5T20(o)	[165]
<i>Ipomoea batatas</i>	ipomoelin	3R51(m),	[99]
<i>Calystegia sepium</i>	Calsepa	1OUW(m), 5AV7(o), 5XF1(o)	[98]
<i>Allium sativum</i>	ASA	1BWU(m), 1KJ1(m)	[215,216]
<i>Galanthus nivalis</i>	GNA	1JPC(o), 1MSA(m), 1NIV(o)	[217,218]
<i>Narcissus pseudonarcissus</i>	NPA	1NPL(o), 3DZW(o)	[219]
<i>Musa acuminata</i>		3MIT(m), 3MIU(o), 4PIK(o), 4PIT(o)	[128,220]
<i>Musa paradisiaca</i>		1X1V(m)	[127]
<i>Oryza sativa</i>	Orysata	5XFH(c), 5XFI(c)	[221]
Fungal/Algal Species:	Lectin:	PDB Code:	Ref.
<i>Griffithsia</i> sp.	griffthsin	2GUC(m), 2GUD(m), 2HYQ(o), 3LL2(c)	[140,222,223]
<i>Saccharomyces cerevisiae</i>	adhesin Flo1	4LHK(o), 4LHN(m)	[151]
<i>Saccharomyces pastorianus</i>	flocculin Flo5	2XJP(m), 2XJR(o), 2XJS(o), 2XJT(o), 2XJU(o)	[150]
<i>Schizosaccharomyces pombe</i>	glucosidase II	4XQM(m)	[152]
<i>Marasmius oreades</i>	cyanovirin-N	4TKC(m)	
<i>Actinomyces</i> sp.	actinohivin	4P6A(o)	[224]

Depending on the molecular complexity of the recognized carbohydrates, two types of closely interlinked carbohydrate-binding specificities can occur at the carbohydrate-binding site of plant and fungal lectins:

1. A monosaccharide-binding specificity, allowing the lectin to specifically recognize a simple sugar, e.g., mannose Man, and its derivatives, e.g., α -methylmannoside. This type of monosaccharide recognition by lectins corresponds to the so-called “broad sugar-binding specificity” of lectins, which relies on the occurrence of a monosaccharide-binding pocket within the carbohydrate-binding site.

2. An oligosaccharide-binding specificity, which consists of the simultaneous accommodation of several sugar units of a complex *N*-glycan, e.g., high-mannose glycans, also known as the “fine sugar-binding specificity” of the lectins. This type of oligosaccharide recognition involves most of the surface of the carbohydrate-binding site, including the monosaccharide-binding site.

The monosaccharide-binding site is part of a more extended oligosaccharide-binding site. In physiological conditions, however, plant and fungal lectins are almost always involved in the recognition of complex glycans, rather than simple sugars, simply because the amount of free monosaccharides in cells and tissues is very low. The binding of plant and fungal lectins to mannose was first observed in hapten inhibition experiments, by introducing free mannose or mannose derivatives to prevent or reverse the *in vitro* interaction between lectins and red blood cells or complex glycans. Obviously, the affinity of mannose-specific lectins for simple sugars, e.g., for Man or Man derivatives, is far weaker compared to the affinity measured for more complex glycans, e.g., for complex *N*-glycans or high-mannose type glycans (Table 4) [10,225].

Table 4. Minimum concentrations (mM) of various oligosaccharidic structures and glycopeptides necessary to completely inhibit red blood cells agglutination by Con A, LcA from lentil and favin (from ref. [225]).

Oligosaccharidic Structures	Con A	LcA	Favin
Man	1.25	2.5	0.625
α Man(1,3) β M α v(1,4)GlcNAc	0.104	0.83	0.104
α M α v(1,2) α M α v(1,3) β Man(1,4)GlcNAc	0.026	0.21	0.105
α M α v(1,2) α Man(1,2) α M α v(1,3) β M α v(1,4)GlcNAc	0.026	0.206	0.105
β GlcNAc(1,2) α Man(1,3) β Man(1,4)GlcNAc β GlcNAc(1,2) α Man(1,6)	0.0003	0.157	0.31
α NeuAc(2,6) β Gal(1,4) β GlcNAc(1,2) α Man(1,3) β Man(1,4)GlcNAc β (1,4)GlcNAc β (1)Asn α NeuAc(2,6) β Gal(1,4) β GlcNAc(1,2) α Man(1,6)	0.026	0.003	0.013
α NeuAc(2,6) β Gal(1,4) β GlcNAc(1,2) α Man α 1,3 β Man(1,4)GlcNAc β (1,4)GlcNAc β (1)Asn α NeuAc(2,6) β Gal(1,4) β GlcNAc(1,2) α Man(1,6) α Fuc	0.026	0.0004	0.0008

4.1. The Mannose-Binding Specificity

The recognition and binding of simple sugars by lectins occurs through non covalent interactions occurring between some hydroxyls of the sugar ring and a few, essentially polar, amino acid residues forming a shallow depression at the lectin surface, the so-called monosaccharide-binding site. Usually, most of these interactions consist of hydrogen bonds (H-bond) often associated to a hydrophobic stacking of the pyranose ring of the sugar to the phenolic ring of an aromatic residue such as Phe (F), Tyr (Y), or Trp (W), located in the close vicinity of the monosaccharide-binding cavity. Acidic residues like Asp (D) and Glu (E), often participate in the interaction with simple sugars, thus attributing a more or less pronounced electronegative character to the monosaccharide-binding site. Both acidic

residues Asp and Glu, play a key role in the binding of simple sugars due to their capacity to create multiple H-bonds with the hydroxyls emerging from the sugar ring.

Detailed structural information is available for the binding of α -D-mannose (Man) to the monosaccharide-binding site of Man-specific legume lectins including Con A [202], LoLI isolectin from *Lathyrus ochrus* [206], favin from the broad bean *Vicia faba* [63], pea lectin PsA [209] and PAL from *Pterocarpus angolensis* [210]. A very similar binding scheme occurs for both the two-chain (LoLI, favin, PsA) and single-chain (Con A) lectins: a few amino acid residues located on three distinct loops exposed at the top of the dome-shaped lectin protomer, form a shallow depression which accommodates the Man ligand via a network of hydrogen bonds connected to the O3, O4, O5 and O6 atoms of the sugar. An acidic residue (Asp208 of Con A, Asp81 of LoLI and PsA), which also participates in the binding of a Ca^{2+} ion located in the close vicinity of the binding site, plays a key role in ligand binding. An additional stacking interaction between the pyranose ring of Man and one (Phe123 of LoLI) or two (Tyr12 and Tyr100 of Con A) aromatic residues located in the vicinity of the monosaccharide-binding site, reinforces anchorage of the sugar to the binding site (Figure 7A–D). A few water molecules also participate in the binding of Man to the monosaccharide-binding site of the lectins. Very similar binding observations were reported for the binding of Man or α -methyl-D-mannoside (MeMan) to other *Canavalia* [20,21,25,27] and *Dioclea* lectins [34–44], *Parkia biglobosa* (PDB code 4MQ0) and *Cymosema roseum* (PDB code 4MYE) Man-specific lectins from the Brazilian flora.

The accommodation of Man by artocarpin, a Man-specific jacalin-related lectin, shows a very similar network of 9 H-bonds between four amino acid residues (Gly15, Asp138, Leu139, Asp141) located at the top of the β -prism protomer, and the O1, O3, O4, O5, and O6 atoms of the sugar (Figure 7E,F). No stacking interactions occur between the aromatic residues of the monosaccharide-binding site and the sugar. In addition, jacalin, another member of the jacalin-related lectins, offers an interesting example of sugar-binding promiscuity because this Gal-specific lectins also interacts, albeit with lower affinity, with other simple sugars like Man, Glc and GalNAc via a very similar H-bond network [77]. Another Man-specific lectin with a β -prism architecture, Heltuba of *Helianthus tuberosus*, also accommodates Man through a very similar network of H-bonds between four amino acid residues (Gly18, Asp136, Val137, Asp139), which form the monosaccharide-binding site also located at the top of the β -prism protomer, and the O3, O4, O5 and O6 atoms of the sugar (Figure 7G,H).

The recognition of Man by GNA, the Man-specific snowdrop (*Galanthus nivalis*) lectin, and other monocot Man-binding lectins harboring a similar β -prism architecture (a β -prism in which the strands composing the β -sheet are arranged perpendicularly to the axis of the prism), exhibits a different mode of binding due to the fact that three out of eight H-bonds connecting the Gln89, Asp91, Asn93 and Tyr97 residues from the 3rd mannose-binding site to the O2, O3, O4, and O6 atoms of Man, are connected to the axial O2 atom (Figure 5I,J). Residue Tyr97 also provides a stacking interaction with one face of the Man pyranose ring. An additional hydrophobic interaction with Val95, another residue of the consensus sequence stretch QXDXNXVXY of the monosaccharide-binding site, reinforces the anchorage of Man to the binding site.

Molecular modeling and in silico docking suggest that other nucleocytoplasmic EUL domain-containing lectins from rice (*Oryza sativa*) and *Arabidopsis* with a β -prism architecture, also interact with mannose via a very similar network of H-bonds and stacking interactions with aromatic amino acid residues located in the close vicinity of the monosaccharide-binding site (Figure 8) [170]. However, some promiscuity was shown to occur at the monosaccharide-binding site of the EUL-lectins, which in addition to high mannose *N*-glycans also recognize blood group B related structures and galactosylated epitopes [226].

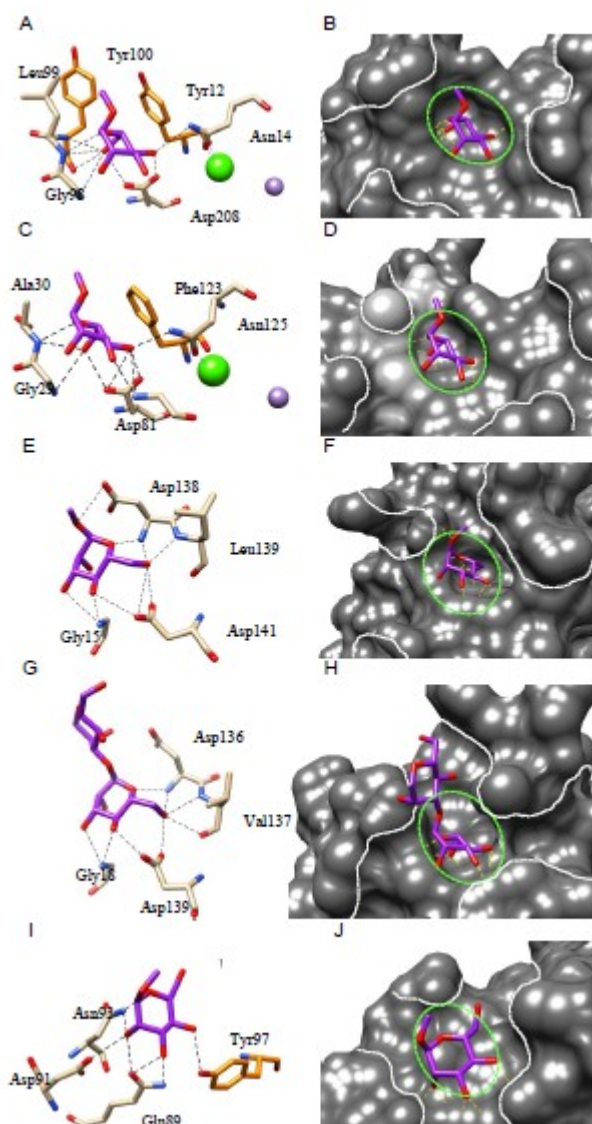


Figure 7. (A,B). ConA from *Canavalia ensiformis* in complex with α -methylmannoside (PDB code 5CNA). (C,D). Isolectin LoLI from *Lathyrus ochrus* in complex with Man (PDB code 1LOB). (E,F). Artocarpin from *Artocarpus integrifolia* in complex with α -methylmannoside (PDB code 1J4U). (G,H). Heltuba from *Helianthus tuberosus* in complex with Man α 1,3Man (PDB code 1C3M). (I,J). Third Man-binding site of GNA from *Galanthus nivalis* in complex with α -methylmannoside (PDB code 1MSA). Hydrogen bonds connecting the monosaccharides to the amino acid residues forming the monosaccharide-binding site are represented by black dashed lines. Aromatic residues participating in stacking interactions with the sugar rings are colored orange. The molecular surface of the lectins is colored dark grey and their extended oligosaccharide-binding areas are delineated by white dashed lines. The shallow depression corresponding to the monosaccharide-binding site that accommodates simple sugars is delineated by a green dashed line. The green and violet spheres correspond to the Ca²⁺ and Mn²⁺ ions, that have a stabilizing effect on the carbohydrate-binding site.

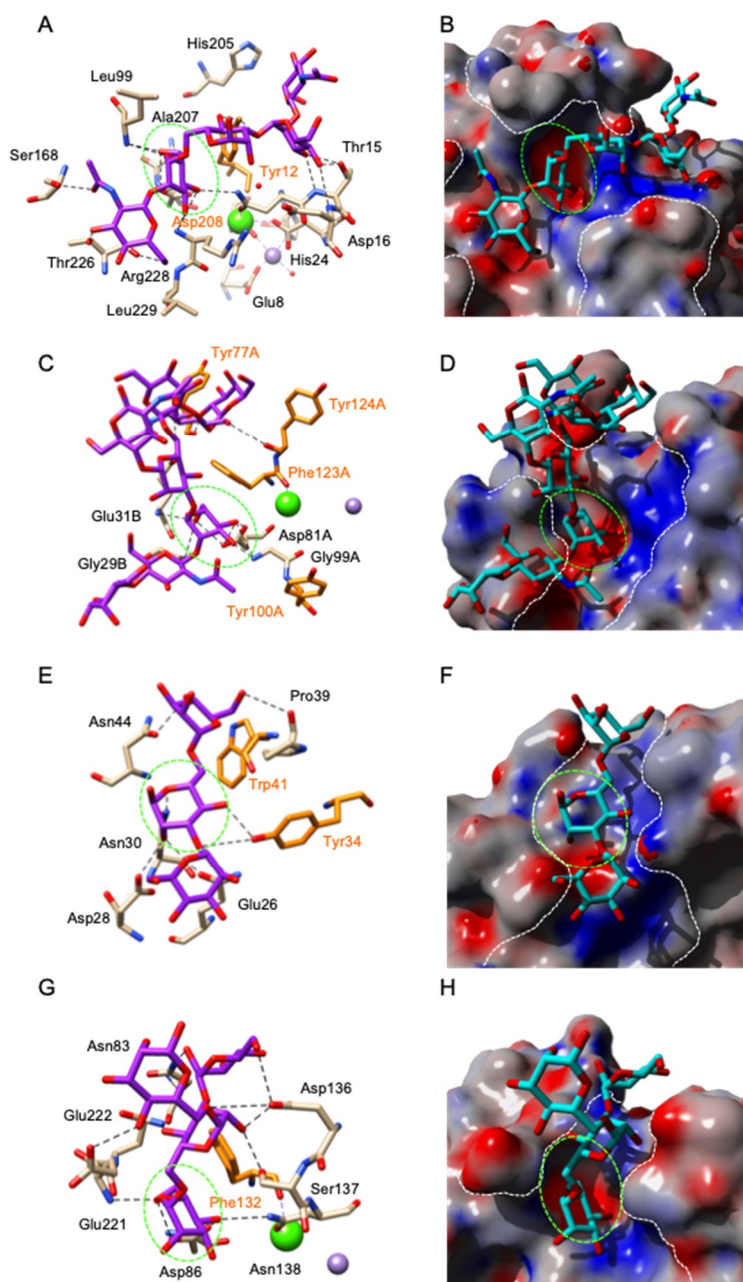


Figure 9. (A,B). ConA from *Canavalia ensiformis* in complex with β -D-GlcNAc-(1,2)- α -D-Man-(1,6)-[β -D-GlcNAc-(1,2)- α -D-Man-(1,6)]- α -D-Man (PDB code 1TEI) [196]. (C,D). Isolectin LoLII from *Lathyrus ochrus* in complex with a biantennary octasaccharide of the *N*-acetyllactosamine type from lactotransferrin (PDB code 1LOF). (E,F). GNA from *Galanthus nivalis* in complex with three mannosyl residues from a mannopentaose (PDB code 1JPC). (G,H). PAL from *Pterocarpus angolensis* in complex with a mannotetraose (PDB code 2PHF). Hydrogen bonds connecting the oligosaccharides to the amino acid residues forming the extended carbohydrate-binding site are represented by black dashed lines. Aromatic residues participating in stacking interactions with the sugar rings are colored orange. The electrostatic potentials were calculated and mapped on the molecular surface of the lectins, using YASARA. The extended oligosaccharide-binding areas are delineated by white dashed lines. The shallow depression corresponding to the monosaccharide-binding site that accommodates simple sugars, is delineated by a green dashed line.

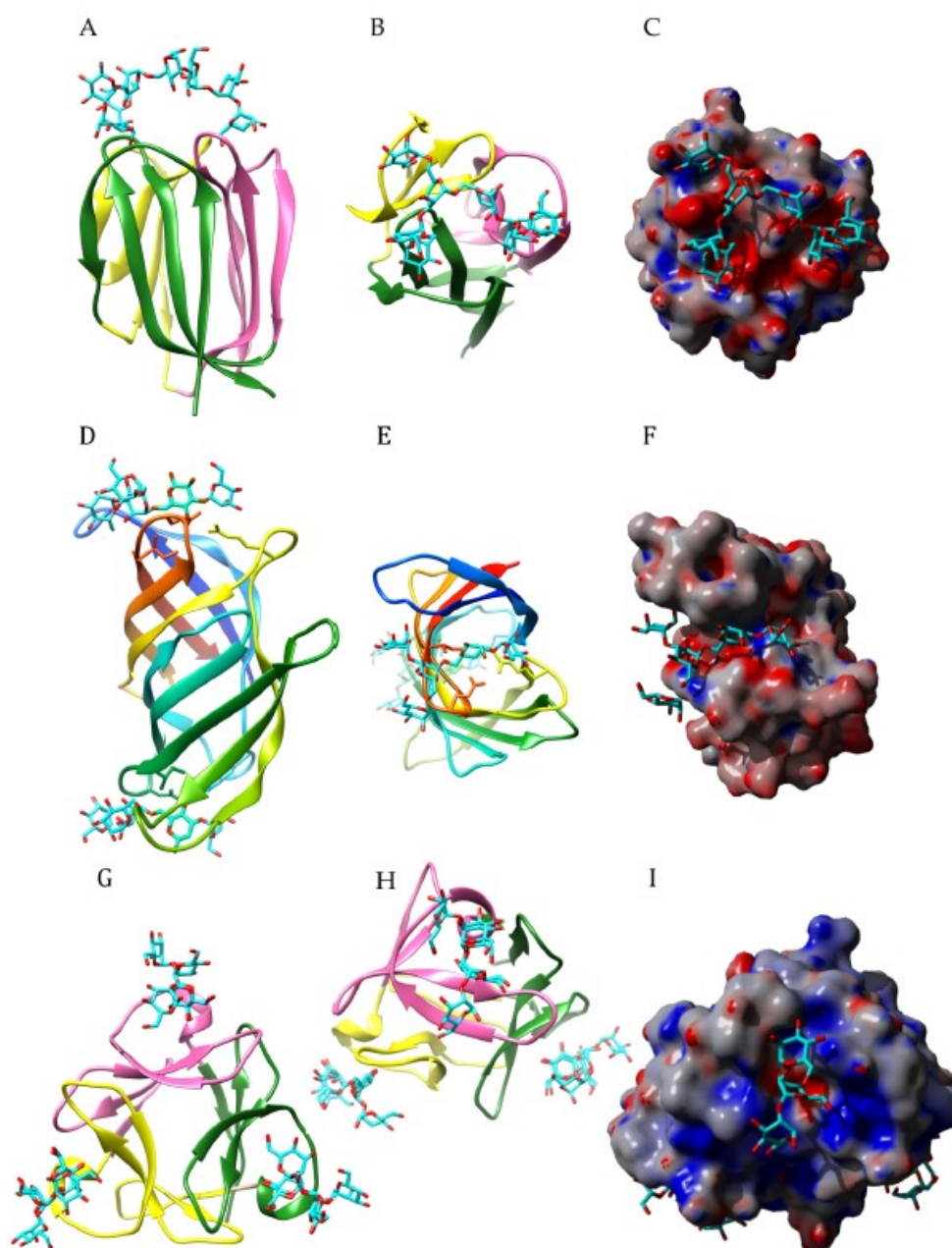


Figure 10. Structural diversity of the mannose-binding lectins. (A–C). Ribbon diagrams (A lateral view, B upper view) and surface electrostatic potentials (C) of griffthsin in complex with a high-mannose branched glycan (colored cyan) (PDB code 3LL2), showing the β -prism organization of the lectin. Note the electronegatively charged character (colored red) of the Man-binding pockets at the upper face of the β -prism. (D–F). Ribbon diagrams (D lateral view, E upper view) and surface electrostatic potentials (F) of actinohivin in complex with a high-mannose branched glycan (colored cyan) (PDB code 3S5X), showing the β -trefoil (β -prism II) organization of the lectin. Note the electronegatively (colored red) and electropositively (colored blue) charged character of the Man-binding pockets at the edges of the β -trefoil. (G–I). Ribbon diagrams (G lateral view, H upper view) and surface electrostatic potentials (I) of actinohivin in complex with α -1,2-mannotriose (colored cyan) (PDB code 4P6A), showing the organization of the lectin. Note the electronegatively charged character (colored red) of the Man-binding pockets.

5. Functions of Mannose-Specific Lectins

The Man-specific lectins present in seeds or storage organs (bulbs, rhizomes) of plants, are abundant proteins with a dual role as storage proteins and defense proteins [230,231]. In contrast, Man-specific lectins occurring in the nucleus or in the cytoplasmic compartment are usually synthesized at low levels. Since lectin concentrations are higher after exposure of the plant to e.g., salt or drought stress, or pathogen infections these stress inducible lectins are involved in plant immunity and can help the plant to cope with environmental stresses [1,231].

5.1. Insecticidal Activity

A large group of GNA-related lectins have been investigated with respect to their insecticidal properties. The interest in the monocot Man-specific lectins was triggered because these lectins showed toxicity towards aphid pests responsible for serious crop damage (Table 6). The expression of GNA and other monocot lectins in various transgenic plants conferred enhanced resistance to sap-sucking aphid predators. In addition, these lectins often caused a higher larval mortality and retardation in larval development. Similarly legume lectins such as Con A were investigated for their deleterious effects on aphid growth and development. At present, the mechanism of entomotoxicity still remain poorly understood and most probably depends on diverse, complementary mechanisms [232].

The detrimental effects of Man-specific lectins on aphids relies on their ability to recognize and bind high-mannose glycan receptors present in the peritrophic membrane and the underlying midgut epithelium. Receptors proteins for the monocot Man-specific lectins (ACA of *Allium cepa*, *Diefenbachia sequina* lectin, CEA of *Colocacia esculenta*, AMA of *Arum maculatum*) have been identified in brush border membrane vesicles of the midgut [233], and two major receptors for AMA of 40 kDa and 35 kDa, respectively, were detected in the brush border membrane vesicles of the aphids *Lipaphis erysimi* and *Aphis craccivora* [234]. A major binding protein for Con A was identified as a membrane-bound aminopeptidase of 130 kDa, in the pea aphid *Acyrtosiphon pisum* [235]. Two other abundant membrane-associated proteins, an alanyl aminopeptidase N and a sucrase, have also been postulated as possible receptors in *Acyrtosiphon pisum*, for both garlic lectins ASAI and ASAI [236]. Interestingly, a putative glycosylated receptor of 37 kDa identified in the mushroom *Rhizoctonia solani* cross-reacted with the homodimeric *Allium sativum* leaf lectin and the interaction, which depends on the oligomeric assembly of the lectin, was specifically inhibited by addition of mannose [237]. Binding partners of CEA, the *Colocasia esculenta* Man-specific lectin, were identified as ATPase and ATP synthase in *Bemisia tabaci*, and ATP synthase, HSP70 and clathrin heavy chain in *Lipaphis erysimi* [238]. The dietary ingestion of Con A resulted in a marked decrease of the α -glucosidase and alkaline phosphatase activity in the bird cherry-oat aphid *Rhopalosiphum padi* [232]. Taken together, these results argue for multiple so-called lectin “receptors” occurring in aphid pests.

Table 6. List of Man-specific lectins investigated for their toxicity towards aphids (aphid predator species are indicated with an asterisk *).

Lectin class	Lectin	Aphid	Ref.
Monocot lectins	GNA (<i>Galanthus nivalis</i>)	<i>Aulacorthum solani</i>	[239]
		<i>Myzus persicae</i>	[240,241]
		<i>Caratovacuna lanigera</i>	[242]
		<i>Myzus persicae</i>	[243]
		<i>Rhopalosiphum maidis</i>	[244]
		<i>Chrysoperla carnea</i> * <i>Adalia punctata</i> *, <i>Coccinella septempunctata</i> *	[245]
		<i>Sitobium avenae</i> , <i>Schizaphis graminum</i> , <i>Rhopalosiphum padi</i>	[246]
	PTA (<i>Pinellia ternata</i>)	<i>Myzus persicae</i>	[247,248]
	PPA (<i>Pinellia pedatisecta</i>)	<i>Sitobium avenae</i>	[249]
	AAA (<i>Allium altaicum</i>)	<i>Aphis gossypii</i>	[100]
ACA (<i>Allium cepa</i>)	<i>Myzus persicae</i>	[250]	

Table 6. Cont.

Lectin class	Lectin	Aphid	Ref.
	ASA (<i>Allium sativum</i>)	<i>Myzus persicae</i>	[251]
		<i>Aphis craccivora</i>	[252]
		<i>Myzus nicotianae</i>	[253]
		<i>Acyrtosiphon pisum</i>	[236]
	AHA (<i>Arisaema heterophyllum</i>)	<i>Myzus persicae</i>	[254]
	MDA (<i>Monstera deliciosa</i>)	<i>Myzus persicae</i>	[255]
	Orysata (<i>Oryza sativa</i>)	<i>Acyrtosiphon pisum</i> , <i>Myzus persicae</i>	[256]
	<i>Dieffenbachia sequina</i>	<i>Aphis craccivora</i> , <i>Lipaphis erysimi</i>	[233]
	CEA (<i>Colocacia esculenta</i>)	<i>Lipaphis erysimi</i> , <i>Aphis craccivora</i>	[233]
	AMA (<i>Arum maculatum</i>)	<i>Aphis craccivora</i> , <i>Lipaphis erysimi</i>	[234]
	ZGA (<i>Zephyranthes grandiflora</i>)	<i>Myzus nicotianae</i>	[257]
Legume lectins	Con A (<i>Canavalia ensiformis</i>)	<i>Acyrtosiphon pisum</i> <i>Rhopalosiphum padi</i>	[235] [232]
β -prism lectins	HTA (<i>Helianthus tuberosus</i>)	<i>Myzus persicae</i>	[258]
Fungal lectins	PeCl (<i>Penicillium chrysogenum</i>)	<i>Myzus persicae</i>	[149]

Beyond the alterations resulting from the binding of Con A to the midgut epithelial cells in the pea aphid *Acyrtosiphon pisum*, e.g., the cellular swelling of epithelial cells associated with hypersecretion [259], other systemic effects of Con A like DNA damage accompanied with an increase in caspase 3 activity in the gut tissues, were observed in the aphid *Rhopalosiphum padi* fed with a Con A-containing diet [232]. A similar entomotoxic effect accompanied by DNA fragmentation and caspase-3-dependent apoptosis, was observed in *Acyrtosiphon pisum* fed with a diet containing the lectin SNA-I from *Sambucus nigra*, a chimerolectin corresponding to a type II RIP with a carbohydrate-binding B chain displaying sialic acid-binding specificity [260]. Finally, in addition to the direct effect of aphicidal lectins on death of gut epithelial cells, an effect on the feeding behavior has been invoked to account for the entomotoxicity of plant lectins towards aphid pests [232].

5.2. Resistance to Abiotic (and Biotic) Stresses

Although most lectins studied at present are constitutively expressed in plant tissues, some lectins are considered as stress inducible proteins. The discovery of Nictaba, a tobacco (*Nicotiana tabacum*) lectin which is synthesized in response to a jasmonic acid (JA) treatment, and insect herbivory, and accumulates in the cytosol and the nucleus of leaf cells [5], shed a new light on plant lectins and allowed the development of very new concepts on the role(s) of plant lectins [4,231,261,262].

Besides Nictaba, which appears as the prototype of a group of closely related lectins [263,264], other groups of stress inducible lectins in the nucleocytoplasmic compartment have been identified, such as the *Euonymus europaeus* EUL-related lectins [170,265] and the group of mannose-binding jacalin-related lectins [221,266]. Among the stress inducible cytoplasmic/nuclear lectins identified so far, Nictaba belonging to the Nictaba-related lectins [267], Orysata belonging to the jacalin-related lectins [268], and OrysaEULD1A belonging to the EUL-related lectins [269], all readily interact with high-mannose glycan structures (Table 7). Accordingly, they participate as signaling molecules in the plant response to stress conditions [270]. In this respect, a member of the EUL-related lectin family, AthEULS3 is involved in abscisic acid (ABA)-induced stomatal closure [271]. Overexpression of the Nictaba-like lectin genes *GmLLL1* and *GmNLL2* from soybean in *Arabidopsis thaliana*, was reported to confer tolerance to *Pseudomonas syringae* infection, aphid (*Aphis glycines*) infestation and salt stress [272]. Similarly, the involvement of Nictaba homologs from *Arabidopsis thaliana* in the plant stress response was recently demonstrated [273].

Table 7. List of the stress inducible, nucleocytoplasmic lectin families identified in plants.

Lectin Families	Carbohydrate-Binding Specificity
Jacalin-related lectin family	High-mannose <i>N</i> -glycans
EUL-related lectin family	Galactosides, high-mannose <i>N</i> -glycans
Nictaba-related lectin family	Chitooligosaccharides, recognition of the (GlcNAc) ₂ -Man ₃ core of high-mannose <i>N</i> -glycans and complex glycans

Recent studies for lectin sequences in several complete plant genomes reported the occurrence of chimeric proteins composed of a lectin domain with known Man-binding specificity, such as e.g., the GNA-like domain or legume lectin domain, linked to an intracellular kinase domain through a transmembrane linker domain. These lectin-receptor-like kinases (LecRLK), play a role in the signaling cascades triggered in response to biotic and abiotic stress [270].

6. Medical Applications for the Mannose-Specific Lectins

So far, medical applications of Man-specific lectins, have been developed in two domains: (1) as inhibitors of the entry of HIV-1 into CD4+ T-lymphocytes and, (2) as anticancer drugs for the chemotherapeutic treatment of cancers.

6.1. Mannose-Specific Lectins as Immunomodulators

Soon after the identification of high-mannose *N*-glycans decorating the gp120 protein of HIV-1 (Figures 11 and 12) [274], many studies focused on the use of mannose-specific lectins from bacteria, mushrooms and plants as tools to decipher the importance of the high-mannose moiety of gp120 for the recognition by the CD4+ T-lymphocytes as well as for preventing the virion infectivity of HIV toward the host cells in vitro [275–280]. Two classes of mannose-specific lectins from the Viciae tribe and the GNA-related lectins, were particularly investigated with respect to their blocking capacity (Table 8).

Mannose-binding lectins of bacterial origin were identified as potent HIV-1-inactivating proteins through their specific binding to the envelope glycoprotein gp120. Studies have been performed for actinohivin [180], cyanovirin-N [281,282], MVL from *Microcystis viridis* [283], OAA from *Oscillatoria agardhii* [284] and the lectin from *Scytonema varium* [285].

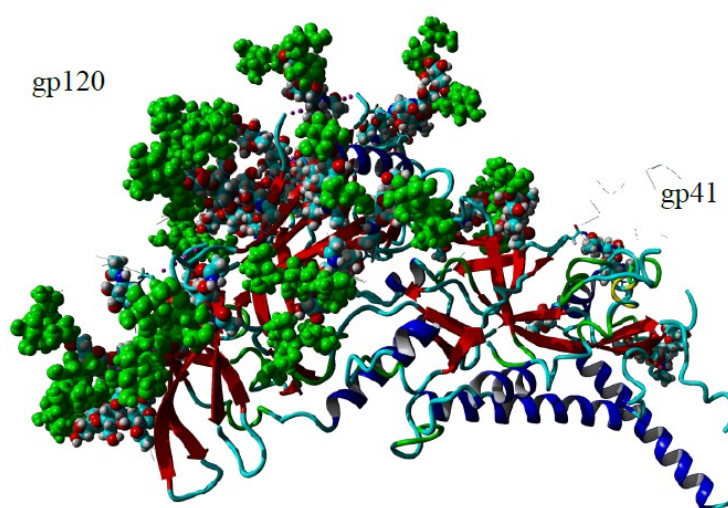


Figure 11. Three-dimensional structure of the highly-mannosylated gp120 molecule associated to the *O*-glycosylated gp41 molecule (PDB code 5FYK). Surface-exposed Man residues of high-mannose *N*-glycoproteins decorating gp120 are colored green. *O*-glycans of gp41 are colored blue.

Table 8. List of the mannose-specific lectins inhibiting HIV infection by binding to the viral gp120 envelope protein.

Lectin Class	Lectin	Ref.
Viciae lectins	Con A (<i>Canavalia ensiformis</i>)	[276,286–294]
	LcA (<i>Lens culinaris</i>)	[280]
	LoLI (<i>Lathyrus ochrus</i>)	[280]
	PsA (<i>Pisum sativum</i>)	[280,295]
Monocot lectins	CHA (<i>Cymbidium hybrid</i>)	[280,296]
	EHA (<i>Epipactis helleborine</i>)	[280,296]
	GNA (<i>Galanthus nivalis</i>)	[280,297–302]
	HHA (<i>Hippeastrum hybrid</i>)	[280,297,302]
	LOA (<i>Listera ovata</i>)	[280,297]
	NPA (<i>Narcissus pseudonarcissus</i>)	[280,297,303]
	NTA (<i>Narcissus tazetta</i>)	[304]
	<i>Narcissus confusus</i> , <i>N. leonensis</i> and <i>N. tortifolius</i>	[124]
	PCL (<i>Polygonatum cytonema</i>)	[96,305]
Convolvulaceae	Calsepa (<i>Calystegia sepium</i>)	[280]
Urticaceae	UDA (<i>Urtica dioica</i>)	[296]
Araceae	RVL (<i>Remusatia vivipara</i>)	[91]
Musaceae	BanLec (<i>Musa acuminata</i>)	[306]
Poaceae	GNAmaze (<i>Zea mays</i>)	[307]
Asteraceae	Heltuba (<i>Helianthus tuberosus</i>)	[280]
Red algae	Griffithsin (<i>Griffithsia</i> sp.)	[139,308]
Green algae	KAA (<i>Kappaphycus alvarezii</i>)	[309]
	BCA (<i>Boodlea coacta</i>)	[143]

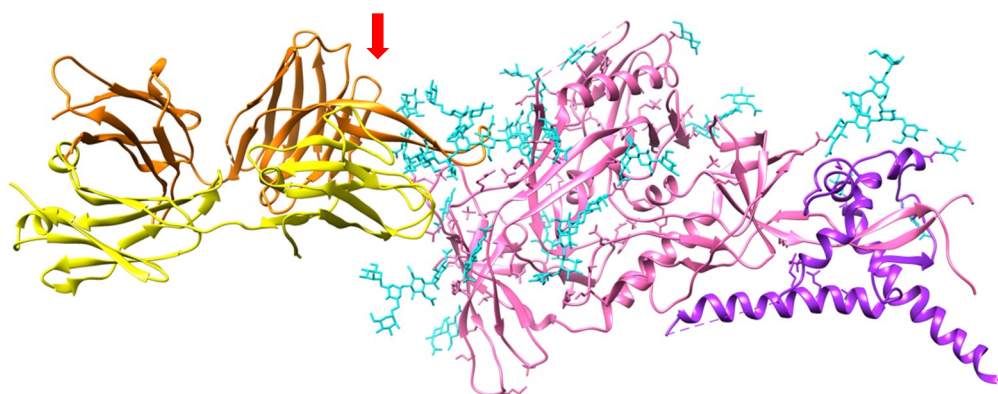


Figure 12. Three-dimensional structure of the gp120-gp41 tandem complexed to a CD4 molecule (PDB code 47VP). Gp120, gp41 and CD4 are colored pink, purple, and orange/yellow, respectively. The high-mannose *N*-glycan chains decorating gp120 are represented in cyan colored sticks. The carbohydrate binding agents (red arrow) specifically recognize some of the high-mannose *N*-glycans exposed at the surface of gp120, thus preventing the recognition of gp120 by the CD4 molecule of the CD4+ T lymphocytes. In fact, the association of three gp120-gp41 tandems forms the HIV-1-envelope spike, which facilitates the HIV-1 entry. The Env spike consists of a transmembrane trimer of gp41 associated to an extracellular trimer of gp120 offering exposed high-mannose glycans to the CD4 recognition process.

Investigating the surface carbohydrates of gp120 showed that resistance of cyanovirin N- and Con A-resistant HIV-1 strains highly depends on mutations that have eliminated N-linked glycans on gp120 [310]. In general, the number of N-glycan deletions in gp120 correlated with the level of phenotypic resistance to cyanovirin of the mutated VIH-1A strains [311]. A similar observation was previously reported in a series of mutant HIV-1 isolates resistant to GNA (*Galanthus nivalis*) and HHA (*Hippeastrum* sp. hybrid) lectins, showing that the major amino acid mutations occur at several putative N-glycosylation sites NXT and NXS, and especially, at the ultimate T or S residues [312]. Removal of two high-mannose N-glycans in gp120 resulted in an enhanced resistance of HIV-1 to griffithsin [308]. In fact, the association of three gp120-gp41 forming the HIV1-envelope spike, will be necessary for the recognition by CD4+ T-lymphocytes [313].

Long term exposure of HIV to cyanovirin or monocot mannose-binding lectins like GNA, HHA and NPA, was shown to progressively result in the deletions of some N-glycan chains decorating the envelope gp120, in an attempt of the retrovirus to diminish the drug pressure and acquire resistance against the carbohydrate-binding agents [314–316]. In addition, the associated treatment of mutant virus strains by 1-deoxymannojirimycin, a potent inhibitor of the $\alpha(1,2)$ -mannosidase, strongly enhanced the suppressive effect of carbohydrate-binding agents on VIH-1 replication [317]. A similar synergistic effect was also observed when combining two carbohydrate-binding agents that recognize distinct N-glycan structures decorating the gp120 [318].

Additionally, a 13 kDa monomeric mannose-binding lectin from edible chive (*Allium tuberosum*), exhibited pronounced inhibitory activity against the HIV-1 reverse transcriptase, a key enzyme in the replication of the HIV-1 genome [319]. However, other lectins with different carbohydrate-binding specificities like PHA from *Phaseolus vulgaris*, RCA from *Ricinus communis* and ABA from the mushroom *Agaricus bisporus*, also exhibited a similar inhibitory activity against the HIV-1 reverse transcriptase [320].

Moreover, the bacterial carbohydrate-binding agents cyanovirin-N, griffithsin and scytovirin, also inhibit the syncytium formation in different HIV-1 infected and uninfected cell lines by preventing the DC-SIGN receptor-directed HIV-1 capture by monocyte-derived dendritic cells (DCs), and subsequent transmission to CD4+ T-lymphocytes [321–324].

Other lectins with very different carbohydrate-binding specificities like the Gal/GalNAc-specific jacalin from *Artocarpus integrifolia* and the GlcNAc-specific Nictaba from *Nicotiana tabacum*, are also potent inhibitors for the HIV-1 infection of CD4+ T lymphocytes [325,326]. In fact, both lectins exhibit some mannose-binding promiscuity as shown from X-ray crystallographic experiments for jacalin [77,78], and glycan array experiments for Nictaba [267], respectively.

6.2. Mannose-Specific Lectins as Cancer Biomarkers and Anti-Cancer Drugs

The ability of mannose-specific lectins to distinguish between normal and diseased cancer cells through the selective recognition of the altered hypermannosylation N-glycans associated to various tumor cell transformations, has led to the application of mannose-binding lectins as potential biomarkers for the detection and the follow up of different tumor cells. In this respect, a variety of legume Man-specific legume lectins and GNA-like lectins were deeply investigated (Table 9).

The recognition of altered N-glycans covering the cancer cells by lectins resulted in programmed cell death through targeting of different apoptotic and autophagic pathways. However, the effects of plant lectins on programmed cell death of cancer cells is not limited to Man-specific lectins since, other plant lectins with distinct carbohydrate-binding specificities, e.g., T/Tn-specific lectins, also interfere with other altered O-glycans covering tumor cells to exert their cytotoxic effects [327].

Plant and fungal lectins affect both apoptosis and autophagy in cancer cells by modulating diverse signaling pathways associated to various pro-apoptotic gene families including, but not exclusively, the Bcl-2 family, caspase family, ROS-p38-p53, P73-Foxo1a-Bim apoptosis, PI3K/Akt, ERK, BNIP3-mediated mitochondrial autophagy, Ras-Raf family and ATG family [328–330] (Table 9).

However, depending on both the lectins and the type of targeted cancer cells, some discrepancies occur with respect to the apoptotic and autophagic pathways leading to the programmed cell death.

Table 9. Cytotoxic effects of Man-specific lectins on cancer cells (reported during the last decade).

Lectin	Cancer Cell	Apoptosis	Autophagy	Ref.
Cabo (<i>Canavalia bonariensis</i>)	glioma		+	[21]
PsA (<i>Pisum sativum</i>)	colorectal cancer	+		[331]
	Erlich acites carcinoma	+		[332]
MOSL (<i>Moringa oleifera</i>)	Erlich acites carcinoma,	+		[333]
	murine malanoma	+		[334]
DLasiL (<i>Dioclea lasiocarpa</i>)	glioma	+		[37]
	ovarian, lung, brestbreast, prostate carcinoma		+	[335]
POL (<i>Polygonatum odoratum</i>)	melanoma	+	+	[336]
	lung adenocarcinoma	+	+	[337]
	breast cancer	+	+	[338]
	lung cancer (non-small cells)	+		[339]
	melanoma	+		[98]
	murine fibrosarcoma	+		[340]
<i>Hyacinthus</i> sp.	Caco-2, Hela	+		[341]
RVL (<i>Remusatia vivipara</i>)	breast cancer	+	+	[342]
ArtinM (<i>Artocarpus heterophyllus</i>)	Jurkat T cells	+	+	[70]
	lung adenocarcinoma	+		[343]
PCL (<i>Polygonatum cyrtonema</i>)	murine fibrosarcoma	+	+	[344]
	melanoma	+	+	[345]
	melanoma	+	+	[346]
AHA (<i>Arisema heterophyllum</i>)	lung cancer	+		[347]
LcA (<i>Lens culinaris</i>)	nasopharyngeal carcinoma	+		[348]
ASA (<i>Allium sativum</i>)	oral carcinoma	+		[349]
Con A (<i>Canavalia ensiformis</i>)	breast carcinoma	+		[350]
	leukemia	+	+	[351]
	glioblastoma	+	+	[352]
	ovarian cancer	+	+	[353]
	melanoma	+	+	[354]
SFL (<i>Sophora flavescens</i>)	HeLa cells	+		[59]
	breast carcinoma	+		[350]
CML (<i>Clematis montana</i>)	HeLa, breast cancer,	+		[83]
	hepatocellular carcinoma			
ConBr (<i>Canavalia brasiliensis</i>)	murine melanoma	+		[355]
	leukemia			[351]
PTA (<i>Pinellia ternata</i>)	hepatoma	+		[356]

Table 9. Cont.

Lectin	Cancer Cell	Apoptosis	Autophagy	Ref.
ESA (<i>Eucheuma serra</i>)	osteosarcoma	+		[357]
	mice colon adenocarcinoma	+		[358]
	colon cancer, HeLa	+		[138]
OJL (<i>Ophiopogon japonicus</i>)	murine fibrosarcoma	+		[96]
LNL (<i>Liparis noversa</i>)	murine fibrosarcoma	+		[96]

Following to these cytotoxic effects on cancer cells, some therapeutic applications have been considered, essentially for the Man-specific legume lectins (Con A) and the GNA-related lectins (*Polygonatum cyrtonema*) [359–361]. To date, however, the use of plant lectins as targeting tools for therapeutic applications has rarely been used [362].

7. Biomedical Perspectives for Mannose-Specific Lectins

Obviously, Man-specific lectins from plants, algae and fungi are interesting probes to target the altered hypermannosylated *N*-glycan expressed at the surface of malignant cells. Our knowledge on the fine carbohydrate-binding specificity of plant and fungal lectins revealed the extreme versatility of the Man-specific lectins to specifically recognize discrete/subtle differences in the expression of altered glycans by tumor cells. Depending on the discrepancies observed in both the shape and size of their extended carbohydrate-binding site, the affinity towards high-mannose *N*-glycans and their chemical substitutions such as sialylation or sulfation varies widely from one lectin to another. The ability of Man-specific lectins to accommodate large mannosylated chains to the extended carbohydrate-binding site via a complex network of hydrogen bonds and hydrophobic interactions, readily accounts for such versatility. Compared to monoclonal antibodies used as standard probes for the detection of the glycan aberrations occurring at the cancer cell surface, plant and fungal Man-specific lectins are a complementary and equally powerful tool for the recognition of high-mannose *N*-glycans [362]. Besides the high-mannose *N*-glycan recognition, Man-specific lectins can exert cytotoxic effects on the targeted cancer cells. They induce apoptotic and autophagic death through modulation of different signaling pathways in cancer cells. These encouraging results suggest the potential use of carefully selected Man-specific lectins for the treatment of cancers [361–363].

Besides their cytotoxic effects detrimental for cancer cells, Man-specific lectins have been proven to act as valuable anti-HIV drugs in vitro and in vivo. The Man-specific lectins from plant, fungal and bacterial origin constitute an important class of HIV entry inhibitors by virtue of their capacity to specifically recognize and bind the oligomannoside chains decorating the envelope gp120 of HIV [363]. Moreover, a long-term exposure of HIV to plant and fungal lectins results in deletions in some of the *N*-glycan chains of gp120, as an attempt of the virus to escape drug pressure, that improves the antiviral activity of these carbohydrate-binding agents [318]. However, the therapeutic use of Man-specific lectins still suffers from several limitations dealing with their high manufacturing costs, formulation and potential mitogenicity, as stated in [364]. In spite of these limitations, encouraging results have been reported using lectins via topical mucosa administration [324].

Author Contributions: A.B. and Y.B. provided the bibliographic informations and analyses. P.R. provided the molecular docking pictures. E.J.M.V.D. and P.R. participated in the writing of the review. All authors approved the final manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ABA	<i>Agaricus bisporus</i> agglutinin
ACA	<i>Allium cepa</i> agglutinin
AMA	<i>Arum maculatum</i> agglutinin
ASA	<i>Allium sativum</i> agglutinin
Asp, D	Aspartic acid
Ath	<i>Arabidopsis thaliana</i>
ATP	Adenosine triphosphate
BMA	<i>Bowringia mildbraedii</i> agglutinin
CBA	Carbohydrate-binding agent
CBM	Carbohydrate-binding module
CBS	Carbohydrate-binding site
CEA	<i>Colocasia esculenta</i> agglutinin
Con A	Concanavalin A
CTL	<i>Centrolobium tomentosum</i> lectin
CVN	Cyanovirin N
EUL	<i>Euonymus europaeus</i> lectin
Glu, E	Glutamic acid
Gly, G	Glycine
GNA	<i>Galanthus nivalis</i> agglutinin
Heltuba	<i>Helianthus tuberosus</i> agglutinin
HHA	<i>Hippeastrum hybrid</i> agglutinin
HIV	Human Immunodeficiency virus
HSP	Heat shock protein
Leu, L	Leucine
LcA	<i>Lens culinaris</i> agglutinin
LoL	<i>Lathyrus ochrus</i> lectin
MPA	<i>Maclura pomifera</i> agglutinin
MVL	<i>Microcystis viridis</i> lectin
OAA	<i>Oscillatoria agardhii</i> agglutinin
PAL	<i>Pterocarpus angolensis</i> lectin
PDB	Protein data bank
PHA	Phytohemagglutinin
Phe, F	Phenylalanine
PNA	Peanut agglutinin
PsA	<i>Pisum sativum</i> agglutinin
ROS	Reactive oxygen species
RIP	Ribosome inactivating protein
SBA	Soybean agglutinin
SNA	<i>Sambucus nigra</i> agglutinin
Trp, W	Tryptophane
Tyr, Y	Tyrosine
Val, V	Valine
VfA	<i>Vicia faba</i> agglutinin

References

1. Van Damme, E.J.M.; Rougé, P.; Peumans, W.J. Plant lectins. In *Carbohydrate-Protein Interactions: Plant Lectins*; Kamerling, J.P., Boons, G.J., Lee, Y.C., Suzuki, A., Taniguchi, N., Voragen, A.G.I., Eds.; Elsevier: New York, NY, USA, 2007; pp. 564–599.
2. Wu, A.M.; Song, S.C.; Tsai, M.S.; Herp, A. A guide to the carbohydrate specificities of applied lectins-2. *Adv. Exp. Med. Biol.* **2001**, *491*, 551–585.

3. De Schutter, K.; Van Damme, E.J.M. Protein-carbohydrate interactions as part of plant defense and animal immunity. *Molecules* **2015**, *20*, 9029–9053. [[CrossRef](#)] [[PubMed](#)]
4. Van Damme, E.J.M.; Lannoo, N.; Fouquaert, E.; Peumans, W.J. The identification of inducible cytoplasmic/nuclear carbohydrate-binding proteins urges to develop novel concepts about the role of plant lectins. *Glycoconj. J.* **2004**, *20*, 449–460. [[CrossRef](#)] [[PubMed](#)]
5. Chen, Y.; Peumans, W.J.; Hause, B.; Bras, J.; Kumar, M.; Proost, P.; Barre, A.; Rougé, P.; Van Damme, E.J.M. Jasmonic acid methyl ester induces the synthesis of a cytoplasmic/nuclear chito-oligosaccharide binding lectin in tobacco leaves. *FASEB J.* **2002**, *16*, 905–907. [[CrossRef](#)] [[PubMed](#)]
6. Van Damme, E.J.M.; Peumans, W.J.; Barre, A.; Rougé, P. Plant lectins: A composite of several distinct families of structurally and evolutionary related proteins with diverse biological roles. *Crit. Rev. Plant Sci.* **1998**, *17*, 575–692. [[CrossRef](#)]
7. Agrawal, B.B.; Goldstein, I.J. Specific binding of concanavalin A to cross-linked dextran gels. *Biochem. J.* **1965**, *96*, 23C–25C. [[CrossRef](#)]
8. Singh, R.S.; Bhari, R.; Kaur, H.P. Mushroom lectins: Current status and future perspectives. *Crit. Rev. Biotechnol.* **2010**, *30*, 99–126. [[CrossRef](#)]
9. Okuyama, S.; Nakamura-Tsuruta, S.; Tateno, H.; Hirabayashi, J.; Matsubara, K.; Hori, K. Strict binding specificity of small-sized lectins from the red alga *Hypnea japonica* for core (α 1-6) fucosylated N-glycans. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 912–920. [[CrossRef](#)]
10. Debray, H.; Rougé, P. The fine sugar specificity of the *Lathyrus ochrus* seed lectin and isolectins. *FEBS Lett.* **1984**, *176*, 120–124. [[CrossRef](#)]
11. Tateno, H.; Nakamura-Tsuruta, S.; Hirabayashi, J. Comparative analysis of core-fucose-binding lectins from *Lens culinaris* and *Pisum sativum* using frontal affinity chromatography. *Glycobiology* **2009**, *19*, 527–536. [[CrossRef](#)]
12. Tateno, H.; Winter, H.C.; Petryniak, J.; Goldstein, I.J. Purification, characterization, molecular cloning, and expression of novel members of jacalin-related lectins from rhizomes of the true fern *Phlebodium aureum* (L.) J. Smith (Polypodiaceae). *J. Biol. Chem.* **2003**, *278*, 10891–10899. [[CrossRef](#)] [[PubMed](#)]
13. Datta, P.K.; Figueroa, M.O.R.; Lajolo, F.M. Purification and characterization of two major lectins from *Araucaria brasiliensis* syn *Araucaria angustifolia* seeds (pinhao). *Plant Physiol.* **1991**, *97*, 856–862. [[CrossRef](#)]
14. Miyakawa, T.; Hatano, K.; Miyauchi, Y.; Suwa, Y.; Sawano, Y.; Tanokura, M. A secreted protein with plant-specific cysteine-rich motif functions as a mannose-binding lectin that exhibits antifungal activity. *Plant Physiol.* **2014**, *166*, 766–778. [[CrossRef](#)] [[PubMed](#)]
15. Yagi, F.; Iwaya, T.; Haraguchi, T.; Goldstein, I.J. The lectin from leaves of Japanese cycad, *Cycas revoluta* Thunb. (Gymnosperm) is a member of the jacalin-related family. *Eur. J. Biochem.* **2002**, *269*, 4335–4341. [[CrossRef](#)] [[PubMed](#)]
16. Shimokawa, M.; Haraguchi, T.; Minami, Y.; Yagi, F.; Hiemori, K.; Tateno, H.; Hirabayashi, J. Two carbohydrate recognizing domains from *Cycas revoluta* leaf lectin show the distinct sugar-binding specificity-A unique manno-oligosaccharide recognition by N-terminal domain. *J. Biochem.* **2016**, *160*, 27–35. [[CrossRef](#)]
17. Animashaun, T.; Hughes, R.C. *Bowringia milbraedii* agglutinin. Specificity of binding to early processing intermediates of asparagine-linked oligosaccharide and use as a marker of endoplasmic reticulum glycoproteins. *J. Biol. Chem.* **1989**, *264*, 4657–4663. [[PubMed](#)]
18. Siddiqui, S.; Hasan, S.; Salahuddin, A. Isolation and characterization of *Cajanus cajan* lectin. *Arch. Biochem. Biophys.* **1995**, *319*, 426–431. [[CrossRef](#)]
19. Souza Teixeira, C.; da Silva, H.C.; de Moura, T.R.; Pereira-Júnior, F.N.; do Nascimento, K.S.; Nagano, C.S.; Sampaio, A.H.; Delatorre, P.; Rocha, B.A.; Cavada, B.S. Crystal structure of the lectin of *Camptosema pedicellatum*: Implication of a conservative substitution at the hydrophobic subsite. *J. Biochem.* **2012**, *152*, 87–98. [[CrossRef](#)]
20. Bezerra, G.A.; Viertlmayr, R.; Moura, T.R.; Delatorre, P.; Rocha, B.A.; do Nascimento, K.S.; Figueiredo, J.G.; Bezerra, I.G.; Teixeira, C.S.; Simões, R.C.; et al. Structural studies of an anti-inflammatory lectin from *Canavalia boliviana* seeds in complex with dimannosides. *PLoS ONE* **2014**, *9*, e97015. [[CrossRef](#)]
21. Cavada, B.S.; Silva, M.T.L.; Osterne, V.J.S.; Pinto-Junior, V.R.; Nascimento, A.P.M.; Wolin, I.A.V.; Heinrich, I.A.; Nobre, C.A.S.; Moreira, C.G.; Lossio, C.F.; et al. *Canavalia bonariensis* lectin: Molecular bases of glycoconjugates interaction and antiglioma potential. *Int. J. Biol. Macromol.* **2018**, *106*, 369–378. [[CrossRef](#)]

22. Sanz-Aparicio, J.; Hermoso, J.; Grangeiro, T.B.; Calvete, J.J.; Cavada, B.S. The crystal structure of *Canavalia brasiliensis* lectin suggests a correlation between its quaternary conformation and its distinct biological properties from Concanavalin A. *FEBS Lett.* **1997**, *405*, 114–118. [[CrossRef](#)]
23. Agrawal, B.B.; Goldstein, I.J. Physical and chemical characterization of concanavalin A, the hemagglutinin from jack bean (*Canavalia ensiformis*). *Biochim. Biophys. Acta* **1967**, *133*, 376–379. [[CrossRef](#)]
24. Kojima, K.; Ogawa, H.; Seno, N.; Matsumoto, I. Purification and characterization of *Canavalia gladiata* agglutinin. *Carbohydr. Res.* **1991**, *213*, 275–282. [[CrossRef](#)]
25. Barroso-Neto, I.L.; Simões, R.C.; Rocha, B.A.; Bezerra, M.J.; Pereira-Junior, F.N.; Silva Osterne, V.J.; Nascimento, K.S.; Nagano, C.S.; Delatorre, P.; Pereira, M.G.; et al. Vasorelaxant activity of *Canavalia grandiflora* seed lectin: A structural analysis. *Arch. Biochem. Biophys.* **2014**, *543*, 31–39. [[CrossRef](#)]
26. Perez, G.; Perez, C.; Sousa-Cavada, B.; Moreira, R.; Richardson, M. Comparison of the amino acid sequence of the lectins from seeds of *Dioclea lehmanni* and *Canavalia maritima*. *Phytochemistry* **1991**, *30*, 2619–2621. [[CrossRef](#)]
27. Osterne, V.J.S.; Silva-Filho, J.C.; Santiago, M.Q.; Pinto-Junior, V.R.; Almeida, A.C.; Barreto, A.A.G.C.; Wolin, I.A.V.; Nascimento, A.P.M.; Amorim, R.M.F.; Rocha, B.A.M.; et al. Structural characterization of a lectin from *Canavalia virosa* seeds with inflammatory and cytotoxic activities. *Int. J. Biol. Macromol.* **2017**, *94*, 271–282. [[CrossRef](#)]
28. Vasconcelos, M.A.; Alves, A.C.; Carneiro, R.F.; Dias, A.H.; Martins, F.W.; Cajazeiras, J.B.; Nagano, C.S.; Teixeira, E.H.; Nascimento, K.S.; Cavada, B.S. Purification and primary structure of a novel mannose-specific lectin from *Centrolobium microchaete* Mart seeds. *Int. J. Biol. Macromol.* **2015**, *81*, 600–607. [[CrossRef](#)]
29. Almeida, A.C.; Osterne, V.J.; Santiago, M.Q.; Pinto-Junior, V.R.; Silva-Filho, J.C.; Lossio, C.F.; Nascimento, F.L.; Almeida, R.P.; Teixeira, C.S.; Leal, R.B.; et al. Structural analysis of *Centrolobium tomentosum* seed lectin with inflammatory activity. *Arch. Biochem. Biophys.* **2016**, *596*, 73–83. [[CrossRef](#)]
30. Van Damme, E.J.M.; Barre, A.; Bemer, V.; Rougé, P.; Van Leuven, F.; Peumans, W.J. A lectin and a lectin-related protein are the two most prominent proteins in the bark of yellow wood (*Cladrastis lutea*). *Plant Mol. Biol.* **1995**, *29*, 579–598. [[CrossRef](#)]
31. Del Sol, F.G.; Cavada, B.S.; Calvete, J.J. Crystal structures of *floribunda* seed lectin at acidic and basic pHs. Insights into the structural basis of the pH-dependent dimer-tetramer transition. *J. Struct. Biol.* **2007**, *158*, 1–9. [[CrossRef](#)]
32. Varejão, N.; Correia, M.T.; Foguel, D. Characterization of the unfolding process of the tetrameric and dimeric forms of *Cratylia mollis* seed lectin (CRAMOLL1): Effects of natural fragmentation on protein stability. *Biochemistry* **2011**, *50*, 7330–7340. [[CrossRef](#)] [[PubMed](#)]
33. Rocha, B.A.; Delatorre, P.; Oliveira, T.M.; Benevides, R.G.; Pires, A.F.; Sousa, A.A.; Souza, L.A.; Assreuy, A.M.; Debray, H.; de Azevedo, X.W.F.; et al. Structural basis for both pro- and anti-inflammatory response induced by mannose-specific legume lectin from *Cymbosema roseum*. *Biochimie* **2011**, *93*, 806–816. [[CrossRef](#)] [[PubMed](#)]
34. Moreira, R.A.; Barros, A.C.; Stewart, J.C.; Pusztai, A. Isolation and characterization of a lectin from the seeds of *Dioclea grandiflora* (Mart.). *Planta* **1983**, *158*, 63–69. [[CrossRef](#)]
35. Rozwarski, D.A.; Swami, B.M.; Brewer, C.F.; Sacchetti, J.C. Crystal structure of the lectin from *Dioclea grandiflora* complexed with core trimannoside of asparagine-linked carbohydrates. *J. Biol. Chem.* **1998**, *273*, 32818–32825. [[CrossRef](#)] [[PubMed](#)]
36. Wah, D.A.; Romero, A.; Gallego del Sol, F.; Cavada, B.S.; Ramos, M.V.; Grangeiro, T.B.; Sampaio, A.H.; Calvete, J.J. Crystal structure of native and Cd/Cd-substituted *Dioclea guianensis* seed lectin. A novel manganese-binding site and structural basis of dimer-tetramer association. *J. Mol. Biol.* **2001**, *310*, 885–894. [[CrossRef](#)] [[PubMed](#)]
37. Nascimento, K.S.; Santiago, M.Q.; Pinto-Junior, V.R.; Osterne, V.J.S.; Martins, F.W.V.; Nascimento, A.P.M.; Wolin, I.A.V.; Heinrich, I.A.; Martins, M.G.Q.; Silva, M.T.L.; et al. Structural analysis of *Dioclea lasiocarpa* lectin: A C6 cells apoptosis-inducing protein. *Int. J. Biochem. Cell Biol.* **2017**, *92*, 79–89. [[CrossRef](#)] [[PubMed](#)]
38. Leal, R.B.; Pinto-Junior, V.R.; Osterne, V.J.S.; Wolin, I.A.V.; Nascimento, A.P.M.; Neco, A.H.B.; Araripe, D.A.; Welter, P.G.; Neto, C.C.; Correia, J.L.A.; et al. Crystal structure of DlyL, a mannose-specific lectin from *Dioclea lasiophylla* Mart. Ex Benth seeds that display cytotoxic effects against C6 glioma cells. *Int. J. Biol. Macromol.* **2018**, *114*, 64–76. [[CrossRef](#)] [[PubMed](#)]

39. Pinto-Junior, V.R.; Osterne, V.J.; Santiago, M.Q.; Correia, J.L.; Pereira-Junior, F.N.; Leal, R.B.; Pereira, M.G.; Chicas, L.S.; Nagano, C.S.; Rocha, B.A.; et al. Structural studies of a vasorelaxant lectin from *Dioclea reflexa* Hook seeds: Crystal structure, molecular docking and dynamics. *Int. J. Biol. Macromol.* **2017**, *98*, 12–23. [[CrossRef](#)] [[PubMed](#)]
40. De Oliveira, T.M.; Delatorre, P.; da Rocha, B.A.; de Souza, E.P.; Nascimento, K.S.; Bezerra, G.A.; Moura, T.R.; Benevides, R.G.; Bezerra, E.H.; Moreno, F.B.; et al. Crystal structure of *Dioclea rostrata* lectin: Insights into understanding the pH-dependent dimer-tetramer equilibrium and the structural basis for carbohydrate recognition in Diocleinae lectins. *J. Struct. Biol.* **2008**, *164*, 177–182. [[CrossRef](#)]
41. Barroso-Neto, I.L.; Delatorre, P.; Teixeira, C.S.; Correia, J.L.; Cajazeiras, J.B.; Pereira, R.I.; Nascimento, K.S.; Laranjeira, E.P.; Pires, A.F.; Assreuy, A.M.; et al. Structural analysis of a *Dioclea sclerocarpa* lectin: Study on the vasorelaxant properties of Dioclea lectins. *Int. J. Biol. Macromol.* **2016**, *82*, 464–470. [[CrossRef](#)]
42. Bezerra, M.J.; Rodrigues, N.V.; Pires Ade, F.; Bezerra, G.A.; Nobre, C.B.; Alencar, K.L.; Soares, P.M.; do Nascimento, K.S.; Nagano, C.S.; Martins, J.L.; et al. Crystal structure of *Dioclea violacea* lectin and a comparative study of vasorelaxant properties with *Dioclea rostrata* lectin. *Int. J. Biochem. Cell Biol.* **2013**, *45*, 807–815. [[CrossRef](#)] [[PubMed](#)]
43. Batista da Nóbrega, R.; Rocha, B.A.; Gadelha, C.A.; Santi-Gadelha, T.; Pires, A.F.; Assreuy, A.M.; Nascimento, K.S.; Nagano, C.S.; Sampaio, A.H.; Cavada, B.S.; et al. Structure of *Dioclea virgata* lectin: Relations between carbohydrate binding site and nitric oxide production. *Biochimie* **2012**, *94*, 900–906. [[CrossRef](#)] [[PubMed](#)]
44. Rangel, T.B.; Rocha, B.A.; Bezerra, G.A.; Assreuy, A.M.; Pires Ade, F.; do Nascimento, A.S.; Bezerra, M.J.; do Nascimento, K.S.; Nagano, C.S.; Sampaio, A.H.; et al. Crystal structure of a pro-inflammatory lectin from the seeds of *Dioclea wilsonii* Standl. *Biochimie* **2012**, *94*, 525–532. [[CrossRef](#)] [[PubMed](#)]
45. Cavada, B.S.; Richardson, M.; Yarwood, A.; Pèrè, D.; Rougé, P. The amino acid sequences of the α subunits of the lectins from *Lathyrus cicera*, *L. aphaca* and *L. articulatus*. *Phytochemistry* **1986**, *25*, 115–118. [[CrossRef](#)]
46. Yarwood, A.; Richardson, M.; Cavada, B.S.; Pèrè, D.; Rougé, P. The amino acid sequences of the α subunits of the lectins from the seeds of *Lathyrus hirsutus* and *Lathyrus tingitanus*. *Phytochemistry* **1986**, *25*, 2109–2112. [[CrossRef](#)]
47. Yarwood, A.; Richardson, M.; Morphet, B.; Westby, M.; Pèrè, D.; Rougé, P. The amino acid sequences of two atypical single-chain Viciae isolectins from seeds of *Lathyrus nissolia* L. *Phytochemistry* **1988**, *27*, 1719–1721. [[CrossRef](#)]
48. Bourne, Y.; Abergel, C.; Cambillau, C.; Frey, M.; Rougé, P.; Fontecilla-Camps, J.C. X-ray crystal structure determination and refinement at 1.9 Å resolution of isolectin I from the seeds of *Lathyrus ochrus*. *J. Mol. Biol.* **1990**, *214*, 571–584. [[CrossRef](#)]
49. Kolberg, J. Isolation and partial characterization of a mitogenic lectin from *Lathyrus odoratus* seeds. *Acta Pathol. Microbiol. Scand. C* **1978**, *86C*, 99–104. [[CrossRef](#)]
50. Sletten, K.; Kolberg, J. The primary structure of the α chain of a mitogenic lectin from the seeds of *Lathyrus sativus*. *Hoppe Seylers Z. Physiol. Chem.* **1983**, *364*, 1047–1051. [[CrossRef](#)]
51. Richardson, M.; Yarwood, A.; Rougé, P. The amino acid sequence of an atypical single-chain lectin from seeds of *Lathyrus sphaericus*. *FEBS Lett.* **1987**, *216*, 145–150. [[CrossRef](#)]
52. Tichá, M.; Zeineddine, I.; Kocourek, J. Studies on lectins. XLVIII. Isolation and characterization of lectins from the seeds of *Lathyrus odoratus* L. and *Lathyrus silvestris* L. *Acta Biol. Med. Ger.* **1980**, *39*, 649–655. [[PubMed](#)]
53. Foriers, A.; Van Driessche, E.; De Neve, R.; Kanarek, L.; Strosberg, A.D. The subunit structure and N-terminal sequences of the α - and β -subunits of the lentil lectin (*Lens culinaris*). *FEBS Lett.* **1977**, *75*, 237–240. [[CrossRef](#)]
54. Gao, S.; An, J.; Wu, C.F.; Gu, Y.; Chen, F.; Yu, Y.; Wu, Q.Q.; Bao, J.K. Effect of amino acid residue and oligosaccharide chain chemical modifications on spectral and hemagglutinating activity of *Milletia dielsiana* Harms. ex Diels. lectin. *Acta Biochim. Biophys. Sin. (Shanghai)* **2005**, *37*, 47–54. [[CrossRef](#)]
55. Young, N.M.; Williams, R.E.; Roy, C.; Yaguchi, M. Structural comparison of the lectin from sainfoin (*Onobrychis viciifolia*) with concanavalin A and other D-mannose specific lectins. *Can. J. Biochem.* **1982**, *60*, 933–941. [[CrossRef](#)]
56. Cavada, B.S.; da Silva, L.I.; Ramos, M.V.; Galvani, F.R.; Grangeiro, T.B.; Leite, K.B.; Assreuy, A.M.; Cajazeiras, J.B.; Calvete, J.J. Seed lectin from *Pisum arvense*: Isolation, biochemical characterization and amino acid sequence. *Protein Pept. Lett.* **2003**, *10*, 607–617. [[CrossRef](#)]

57. Einspahr, H.; Pareks, E.H.; Suguna, K.; Subramanian, E.; Suddath, F.L. The crystal structure of pea lectin at 3.0-Å resolution. *J. Biol. Chem.* **1986**, *261*, 16518–16527.
58. Loris, R.; Imberty, A.; Beeckmans, S.; Van Driessche, E.; Read, J.S.; Bouckaert, J.; De Greve, H.; Buts, L.; Wyns, L. Crystal structure of *Pterocarpus angolensis* lectin in complex with glucose, sucrose, and turanose. *J. Biol. Chem.* **2003**, *278*, 16297–16303. [[CrossRef](#)]
59. Liu, Z.; Liu, B.; Zhang, Z.T.; Zhou, T.T.; Bian, H.J.; Min, M.W.; Liu, Y.H.; Chen, J.; Bao, J.K. A mannose-binding lectin from *Sophora flavescens* induces apoptosis in HeLa cells. *Phytomedicine* **2008**, *15*, 867–875. [[CrossRef](#)]
60. Naeem, A.; Ahmad, E.; Ashraf, M.T.; Khan, R.H. Purification and characterization of mannose/glucose-specific lectin from seeds of *Trigonella foenumgraecum*. *Biochemistry (Mosc)* **2007**, *72*, 44–48. [[CrossRef](#)]
61. Baumann, C.M.; Strosberg, A.D.; Rüdiger, H. Purification and characterization of a mannose/glucose-specific lectin from *Vicia cracca*. *Eur. J. Biochem.* **1982**, *122*, 105–110. [[CrossRef](#)]
62. Fornstedt, N.; Porath, J. Characterization studies on a new lectin found in seeds of *Vicia ervilia*. *FEBS Lett.* **1975**, *57*, 187–191. [[CrossRef](#)]
63. Reeke, G.N., Jr.; Becker, J.W. Three-dimensional structure of favin: Saccharide binding-cyclic permutation in leguminous lectins. *Science* **1986**, *234*, 1108–1111. [[CrossRef](#)] [[PubMed](#)]
64. Gebauer, G.; Schiltz, E.; Rüdiger, H. The amino-acid sequence of the alpha subunit of the mitogenic lectin from *Vicia sativa*. *Eur. J. Biochem.* **1981**, *113*, 319–325. [[CrossRef](#)] [[PubMed](#)]
65. Silva, H.C.; Bari, A.U.; Rocha, B.A.; Nascimento, K.S.; Ponte, E.L.; Pires, A.F.; Delatorre, P.; Teixeira, E.H.; Debray, H.; Assreuy, A.M.; et al. Purification and primary structure of a mannose/glucose-binding lectin from *Parkia biglobosa* Jacq. seeds with antinociceptive and anti-inflammatory properties. *J. Mol. Recognit.* **2013**, *26*, 470–478. [[CrossRef](#)] [[PubMed](#)]
66. Mann, K.; Farias, C.M.; Del Sol, F.G.; Santos, C.F.; Grangeiro, T.B.; Nagano, C.S.; Cavada, B.S.; Calvete, J.J. The amino acid sequence of the glucose/mannose-specific lectin isolated from *Parkia platycephala* seeds reveals three tandemly arranged jacalin-related domains. *Eur. J. Biochem.* **2001**, *268*, 4414–4422. [[CrossRef](#)] [[PubMed](#)]
67. Cavada, B.S.; Araripe, D.A.; Silva, I.B.; Pinto-Junior, V.R.; Osterne, V.J.S.; Neco, A.H.B.; Laranjeira, E.P.P.; Lossio, C.F.; Correia, J.L.A.; Pires, A.F.; et al. Structural studies and nociceptive activity of a native lectin from *Platypodium elegans* seeds (nPELa). *Int. J. Biol. Macromol.* **2018**, *107*, 236–246. [[CrossRef](#)] [[PubMed](#)]
68. Pereira-Junior, F.N.; Silva, H.C.; Freitas, B.T.; Rocha, B.A.; Nascimento, K.S.; Nagano, C.S.; Leal, R.B.; Sampaio, A.H.; Cavada, B.S. Purification and characterization of a mannose/*N*-acetyl-D-glucosamine-specific lectin from the seeds of *Platymiscium floribundum* Vogel. *J. Mol. Recognit.* **2012**, *25*, 443–449. [[CrossRef](#)] [[PubMed](#)]
69. Nomura, K.; Ashida, H.; Uemura, N.; Kushibe, S.; Ozaki, T.; Yoshida, M. Purification and characterization of a mannose/glucose-specific lectin from *Castanea crenata*. *Phytochemistry* **1998**, *49*, 667–673. [[CrossRef](#)]
70. Da Silva, T.A.; Oliveira-Brito, P.K.M.; Gonçalves, T.E.; Vendruscolo, P.E.; Roque-Barreira, M.C. ArtinM mediates murine T cell activation and induces cell death in Jurkat human leukemic T cells. *Int. J. Mol. Sci.* **2017**, *18*, 1400. [[CrossRef](#)]
71. Pereira-da-Silva, G.; Roque-Barreira, M.C.; Van Damme, E.J. ArtinM: A rational substitution for the names artocarpin and KM+. *Immunol. Lett.* **2008**, *119*, 114–115. [[CrossRef](#)]
72. de Sousa, F.D.; da Silva, B.B.; Furtado, G.P.; Carneiro, I.S.; Lobo, M.D.P.; Guan, Y.; Guo, J.; Coker, A.R.; Lourenzoni, M.R.; Guedes, M.I.F.; et al. Frutapin, a lectin from *Artocarpus incisa* (breadfruit): Cloning, expression and molecular insights. *Biosci. Rep.* **2017**, *37*. [[CrossRef](#)] [[PubMed](#)]
73. Gabrielsen, M.; Abdul-Rahman, P.S.; Isaacs, N.W.; Hashim, O.H.; Copgdell, R.J. Crystallization and initial X-ray diffraction analysis of a mannose-binding lectin from champedak. *Acta Crystallogr. Sect. F Struct. Biol. Cryst. Commun.* **2010**, *66*, 592–594. [[CrossRef](#)] [[PubMed](#)]
74. Gabrielsen, M.; Abdul-Rahman, P.S.; Othman, S.; Hashim, O.H.; Cogdell, R.J. Structures and binding specificity of galactose- and mannose-binding lectins from champedak: Differences from jackfruit lectins. *Acta Crystallogr. F Struct. Biol. Commun.* **2014**, *70*, 709–716. [[CrossRef](#)]
75. Rosa, J.C.; De Oliveira, P.S.; Garratt, R.; Beltramini, L.; Resing, K.; Roque-Barreira, M.C.; Greene, L.J. KM+, a mannose-binding lectin from *Artocarpus integrifolia*: Amino acid sequence, predicted tertiary structure, carbohydrate recognition, and analysis of the β -prism fold. *Protein Sci.* **1999**, *8*, 13–24. [[CrossRef](#)] [[PubMed](#)]
76. Misquith, S.; Rani, P.G.; Surolia, A. Carbohydrate binding specificity of the B-cell maturation mitogen from *Artocarpus integrifolia* seeds. *J. Biol. Chem.* **1994**, *269*, 30393–30401. [[PubMed](#)]

77. Bourne, Y.; Houlès-Astoul, C.; Zamboni, V.; Peumans, W.J.; Menu-Bouaouiche, L.; Van Damme, E.J.M.; Barre, A.; Rougé, P. Structural basios for the unusual carbohydrate-binding specificity of jacalin towards galactose and mannose. *Biochem. J.* **2002**, *364*, 173–180. [[CrossRef](#)] [[PubMed](#)]
78. Jeyaprakash, A.A.; Jayashree, G.; Mahanta, S.K.; Swaminathan, C.P.; Sekar, K.; Surolia, A.; Vijayan, M. Structural basis for the energetics of jacalin-sugar interactions: Promiscuity versus specificity. *J. Mol. Biol.* **2005**, *347*, 181–188. [[CrossRef](#)] [[PubMed](#)]
79. Chjowdhury, S.; Ahmed, H.; Chatterjee, B.P. Chemical modificatrion studies of *Artocarpus lakoocha* lectin artocarpin. *Biochimie* **1991**, *73*, 563–571. [[CrossRef](#)]
80. Van Damme, E.J.; Hause, B.; Hu, J.; Barre, A.; Rougé, P.; Proost, P.; Peumans, W.J. Two distinct jacalin-related lectins with a different specificity and subcellular location are major vegetative storage proteins in the bark of the black mulberry tree. *Plant Physiol.* **2002**, *130*, 757–769. [[CrossRef](#)]
81. Bourne, Y.; Zamboni, V.; Barre, A.; Peumans, W.J.; Van Damme, E.J.; Rougé, P. *Helianthus tuberosus* lectin reveals a widespread scaffold for mannose-binding lectins. *Structure* **1999**, *7*, 1473–1482. [[CrossRef](#)]
82. Beneteau, J.; Renard, D.; Marché, L.; Douville, E.; Lavenant, L.; Rahbé, Y.; Dupont, D.; Vilaine, F.; Dinant, S. Binding properties of the *N*-acetylglucosamine and high-mannose *N*-glycan PP2-A1 phloem lectin in *Arabidopsis*. *Plant Physiol.* **2010**, *153*, 1345–1361. [[CrossRef](#)]
83. Peng, H.; Lv, H.; Wang, Y.; Liu, Y.H.; Li, C.Y.; Meng, L.; Chen, F.; Bao, J.K. *Clematis montana* lectin, a novel mannose-binding lectin from traditional Chinese medicine with antiviral and apoptosis-inducing activities. *Peptides* **2009**, *30*, 1805–1815. [[CrossRef](#)] [[PubMed](#)]
84. Koike, T.; Titani, K.; Suzuki, M.; Beppu, H.; Kuzuya, H.; Maruta, K.; Shimpō, K.; Fujita, K. The complete amino acid sequence of a mannose-binding lectin from "Kidachi Aloe" (*Aloe arborescens* Miller var. *natalensis* Berger). *Biochem. Biophys. Res. Commun.* **1995**, *214*, 163–170. [[CrossRef](#)] [[PubMed](#)]
85. Lin, J.; Zhou, X.; Pang, Y.; Gao, H.; Fei, J.; Shen, G.A.; Wang, J.; Li, X.; Sun, X.; Tang, K. Cloning and characterization of an agglutinin gene from *Arisaema lobatum*. *Biosci. Rep.* **2005**, *25*, 345–362. [[CrossRef](#)] [[PubMed](#)]
86. Zhao, X.; Yao, J.; Liao, Z.; Zhang, H.; Chen, F.; Wang, L.; Lu, Y.; Sun, X.; Yu, S.; Tang, K. Molecular cloning of a novel mannose-binding lectin gene from *Arisaema heterophyllum*. *Plant Sci.* **2003**, *165*, 55–60. [[CrossRef](#)]
87. Van Damme, E.J.; Goossens, K.; Smeets, K.; Van Leuven, F.; Verhaert, P.; Peumans, W.J. The major tuber storage protein of araceae species is a lectin. Characterization and molecular cloning of the lectin from *Arum maculatum* L. *Plant Physiol.* **1995**, *107*, 1147–1158. [[CrossRef](#)]
88. Pereira, P.R.; Winter, H.C.; Vericimo, M.A.; Meagher, J.L.; Stckey, J.A.; Goldstein, I.J.; Paschoalin, V.M.; Silva, J.T. Structural analysis and binding properties of isoforms of tarin, the GNA-related lectin from *Colocasia esculenta*. *Biochim. Biophys. Acta* **2015**, *1854*, 20–30. [[CrossRef](#)]
89. Nakagawa, Y.; Sakamoto, H.; Tateno, H.; Hirabayashi, J.; Oguri, S. Purification, characterization, and molecular cloning of lectin from winter buds of *Lysichiton camtschatcensis* (L.) Schott. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 25–33. [[CrossRef](#)]
90. Yao, J.H.; Zhao, X.Y.; Liao, Z.H.; Lin, J.; Chen, Z.H.; Chen, F.; Song, J.; Sun, X.F.; Tang, K.X. Cloning and molecular characterization of a novel lectin gene from *Pinellia ternata*. *Cell Res.* **2003**, *13*, 301–308. [[CrossRef](#)]
91. Shetty, K.N.; Bhat, G.G.; Inamdar, S.R.; Swamy, B.M.; Suguna, K. Crystal structure of a β -prism II lectin from *Remusatia vivipara*. *Glycobiology* **2012**, *22*, 56–69. [[CrossRef](#)]
92. Luo, Y.; Xu, X.; Liu, J.; Li, J.; Sun, Y.; Liu, Z.; Liu, J.; Van Damme, E.; Balzarini, J.; Bao, J. A novel mannose-binding tuber lectin from *Typhonium divaricatum* (L.) Decne (family Araceae) with antiviral activity against HSV-II and anti-proliferative effect on human cancer cell lines. *J. Biochem. Mol. Biol.* **2007**, *40*, 358–367. [[CrossRef](#)] [[PubMed](#)]
93. Mo, H.; Rice, K.G.; Evers, D.L.; Winter, H.C.; Peumans, W.J.; Van Damme, E.J.; Goldstein, I.J. *Xanthosoma sagittifolium* tubers contain a lectin with two different types of carbohydrate-binding sites. *J. Biol. Chem.* **1999**, *274*, 33300–33305. [[CrossRef](#)]
94. Chen, Z.; Pang, Y.; Liu, X.; Wang, X.; Deng, Z.; Sun, X.; Tang, K. Molecular cloning and characterization of a novel mannose-binding lectin cDNA from *Zantedeschia aethiopica*. *Biocell* **2005**, *29*, 187–193.
95. Liu, B.; Peng, H.; Yao, Q.; Li, J.; Van Damme, E.; Balzarini, J.; Bao, J.K. Bioinformatics analyses of the mannose-binding lectins from *Polygonatum cyrtoneuma*, *Ophiopogon japonicus* and *Liparis noversa* with antiproliferative and apoptosis-inducing activities. *Phytomedicine* **2009**, *16*, 601–608. [[CrossRef](#)] [[PubMed](#)]

96. Ding, J.; Bao, J.; Zhu, D.; Zhang, Y.; Wang, D.C. Crystal structure of a novel anti-HIV mannose-binding lectin from *Polygonatum cyrtonema* Hua with unique ligand-binding property and super-structure. *J. Struct. Biol.* **2010**, *171*, 309–317. [[CrossRef](#)] [[PubMed](#)]
97. Van Damme, E.J.; Barre, A.; Rougé, P.; Van Leuven, F.; Balzarini, J.; Peumans, W.J. Molecular cloning of the lectin and a lectin-related protein from common Solomon's seal (*Polygonatum multiflorum*). *Plant Mol. Biol.* **1996**, *31*, 657–672. [[CrossRef](#)] [[PubMed](#)]
98. Yang, Y.; Xu, H.L.; Zhang, Z.T.; Liu, J.J.; Li, W.W.; Ming, H.; Bao, J.K. Characterization, molecular cloning, and *in silico* analysis of a novel mannose-binding lectin from *Polygonatum odoratum* (Mill.) with anti-HSV-II and apoptosis-inducing activities. *Phytomedicine* **2011**, *18*, 748–755. [[CrossRef](#)] [[PubMed](#)]
99. Bourne, Y.; Roig-Zamboni, V.; Barre, A.; Peumans, W.J.; Astoul, C.H.; Van Damme, E.J.; Rougé, P. The crystal structure of the *Calystegia sepium* agglutinin reveals a novel quaternary arrangement of lectin subunits with a β -prism fold. *J. Biol. Chem.* **2004**, *279*, 527–533. [[CrossRef](#)]
100. Chang, W.C.; Liu, K.L.; Hsu, F.C.; Jeng, S.T.; Cheng, Y.S. Ipomoelin, a jacalin-related lectin with a compact tetrameric association and versatile carbohydrate binding properties regulated by its N terminus. *PLoS ONE* **2012**, *7*, e40618. [[CrossRef](#)]
101. Upadhyay, S.K.; Saurabh, S.; Singh, R.; Rai, P.; Dubey, N.K.; Chandrashekar, K.; Negi, K.S.; Tuli, R.; Singh, P.K. Purification and characterization of a lectin with high hemagglutination property isolated from *Allium altaicum*. *Protein J.* **2011**, *30*, 374–383. [[CrossRef](#)]
102. Mo, H.; Van Damme, E.J.; Peumans, W.J.; Goldstein, I.J. Purification and characterization of a mannose-specific lectin from shallot (*Allium ascalonicum*) bulbs. *Arch. Biochem. Biophys.* **1993**, *306*, 431–438. [[CrossRef](#)] [[PubMed](#)]
103. Van Damme, E.J.; Smeets, K.; Engelborghs, I.; Aelbers, H.; Balzarini, J.; Pusztai, A.; van Leuven, F.; Goldstein, I.J.; Peumans, W.J. Cloning and characterization of the lectin cDNA clones from onion, shallot and leek. *Plant Mol. Biol.* **1993**, *23*, 365–376. [[CrossRef](#)] [[PubMed](#)]
104. Van Damme, E.J.; Smeets, K.; Torrekens, S.; van Leuven, F.; Goldstein, I.J.; Peumans, W.J. The closely related homomeric and heterodimeric mannose-binding lectins from garlic are encoded by one-domain and two-domain lectin genes, respectively. *Eur. J. Biochem.* **1992**, *206*, 413–420. [[CrossRef](#)] [[PubMed](#)]
105. Ooi, L.S.; Yu, H.; Chen, C.M.; Sun, S.S.; Ooi, V.E. Isolation and characterization of a bioactive mannose-binding protein from the Chinese chive *Allium tuberosum*. *J. Agric. Food Chem.* **2002**, *50*, 696–700. [[CrossRef](#)] [[PubMed](#)]
106. Van Damme, E.J.; Smeets, K.; Torrekens, S.; Van Leuven, F.; Peumans, W.J. The mannose-specific lectins from ramsons (*Allium ursinum* L.) are encoded by three sets of genes. *Eur. J. Biochem.* **1993**, *217*, 123–129. [[CrossRef](#)] [[PubMed](#)]
107. Wu, C.-F.; An, J.; He, X.-J.; Deng, J.; Hong, Z.-X.; Liu, C.; Hong-Zhou, L.; Li, Y.-J.; Wang, C.-J.; Chen, F.; Bao, J. Molecular cloning of a novel mannose-binding lectin gene from bulbs of *Amaryllis vittata* (Amaryllidaceae). *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* **2004**, *46*, 1301–1306. (In Chinese)
108. Van Damme, E.J.M.; Smeets, K.; Van Leuven, F.; Peumans, W.J. Molecular cloning of mannose-binding lectins from *Clivia miniata*. *Plant Mol. Biol.* **1994**, *24*, 825–830. [[CrossRef](#)]
109. Chai, Y.; Pang, Y.; Liao, Z.; Zhang, L.; Sun, X.; Lu, Y.; Wang, S.; Tang, K. Molecular cloning and characterization of a mannose-binding lectin gene from *Crinum asiaticum*. *J. Plant Physiol.* **2003**, *160*, 913–920. [[CrossRef](#)]
110. Van Damme, E.J.; Kaku, H.; Perini, F.; Goldstein, I.J.; Peeters, B.; Yagi, F.; Decock, B.; Peumans, W.J. Biosynthesis, primary structure and molecular cloning of snowdrop (*Galanthus nivalis* L.) lectin. *Eur. J. Biochem.* **1991**, *202*, 23–30. [[CrossRef](#)] [[PubMed](#)]
111. Kaku, H.; Van Damme, E.J.; Peumans, W.J.; Goldstein, I.J. Carbohydrate-binding specificity of the daffodil (*Narcissus pseudonarcissus*) and amaryllis (*Hippeastrum hybr.*) bulb lectins. *Arch. Biochem. Biophys.* **1990**, *279*, 298–304. [[CrossRef](#)]
112. Antoniuk, L.L.A.; Antoniuk, V.O. Interaction of immobilized lectin from *Leucojum vernum* L. with polysaccharides and glycoproteins. *Ukrainskii Biokhimicheskii Zhurnal* **1978**, *65*, 69–77. (In Ukrainian)
113. Wu, C.-F.; Li, J.; An, J.; Chang, L.-Q.; Che, F.; Bao, J.-K. Purification, biological activities, and molecular cloning of a novel mannose-binding lectin from bulbs of *Zephyranthes candida* herb (Amaryllidaceae). *J. Integr. Plant Biol.* **2006**, *48*, 223–231. [[CrossRef](#)]
114. Bao, J.; Wu, C.; An, J.; Gao, S.; Zhao, X.; Chang, L.; Rong, Y.; Wang, C.; Chen, F. Molecular cloning and analysis of a monocot mannose-binding agglutinin from *Zephyranthes grandiflora* (family Amaryllidaceae). *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* **2004**, *21*, 812–818. (In Chinese) [[PubMed](#)]

115. Liu, J.; Xu, X.; Liu, J.; Balzarini, J.; Luo, Y.; Kong, Y.; Li, J.; Chen, F.; Van Damme, E.J.; Bao, J. A novel tetrameric lectin from *Lycoris aurea* with four mannose binding sites per monomer. *Acta Biochim. Pol.* **2007**, *54*, 159–166. [[PubMed](#)]
116. Zhao, X.; Yao, J.; Sun, X.; Tang, K. Molecular cloning and characterization of a novel lectin gene from *Lycoris radiata*. *DNA Seq.* **2003**, *14*, 223–226. [[CrossRef](#)] [[PubMed](#)]
117. Ohizumi, Y.; Gaidamashvili, M.; Ohwada, S.; Matsuda, K.; Kominami, J.; Nakamura-Tsuruta, S.; Hirabayashi, J.; Naganuma, T.; Ogawa, T.; Muramoto, K. Mannose-binding lectin from yam (*Dioscorea batatas*) tubers with insecticidal properties against *Helicoverpa armigera* (Lepidoptera:Noctuidae). *J. Agric. Food Chem.* **2009**, *57*, 2896–2902. [[CrossRef](#)]
118. Sharma, M.; Vishwanathreddy, H.; Sindhura, B.R.; Kamalanathan, A.S.; Swamy, B.M.; Inamdar, S.R. Purification, characterization and biological significance of mannose binding lectin from *Dioscorea bulbifera* bulbils. *Int. J. Biol. Macromol.* **2017**, *101*, 1146–1155. [[CrossRef](#)] [[PubMed](#)]
119. Oda, Y.; Nakayama, K.; Abdul-Rahman, B.; Kinoshita, M.; Hashimoto, O.; Kawasaki, N.; Hayakawa, T.; Kakehi, K.; Tomiya, N.; Lee, Y.C. *Crocus sativus* lectin recognizes Man3GlcNAc in the N-glycan core structure. *J. Biol. Chem.* **2000**, *275*, 26772–27779. [[PubMed](#)]
120. Escribano, J.; Rubio, A.; Alvarez-Ortí, M.; Molina, A.; Fernández, J.A. Purification and characterization of a mannan-binding lectin specifically expressed in corms of saffron plant (*Crocus sativus* L.). *J. Agric. Food Chem.* **2000**, *48*, 457–463. [[CrossRef](#)]
121. Van Damme, E.J.; Astoul, C.H.; Barre, A.; Rougé, P.; Peumans, W.J. Cloning and characterization of a monocot mannose-binding lectin from *Crocus vernus* (family Iridaceae). *Eur. J. Biochem.* **2000**, *267*, 5067–5077. [[CrossRef](#)]
122. Xu, X.; Wu, C.; Liu, C.; Luo, C.; Luo, Y.; Li, J.; Zhao, X.; Van Damme, E.; Bao, J. Purification and characterization of a mannose-binding lectin from the rhizomes of *Aspidistra elatior* Blume with antiproliferative activity. *Acta Biochim. Biophys. Sin. (Shanghai)* **2007**, *39*, 507–519. [[CrossRef](#)]
123. Ooi, L.S.; Ho, W.S.; Ngai, K.L.; Tian, L.; Chan, P.K.; Sun, S.S.; Ooi, V.E. *Narcissus tazetta* lectin shows strong inhibitory effects against respiratory syncytial virus, influenza A (H1N1, H3N2, H5N1) and B viruses. *J. Biosci.* **2010**, *35*, 95–103. [[CrossRef](#)] [[PubMed](#)]
124. López, S.; Armand-Ugon, M.; Bastida, J.; Viladomat, F.; Esté, J.A.; Stewart, D.; Codina, C. Anti-human immunodeficiency virus type 1 (HIV-1) activity of lectins from *Narcissus* species. *Planta Med.* **2003**, *69*, 109–112. [[CrossRef](#)] [[PubMed](#)]
125. Van Damme, E.J.; Briké, F.; Winter, H.C.; Van Leuven, F.; Goldstein, I.J.; Peumans, W.J. Molecular cloning of two different mannose-binding lectins from tulip bulbs. *Eur. J. Biochem.* **1996**, *236*, 419–427. [[CrossRef](#)] [[PubMed](#)]
126. Ooi, L.S.; Sun, S.S.; Wang, H.; Ooi, V.E. New mannose-binding lectin isolated from the rhizome of *Sarsaparilla Smilax glabra* Roxb. (Liliaceae). *J. Agric. Food Chem.* **2004**, *52*, 6091–6095. [[CrossRef](#)] [[PubMed](#)]
127. Wright, L.M.; Wood, S.D.; Reynolds, C.D.; Rizkallah, P.J.; Peumans, W.J.; Van Damme, E.J.; Allen, A.K. Purification, crystallography and preliminary X-ray analysis of a mannose-binding lectin from bluebell (*Scilla campanulata*) bulbs. *Acta Crystallogr. D Biol. Crystallogr.* **1996**, *52*, 1021–1023. [[CrossRef](#)] [[PubMed](#)]
128. Sharma, A.; Vijayan, M. Influence of glycosidic linkage on the nature of carbohydrate binding in β -prism I fold lectins: An X-ray and molecular dynamics investigation on banana lectin-carbohydrate complexes. *Glycobiology* **2011**, *21*, 23–33. [[CrossRef](#)]
129. Singh, D.D.; Saikrishnan, K.; Kumar, P.; Surolia, A.; Sekar, K.; Vijayan, M. Unusual sugar specificity of banana lectin from *Musa paradisiaca* and its probable evolutionary origin. Crystallographic and modelling studies. *Glycobiology* **2005**, *15*, 1025–1032. [[CrossRef](#)]
130. Ooi, L.S.; Sun, S.S.; Ooi, V.E. Purification and characterization of a new antiviral protein from the leaves of *Pandanus amaryllifolius* (Pandanaeae). *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1440–1446. [[CrossRef](#)]
131. Van Damme, E.J.; Smeets, K.; Torrekens, S.; Van Leuven, F.; Peumans, W.J. Characterization and molecular cloning of mannose-binding lectins from the Orchidaceae species *Listera ovata*, *Epipactis helleborine* and *Cymbidium hybrid*. *Eur. J. Biochem.* **1994**, *221*, 769–777. [[CrossRef](#)]
132. Chen, Z.; Sun, X.; Tang, K. Cloning and expression of a novel cDNA encoding a mannose-binding lectin from *Dendrobium officinale*. *Toxicon* **2005**, *45*, 535–540. [[CrossRef](#)]

133. Liu, W.; Yang, N.; Ding, J.; Huang, R.H.; Hu, Z.; Wang, D.C. Structural mechanism governing the quaternary organization of monocot mannose-binding lectin revealed by the novel monomeric structure of an orchid lectin. *J. Biol. Chem.* **2005**, *280*, 14865–14976. [[CrossRef](#)] [[PubMed](#)]
134. Zhang, W.; Peumans, W.J.; Barre, A.; Astoul, C.H.; Rovira, P.; Rougé, P.; Proost, P.; Truffa-Bachi, P.; Jalali, A.A.; Van Damme, E.J. Isolation and characterization of a jacalin-related mannose-binding lectin from salt-stressed rice (*Oryza sativa*) plants. *Planta* **2000**, *210*, 970–978. [[PubMed](#)]
135. Do Nascimento-Neto, L.G.; Carneiro, R.F.; da Silva, S.R.; Rocha da Silva, B.; Arruda, F.V.S.; Carneiro, V.A.; do Nascimento, K.S.; Saker-Sampaio, S.; da Silva, V.A., Jr.; Figueiredo Porto, A.L.; et al. Characterization of isoforms of the lectin isolated from the red algae *Bryothamnion seaforthii* and its pro-healing effect. *Mar. Drugs* **2012**, *10*, 1936–1954. [[CrossRef](#)] [[PubMed](#)]
136. Calvete, J.J.; Costa, F.H.; Saker-Sampaio, S.; Murciano, M.P.; Nagano, C.S.; Cavada, B.S.; Grangeiro, T.B.; Ramos, M.V.; Bloch, C., Jr.; Silveira, S.B.; et al. The amino acid sequence of the agglutinin isolated from the red marine alga *Bryothamnion triquetrum* defines a novel lectin structure. *Cell Mol. Life Sci.* **2000**, *57*, 343–350. [[CrossRef](#)]
137. Hung, L.D.; Hirayama, M.; Ly, B.M.; Hori, K. Purification, primary structure, and biological activity of the high-mannose *N*-glycan-specific lectin from cultivated *Euचेuma denticulatum*. *J. Appl. Phycol.* **2015**, *27*, 1657–1669. [[CrossRef](#)]
138. Sugahara, T.; Ohama, Y.; Fukuda, A.; Hayashi, M.; Kawakubo, A.; Kato, K. The cytotoxic effect of *Euचेuma serrata* agglutinin (ESA) on cancer cells and its application to molecular probe for drug delivery system using lipid vesicles. *Cytotechnology* **2001**, *36*, 93–99. [[CrossRef](#)]
139. Mori, T.; O'Keefe, B.R.; Sowder, R.C., 2nd; Bringans, S.; Gardella, R.; Berg, S.; Cochran, P.; Turpin, J.A.; Buckheit, R.W., Jr.; McMahon, J.B.; et al. Isolation and characterization of griffithsin, a novel HIV-inactivating protein, from the red alga *Griffithsia* sp. *J. Biol. Chem.* **2005**, *280*, 9345–9353. [[CrossRef](#)]
140. Złólkowska, N.E.; O'Keefe, B.R.; Mori, T.; Zhu, C.; Giomarelli, B.; Vojdani, F.; Palmer, K.E.; McMahon, J.B.; Wlodawer, A. Domain-swapped structure of the potent antiviral protein griffithsin and its mode of carbohydrate binding. *Structure* **2006**, *14*, 1127–1138. [[CrossRef](#)]
141. Nascimento, K.S.; Nagano, C.S.; Nunes, E.V.; Rodrigues, R.F.; Goersch, G.V.; Cavada, B.S.; Calvete, J.J.; Saker-Sampaio, S.; Farias, W.R.; Sampaio, A.H. Isolation and characterization of a new agglutinin from the red marine alga *Hypnea cervicornis* J. Agardh. *Biochem. Cell Biol.* **2006**, *84*, 49–54. [[CrossRef](#)]
142. Nagano, C.S.; Moreno, F.B.; Bloch, C., Jr.; Prates, M.V.; Calvete, J.J.; Saker-Sampaio, S.; Farias, W.R.; Tavares, T.D.; Nascimento, K.S.; Grangeiro, T.B.; et al. Purification and characterization of a new lectin from the red marine alga *Hypnea musciformis*. *Protein Pept. Lett.* **2002**, *9*, 159–166. [[CrossRef](#)]
143. Sato, Y.; Morimoto, K.; Hirayama, M.; Hori, K. High mannose-specific lectin (KAA-2) from the red alga *Kappaphycus alvarezii* potently inhibits influenza virus infection in a strain-independent manner. *Biochem. Biophys. Res. Commun.* **2011**, *405*, 291–296. [[CrossRef](#)] [[PubMed](#)]
144. Hung, L.D.; Sato, Y.; Hori, K. High-mannose *N*-glycan-specific lectin from the red alga *Kappaphycus striatum* (Carrageenophyte). *Phytochemistry* **2011**, *72*, 855–861. [[CrossRef](#)] [[PubMed](#)]
145. Sato, Y.; Hirayama, M.; Morimoto, K.; Yamamoto, N.; Okuyama, S.; Hori, K. High-mannose-binding lectin with preference for the cluster of α 1-2-mannose from the green alga *Boodlea coacta* is a potent entry inhibitor of HIV-1 and influenza viruses. *J. Biol. Chem.* **2011**, *286*, 19446–19458. [[CrossRef](#)]
146. Mu, J.; Hirayama, M.; Sato, Y.; Morimoto, K.; Hori, K. A novel high-mannose specific lectin from the green alga *Halimeda renschii* exhibits a potent anti-influenza virus activity through high-affinity binding to the viral hemagglutinin. *Mar. Drugs* **2017**, *15*, 255. [[CrossRef](#)] [[PubMed](#)]
147. Wohlschlager, T.; Buttschi, A.; Grassi, P.; Sutov, G.; Gauss, R.; Hauck, D.; Schmieder, S.S.; Knobel, M.; Titz, A.; Dell, A.; et al. Methylated glycans as conserved targets of animal and fungal innate defense. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E2787–E2796. [[CrossRef](#)]
148. Sommer, R.; Makshakova, O.N.; Wohlschlager, T.; Hutin, S.; Marsh, M.; Titz, A.; Künzler, M.; Varrot, A. Crystal structure of fungal tectonin in complex with O-methylated glycans suggest key role in innate immune defense. *Structure* **2018**, *26*, 391–402. [[CrossRef](#)] [[PubMed](#)]
149. Francis, F.; Jaber, K.; Colinet, F.; Portetelle, D.; Haubruge, E. Purification of a new fungal mannose-specific lectin from *Penicillium chrysogenum* and its aphicidal properties. *Fungal Biol.* **2011**, *115*, 1093–1099. [[CrossRef](#)] [[PubMed](#)]

150. Veelders, M.; Brückner, S.; Ott, D.; Unverzagt, C.; Mösch, H.U.; Essen, L.O. Structural basis of flocculin-mediated social behavior in yeast. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 22511–22516. [[CrossRef](#)]
151. Goossens, K.V.; Ielasi, F.S.; Nookaew, I.; Stals, I.; Alonso-Sarduy, L.; Daenen, L.; Van Mulders, S.E.; Stassen, C.; van Eijsden, R.G.; Siewers, V.; et al. Molecular mechanism of flocculation self-recognition in yeast and its role in mating and survival. *MBio* **2015**, *6*, e00427-15. [[CrossRef](#)]
152. Olson, L.J.; Orsi, R.; Peterson, F.C.; Parodi, A.J.; Kim, J.J.; D'Alessio, C.; Dahms, N.M. Crystal structure and functional analyses of the lectin domain of glucosidase II: Insights into oligomannose recognition. *Biochemistry* **2015**, *54*, 4097–4111. [[CrossRef](#)]
153. Suzuki, T.; Sugiyama, K.; Hirai, H.; Ito, H.; Morita, T.; Dohra, H.; Murata, T.; Usui, T.; Tateno, H.; Hirabayashi, J.; et al. Mannose-specific lectin from the mushroom *Hygrophorus russula*. *Glycobiology* **2012**, *22*, 616–629. [[CrossRef](#)]
154. Shimokawa, M.; Fukudome, A.; Yamashita, R.; Minami, Y.; Yagi, F.; Tateno, H.; Hirabayashi, J. Characterization and cloning of GNA-like lectin from the mushroom *Marasmius oreades*. *Glycoconj. J.* **2012**, *29*, 457–465. [[CrossRef](#)] [[PubMed](#)]
155. Koharudin, L.M.; Viscomi, A.R.; Jee, J.G.; Ottonello, S.; Gronenborn, A.M. The evolutionary conserved family of cyanovirin-N homologs: Structures and carbohydrate specificity. *Structure* **2008**, *16*, 570–584. [[CrossRef](#)] [[PubMed](#)]
156. Loris, R.; Van Overberge, D.; Dao-Thi, M.H.; Poortmans, F.; Maene, N.; Wyns, L. Structural analysis of two crystal forms of lentil lectin at 1.8 Å resolution. *Proteins* **1994**, *20*, 330–346. [[CrossRef](#)] [[PubMed](#)]
157. Hardman, K.D.; Ainsworth, C.F. Structure of concanavalin A at 2.4-Å resolution. *Biochemistry* **1972**, *11*, 4910–4919. [[CrossRef](#)] [[PubMed](#)]
158. Olsen, L.R.; Dessen, A.; Gupta, D.; Sabesan, S.; Sacchettini, J.C.; Brewer, C.F. X-ray crystallographic studies of unique cross-linked lattices between four isomeric biantennary oligosaccharides and soybean agglutinin. *Biochemistry* **1997**, *36*, 15073–15080. [[CrossRef](#)] [[PubMed](#)]
159. Banerjee, R.; Das, K.; Ravishankar, R.; Suguna, K.; Surolia, A.; Vijayan, M. Conformation, protein-carbohydrate interactions and a novel subunit association in the refined structure of peanut lectin-lactose complex. *J. Mol. Biol.* **1996**, *259*, 281–296. [[CrossRef](#)]
160. Elgavish, S.; Shaanan, B. Structures of the *Erythrina corallodendron* lectin and of its complexes with mono- and disaccharides. *J. Mol. Biol.* **1998**, *277*, 917–932. [[CrossRef](#)]
161. Hamelryck, T.W.; Dao-Thi, M.H.; Poortmans, F.; Chrispeels, M.J.; Wyns, L.; Loris, R. The crystallographic structure of phytohemagglutinin-L. *J. Biol. Chem.* **1996**, *271*, 20479–20485. [[CrossRef](#)]
162. Nagae, M.; Soga, K.; Morita-Matsumoto, K.; Hanashima, S.; Ikeda, A.; Yamamoto, K.; Yamaguchi, Y. Phytohemagglutinin from *Phaseolus vulgaris* (PHA-E) displays a novel glycan recognition mode using a common legume lectin fold. *Glycobiology* **2014**, *24*, 368–378. [[CrossRef](#)] [[PubMed](#)]
163. Pratap, J.V.; Jeyaprakash, A.A.; Rani, P.G.; Sekar, K.; Surolia, A.; Vijayan, M. Crystal structure of artocarpin, a Moraceae lectin with mannose specificity, and its complex with methyl- α -D-mannose: Implications to the generation of carbohydrate specificity. *J. Mol. Biol.* **2002**, *317*, 237–247. [[CrossRef](#)] [[PubMed](#)]
164. Sankaranarayanan, R.; Sekar, K.; Banerjee, R.; Sharma, V.; Surolia, A.; Vijayan, M. A novel mode of carbohydrate recognition in jacalin, a Moraceae plant lectin with a β -prism fold. *Nat. Struct. Biol.* **1996**, *3*, 596–603. [[CrossRef](#)]
165. Lee, X.; Thompson, A.; Zhang, Z.; Ton-that, H.; Biesterfeldt, J.; Ogata, C.; Xu, L.; Johnston, R.A.; Young, N.M. Structure of the complex of *Maclura pomifera* agglutinin and the T-antigen disaccharide, Gal β 1,3GalNAc. *J. Biol. Chem.* **1998**, *273*, 6312–6318. [[CrossRef](#)]
166. Rabijns, A.; Barre, A.; Van Damme, E.J.M.; Peumans, W.J.; De Ranter, C.J.; Rougé, P. Structural analysis of the jacalin-related lectin MornigaM from the black mulberry (*Morus nigra*) in complex with mannose. *FEBS J.* **2005**, *272*, 3725–3732. [[CrossRef](#)] [[PubMed](#)]
167. Hester, G.; Kaku, H.; Goldstein, I.J.; Wright, C.S. Structure of mannose-specific snowdrop (*Galanthus nivalis*) lectin is representative of a new plant lectin family. *Nat. Struct. Biol.* **1995**, *2*, 472–479. [[CrossRef](#)] [[PubMed](#)]
168. Pereira, P.R.; Meagher, J.L.; Winter, H.C.; Goldstein, I.J.; Paschoalin, V.M.; Silva, J.T.; Stuckey, J.A. High-resolution crystal structures of *Colocasia esculenta* tarin lectin. *Glycobiology* **2017**, *27*, 50–56. [[CrossRef](#)]
169. Transue, T.R.; Smith, A.K.; Mo, H.; Goldstein, I.J.; Saper, M.A. Structure of benzyl T-antigen disaccharide bound to *Amaranthus caudatus* agglutinin. *Nat. Struct. Biol.* **1997**, *4*, 779–783. [[CrossRef](#)] [[PubMed](#)]

170. De Schutter, K.; Tsaneva, M.; Kulkarni, S.R.; Rougé, P.; Vandepoele, K.; Van Damme, E.J.M. Evolutionary relationships and expression analysis of EUL domain proteins in rice (*Oryza sativa*). *Rice* **2017**, *10*, 26. [[CrossRef](#)]
171. Sharma, U.; Katre, U.V.; Suresh, C.G. Crystal structure of a plant albumin from *Cicer arietinum* (chickpea) possessing hemopexin fold and hemagglutination activity. *Planta* **2015**, *241*, 1061–1073. [[CrossRef](#)]
172. Kostlánová, N.; Mitchell, E.P.; Lortat-Jacob, H.; Oscarson, S.; Lahmann, M.; Gilboa-Garber, N.; Chambat, G.; Wimmerová, M.; Imberty, A. The fucose-binding lectin from *Ralstonia solanacearum*. A new type of β -propeller architecture formed by oligomerization and interacting with fucoside, fucosyllactose, and plant xyloglucan. *J. Biol. Chem.* **2005**, *280*, 27839–27849. [[CrossRef](#)] [[PubMed](#)]
173. Kumar, A.; Sýkorová, P.; Demo, G.; Dobeš, P.; Hyršl, P.; Wimmerová, M. A novel fucose-binding lectin from *Photobacterium luminescens* (PPL) with an unusual heptabladed β -propeller tetrameric structure. *J. Biol. Chem.* **2016**, *291*, 25032–25049. [[CrossRef](#)] [[PubMed](#)]
174. Jančaříková, G.; Houser, J.; Dobeš, P.; Demo, G.; Hyršl, P.; Wimmerová, M. Characterization of novel bangle lectin from *Photobacterium asymbiotica* with dual sugar-binding specificity and its effect on host immunity. *PLoS Pathog.* **2017**, *13*, e1006564. [[CrossRef](#)] [[PubMed](#)]
175. Yadid, I.; Kirshenbaum, N.; Sharon, M.; Dym, O.; Tawfik, D.S. Metamorphic proteins mediate evolutionary transitions of structure. *Proc. Natl Acad. Sci. USA* **2010**, *107*, 7287–7292. [[CrossRef](#)] [[PubMed](#)]
176. Cioci, G.; Mitchell, E.P.; Chazalet, V.; Debray, H.; Oscarson, S.; Lahmann, M.; Gautier, C.; Breton, C.; Perez, S.; Imberty, A. Beta-propeller crystal structure of *Psathyrella velutina* lectin: An integrin-like fungal protein interacting with monosaccharides and calcium. *J. Mol. Biol.* **2006**, *357*, 1575–1591. [[CrossRef](#)] [[PubMed](#)]
177. Ribeiro, J.P.; Ali Abol Hassan, M.; Rouf, R.; Tiralongo, E.; May, T.W.; Day, C.J.; Imberty, A.; Tiralongo, J.; Varrot, A. Biophysical characterization and structural determination of the potent cytotoxic *Psathyrella asperospora* lectin. *Proteins* **2017**, *85*, 969–975. [[CrossRef](#)]
178. Audfray, A.; Claudinon, J.; Abounit, S.; Ruvoën-Clouet, N.; Larson, G.; Smith, D.F.; Wimmerová, M.; Le Pendu, J.; Römer, W.; Varrot, A.; et al. Fucose-binding lectin from opportunistic pathogen *Burkholderia ambifaria* binds to both plant and human oligosaccharidic epitopes. *J. Biol. Chem.* **2012**, *287*, 4335–4347. [[CrossRef](#)]
179. Shahzad-ul-Huassan, S.; Gustchina, E.; Ghirlando, R.; Clore, G.M.; Bewley, C.A. Solution structure of the monovalent lectin microvirin in complex with Man α (1-2)Man provides a basis for anti-HIV activity with low toxicity. *J. Biol. Chem.* **2011**, *286*, 20788–20796. [[CrossRef](#)]
180. Chiba, H.; Inokoshi, J.; Okamoto, M.; Matsuzaki, K.; Iwama, M.; Mizumoto, K.; Tanaka, H.; Oheda, M.; Fujita, K.; Nakashima, H.; et al. Actinohivin, a novel anti-HIV protein from an actinomycete that inhibits syncytium formation: Isolation, characterization, and biological activities. *Biochem. Biophys. Res. Commun.* **2001**, *282*, 595–601. [[CrossRef](#)] [[PubMed](#)]
181. Lameignere, E.; Malinová, L.; Sláviková, M.; Duchaud, E.; Mitchell, E.P.; Varrot, A.; Sedo, O.; Imberty, A.; Wimmerová, M. Structural basis for mannose recognition by a lectin from opportunistic bacteria *Burkholderia cenocapacia*. *Biochem. J.* **2008**, *411*, 307–318. [[CrossRef](#)] [[PubMed](#)]
182. Matei, E.; Basu, R.; Furey, W.; Shi, J.; Calnan, C.; Aiken, C.; Gronenborn, A.M. Structure and glycan binding of a new cyanovirin-N homolog. *J. Biol. Chem.* **2016**, *291*, 18967–18976. [[CrossRef](#)] [[PubMed](#)]
183. Matei, E.; Louis, J.M.; Jee, J.; Gronenborn, A.M. NMR solution structure of a cyanovirin homolog from wheat head blight fungus. *Proteins* **2011**, *79*, 1538–1549. [[CrossRef](#)] [[PubMed](#)]
184. Koharudin, L.M.I.; Furey, W.; Gronenborn, A.M. Novel fold and carbohydrate specificity of the potent anti-HIV cyanobacterial lectin from *Oscillatoria agardhii*. *J. Biol. Chem.* **2011**, *286*, 1588–1597. [[CrossRef](#)] [[PubMed](#)]
185. Williams, D.C., Jr.; Lee, J.Y.; Cai, M.; Bewley, C.A.; Clore, G.M. Crystal structures of the HIV-1 inhibitory protein MVL free and bound to Man3GlcNAc2: Structural basis for specificity and high-affinity binding to the core pentasaccharide from N-linked oligomannoside. *J. Biol. Chem.* **2005**, *280*, 29269–29276. [[CrossRef](#)] [[PubMed](#)]
186. Koharudin, L.M.; Kollipara, S.; Aiken, C.; Gronenborn, A.M. Structural insights into the anti-HIV activity of the *Oscillatoria agardhii* agglutinin homolog lectin family. *J. Biol. Chem.* **2012**, *287*, 33796–33811. [[CrossRef](#)] [[PubMed](#)]

187. Clore, G.M.; Bewley, C.A. Using conjoined rigid body torsion angle simulated annealing to determine the relative orientation of covalently linked protein domains from dipolar couplings. *J. Magn. Reson.* **2002**, *154*, 329–335. [[CrossRef](#)] [[PubMed](#)]
188. Ghequire, M.G.; Garcia-Pino, A.; Lebbe, E.K.; Spaepen, S.; Loris, R.; De Mot, R. Structural determinants for activity and specificity of the bacterial toxin LlpA. *PLoS Pathog.* **2013**, *9*, e1003199. [[CrossRef](#)] [[PubMed](#)]
189. McFeeters, R.L.; Xiong, C.; O’Keefe, B.R.; Bokesh, H.R.; McMahon, J.B.; Ratner, D.M.; Castelli, R.; Seeberger, P.H.; Byrd, R.A. The novel fold of scytovirin reveals a new twist for antiviral entry inhibitors. *J. Mol. Biol.* **2007**, *369*, 451–461. [[CrossRef](#)]
190. Boraston, A.B.; Revett, T.J.; Boraston, C.M.; Nurizzo, D.; Davies, G.J. Structural and thermodynamic dissection of specific mannan recognition by a carbohydrate binding module, TmCBM27. *Structure* **2003**, 665–675. [[CrossRef](#)]
191. Bourne, Y.; Rougé, P.; Cambillau, C. X-ray structure of a (α -Man(1-3) β -Man(1-4)GlcNAc)-lectin complex at 2.1-Å resolution. The role of water in sugar-lectin interaction. *J. Biol. Chem.* **1990**, *265*, 18161–18165. [[PubMed](#)]
192. Bourne, Y.; Rougé, P.; Cambillau, C. X-ray structure of a biantennary octasaccharide-lectin complex refined at 2.3-Å resolution. *J. Biol. Chem.* **1992**, *267*, 197–203. [[PubMed](#)]
193. Bourne, Y.; Mazurier, J.; Legrans, D.; Rougé, P.; Montreuil, J.; Spik, G.; Cambillau, C. Structure of a legume lectin complexed with the human lactotransferrin N2 fragment, and with an isolated biantennary glycopeptide: Role of the fucose moiety. *Structure* **1994**, *2*, 209–219. [[CrossRef](#)]
194. Buts, L.; Garcia-Pino, A.; Wyns, L.; Loris, R. Structural basis of carbohydrate recognition by a Man(α 1-2)Man-specific lectin from *Bowringia milbraedii*. *Glycobiology* **2006**, *16*, 635–640. [[CrossRef](#)] [[PubMed](#)]
195. Naismith, J.H.; Field, R.A. Structural basis of trimannoside recognition by concanavalin A. *J. Biol. Chem.* **1996**, *271*, 972–976. [[CrossRef](#)] [[PubMed](#)]
196. Moothoo, D.N.; Naismith, J.H. Concanavalin A distorts the β -GlcNAc-(1,2)-Man linkage of β -GlcNAc-(1,2)- α -Man-(1,3)-[β -GlcNAc-(1,2)- α -Man](1,6)-Man upon binding. *Glycobiology* **1998**, *8*, 173–181. [[CrossRef](#)] [[PubMed](#)]
197. Moothoo, D.N.; Canan, B.; Field, R.A.; Naismith, J.H. Man α 1-2Man α -OMe-concanavalin A complex reveals a balance of forces involved in carbohydrate recognition. *Glycobiology* **1999**, *9*, 539–545. [[CrossRef](#)] [[PubMed](#)]
198. Sanders, D.A.; Moothoo, D.N.; Reftery, J.; Howard, A.J.; Helliwell, J.R.; Naismith, J.H. The 1.2 Å resolution structure of the Con A-dimannose complex. *J. Mol. Biol.* **2001**, *310*, 875–884. [[CrossRef](#)]
199. Loris, R.; Maes, D.; Poortmans, F.; Wyns, L.; Bouckaert, J. A structure of the complex between concanavalin A and methyl-3,6-di-O-(α -D-mannopyranosyl)- α -D-mannopyranoside reveals two binding modes. *J. Biol. Chem.* **1996**, *271*, 30614–30618. [[CrossRef](#)]
200. Bouckaert, J.; Hamelryck, T.W.; Wyns, L.; Loris, R. The crystal structure of Man(α 1-3)Man(α 1-O)Me and Man(α 1-6)Man(α 1-O)Me in complex with concanavalin A. *J. Biol. Chem.* **1999**, *274*, 29188–29195. [[CrossRef](#)]
201. Kanellopoulos, P.N.; Pavlou, K.; Perrakis, A.; Agianian, B.; Vorgias, C.E.; Mavrommatis, C.; Soufi, M.; Tucker, P.A.; Hamodrakas, S.J. The crystal structure of the complexes of concanavalin A with 4'-nitrophenyl- α -D-mannopyranoside and 4'-nitrophenyl- α -D-glycopyranoside. *J. Struct. Biol.* **1996**, *116*, 345–355. [[CrossRef](#)]
202. Naismith, J.H.; Emmerich, C.; Habash, J.; Harrop, S.J.; Helliwell, J.R.; Hunter, W.N.; Raftery, J.; Kalb, A.J.; Yariv, J. Refined structure on concanavalin A complexed with methyl α -D-mannopyranoside at 2.0 Å resolution and comparison with the saccharide-free structure. *Acta Crystallogr. D Biol. Crystallogr.* **1994**, *50*, 847–858. [[CrossRef](#)]
203. Gerlits, O.O.; Coates, L.; Woods, R.J.; Kovalevsky, A. Mannobiose binding induces changes in hydrogen bonding and protonation states of acidic residues in concanavalin A as revealed by neutron crystallography. *Biochemistry* **2017**, *56*, 4747–4750. [[CrossRef](#)]
204. Delatorre, P.; Rocha, B.A.; Souza, E.P.; Oliveira, T.M.; Benzerra, G.A.; Moreno, F.B.; Freitas, B.T.; Santi-Gadelha, T.; Sampaio, A.H.; Azevedo, W.F., Jr.; et al. Structure of a lectin from *Canavalia gladiata* seeds: New structure insights for old molecules. *BMC Struct. Biol.* **2007**, *7*, 52. [[CrossRef](#)] [[PubMed](#)]
205. Bezerra, G.A.; Oliveira, T.M.; Moreno, F.B.; de Souza, E.P.; da Rocha, B.A.; Benevides, R.G.; Delatorre, P.; de Azevedo, W.F., Jr.; Cavada, B.S. Structural analysis of *Canavalia maritima* and *Canavalia gladiata* lectins complexed with different dimannosides: New insights into the understanding of the structure-biological activity relationship in legume lectins. *J. Struct. Biol.* **2007**, *160*, 168–176. [[CrossRef](#)] [[PubMed](#)]

206. Bourne, Y.; Roussel, A.; Frey, M.; Rougé, P.; Fontecilla-Camps, J.C.; Cambillau, C. Three-dimensional structures of Lathyrus ochrus isolectin I with glucose and mannose: Fine specificity of the monosaccharide-binding site. *Proteins* **1990**, *8*, 365–376. [[CrossRef](#)] [[PubMed](#)]
207. Pinto-Junior, V.R.; Santiago, M.Q.; Nobre, C.B.; Osterne, V.J.S.; Leal, R.B.; Cajazeiras, J.B.; Lossio, C.F.; Rocha, B.A.M.; Martins, M.G.Q.; Nobre, C.A.S.; et al. Crystal structure of *Pisum arvense* seed lectin (PAL) and characterization of its interaction with carbohydrates by molecular docking and dynamics. *Arch. Biochem. Biophys.* **2017**, *630*, 27–37. [[CrossRef](#)] [[PubMed](#)]
208. Ruzheinikov, S.N.; Mikhailova, I.Y.; Tsygannik, I.N.; Pangborn, W.; Duax, W.; Pletnev, V.Z. The structure of the pea lectin-D-mannopyranose complex at 2.1 Å resolution. *Russ. J. Bioorg. Chem.* **1998**, *24*, 277–279.
209. Rini, J.M.; Hardman, K.D.; Einspahr, H.; Suddath, F.L.; Carver, J.P. X-ray crystal structure of a pea lectin-trimannoside complex at 2.6 Å resolution. *J. Biol. Chem.* **1993**, *268*, 10126–10132.
210. Loris, R.; Van Walle, I.; De Greve, H.; Beeckmans, S.; Deboeck, F.; Wyns, L.; Bouckaert, J. Structural basis of oligomannose recognition by the *Pterocarpus angolensis* seed lectin. *J. Mol. Biol.* **2004**, *335*, 1227–1240. [[CrossRef](#)]
211. Buts, L.; Garcia-Pino, A.; Imberty, A.; Amiot, N.; Boon, G.J.; Beeckmans, S.; Versées, W.; Wyns, L.; Loris, R. Structural basis for the recognition of complex-type biantennary oligosaccharides by *Pterocarpus angolensis* lectin. *FEBS J.* **2006**, *273*, 2407–2420. [[CrossRef](#)]
212. Garcia-Pino, A.; Buts, L.; Wyns, L.; Loris, R. Interplay between metal binding and cis/trans isomerization in legume lectins: Structural and thermodynamic study of *P. angolensis* lectin. *J. Mol. Biol.* **2006**, *361*, 153–167. [[CrossRef](#)] [[PubMed](#)]
213. Garcia-Pino, A.; Buts, L.; Wyns, L.; Imberty, A.; Loris, R. How a plant lectin recognizes high mannose oligosaccharides. *Plant Physiol.* **2007**, *144*, 1733–1741. [[CrossRef](#)] [[PubMed](#)]
214. Jeyaprakash, A.A.; Srivastav, A.; Surolia, A.; Vijayan, M. Structural basis for the carbohydrate specificities of artocarpin: Variation in the length of a loop as a strategy for generating ligand specificity. *J. Mol. Biol.* **2004**, *338*, 757–770. [[CrossRef](#)] [[PubMed](#)]
215. Chandra, N.R.; Ramachandraiah, G.; Bachhawat, K.; Dam, T.K.; Surolia, A.; Vijayan, M. Crystal structure of a dimeric mannose-specific agglutinin from garlic: Quaternary association and carbohydrate specificity. *J. Mol. Biol.* **1999**, *285*, 1157–1168. [[CrossRef](#)]
216. Ramachandraiah, G.; Chandra, N.R.; Surolia, A.; Vijayan, M. Re-refinement using processed data to improve the quality of the structure: A case study involving garlic lectin. *Acta Crystallogr. D Biol. Crystallogr.* **2002**, *58*, 414–420. [[CrossRef](#)] [[PubMed](#)]
217. Wright, C.S.; Hester, G. The 2.0 Å structure of a cross-linked complex between snowdrop lectin and a branched mannopentaose: Evidence for two unique binding modes. *Structure* **1996**, *4*, 1339–1352. [[CrossRef](#)]
218. Hester, G.; Wright, C.S. The mannose-specific bulb lectin from *Galanthus nivalis* (snowdrop) binds mono- and dimannosides at distinct sites. Structure analysis of refined complexes at 2.3 Å and 3.0 Å resolution. *J. Mol. Biol.* **1996**, *262*, 516–531. [[CrossRef](#)] [[PubMed](#)]
219. Sauerborn, M.K.; Wright, L.M.; Reynolds, C.D.; Grossmann, J.G.; Rizkallah, P.J. Insights into carbohydrate recognition by *Narcissus pseudonarcissus* lectin: The crystal structure at 2 Å resolution in complex with α 1-3 mannobiose. *J. Mol. Biol.* **1999**, *290*, 185–199. [[CrossRef](#)] [[PubMed](#)]
220. Swanson, M.D.; Boudreaux, D.M.; Salmon, L.; Chugh, J.; Winter, H.C.; Meagher, J.L.; Andre, S.; Murphy, P.V.; Oscarson, S.; Roy, R.; et al. Engineering a therapeutic lectin by uncoupling mitogenicity from antiviral activity. *Cell* **2015**, *163*, 746–758. [[CrossRef](#)]
221. Nagae, M.; Mishra, S.K.; Hanashima, S.; Tateno, H.; Yamaguchi, Y. Distinct roles for each N-glycan branch interacting with mannose-binding type jacalin-related lectins Orysta and Calsepa. *Glycobiology* **2017**, *27*, 1120–1133. [[CrossRef](#)]
222. Zlólkowska, N.E.; Shenoy, S.R.; O’Keefe, B.R.; McMahon, J.B.; Palmer, K.E.; Dwek, R.A.; Wormald, M.R.; Wlodawer, A. Crystallographic, thermodynamic, and molecular modeling studies of the mode of binding of oligosaccharides to the potent antiviral protein griffithsin. *Proteins* **2007**, *67*, 661–670. [[CrossRef](#)] [[PubMed](#)]
223. Moulaei, T.; Shenoy, S.R.; Giomarelli, B.; Thomas, C.; McMahon, J.B.; Dauter, Z.; O’Keefe, B.R.; Wlodawer, A. Monomerization of viral entry inhibitor griffithsin elucidates the relationship between multivalent binding to carbohydrates and anti-HIV activity. *Structure* **2010**, *18*, 1104–1115. [[CrossRef](#)] [[PubMed](#)]

224. Zhang, F.; Hoque, M.M.; Jiang, J.; Suzuki, K.; Tsunoda, M.; Takeda, Y.; Ito, Y.; Kawai, G.; Tanaka, H.; Takenaka, A. The characteristic structure of anti-HIV actinohivin in complex with three HMTG D1 chains of HIV-gp120. *Chembiochem*. **2014**, *15*, 2766–2773. [[CrossRef](#)] [[PubMed](#)]
225. Debray, H.; Decout, D.; Strecker, G.; Spik, G.; Montreuil, J. Specificity of twelve lectins towards oligosaccharides and glycopeptides related to N-glycosylproteins. *Eur. J. Biochem.* **1981**, *117*, 41–55. [[CrossRef](#)] [[PubMed](#)]
226. Fouquaert, E.; Van Damme, E.J.M. Promiscuity of the *Euonymus* carbohydrate-binding domain. *Biomecules* **2012**, *2*, 415–434. [[CrossRef](#)] [[PubMed](#)]
227. Koharudin, L.M.; Gronenborn, A.M. Structural basis of the anti-HIV activity of the cyanobacterial *Oscillatoria agardhii* agglutinin. *Structure* **2011**, *19*, 1170–1181. [[CrossRef](#)]
228. Van Damme, E.J.M.; Smith, D.; Cummings, R.; Peumans, W.J. Glycan arrays to decipher the specificity of plant lectins. *Adv. Exp. Med. Biol.* **2011**, *705*, 757–767.
229. Hirabayashi, J.; Arata, Y.; Kasai, K. Reinforcement of frontal affinity chromatography for effective analysis of lectin-oligosaccharide interactions. *J. Chromatogr. A* **2000**, *890*, 261–271. [[CrossRef](#)]
230. Peumans, W.J.; Van Damme, E.J.M. Lectins as plant defense proteins. *Plant Physiol.* **1995**, *109*, 347–352. [[CrossRef](#)]
231. Van Damme, E.J.M.; Fouquaert, E.; Lannoo, N.; Vanderborre, G.; Schoupe, D.; Peumans, W.J. Novel concepts about the role of lectins in the plant cell. *Adv. Exp. Med. Biol.* **2011**, *705*, 271–294.
232. Sprawka, I.; Golawska, S.; Parzych, T.; Golawski, A.; Czerniewicz, P.; Sytykiewicz, H. Mechanism of entomotoxicity of the concanavalin A in *Rhopalosiphum padi* (Hemiptera: Aphididae). *J. Insect Sci.* **2014**, *14*, 232. [[CrossRef](#)] [[PubMed](#)]
233. Majumder, P.; Banerjee, S.; Das, S. Identification of receptors responsible for binding of the mannose specific lectin to the gut epithelial membrane of the target insects. *Glycoconj. J.* **2004**, *20*, 525–530. [[CrossRef](#)] [[PubMed](#)]
234. Majumder, P.; Mondal, H.A.; Das, S. Insecticidal activity of *Arum maculatum* tuber lectin and its binding to the glycosylated insect gut receptors. *J. Agric. Food Chem.* **2005**, *53*, 6725–6729. [[CrossRef](#)] [[PubMed](#)]
235. Cristofolletti, P.T.; de Sousa, F.A.; Rahbé, Y.; Terra, W.R. Characterization of a membrane-bound aminopeptidase purified from *Acyrtosiphon pisum* midgut cells. A major binding site for toxic mannose lectins. *FEBS Lett.* **2006**, *273*, 5574–5588. [[CrossRef](#)] [[PubMed](#)]
236. Fitches, E.; Wiles, D.; Douglas, A.E.; Hinchliffe, G.; Audsley, N.; Gatehouse, J.A. The insecticidal activity of recombinant garlic lectins towards aphids. *Insect Biochem. Mol. Biol.* **2008**, *38*, 905–915. [[CrossRef](#)] [[PubMed](#)]
237. Banerjee, N.; Sengupta, S.; Roy, A.; Ghosh, P.; Das, K.; Das, S. Functional anteration of a dimeric insecticidal lectin to a monomeric antifungal protein correlated to its oligomeric status. *PLoS ONE* **2011**, *6*, e18593. [[CrossRef](#)]
238. Roy, A.; Gupta, S.; Hess, D.; Das, K.P.; Das, S. Binding of insecticidal lectin *Colocasia esculenta* tuber agglutinin (CEA) to midgut receptors of *Bemisia tabaci* and *Lipaphis erysimi* provides clues to its insecticidal potential. *Proteomics* **2014**, *14*, 1646–1659. [[CrossRef](#)]
239. Down, R.E.; Gatehouse, A.M.R.; Hamilton, W.D.O.; Gatehouse, J.A. Snowdrop lectin inhibits development and decreases fecundity of the glasshouse potato aphid (*Aulacorthum solani*) when administered in vitro and via transgenic plants both in laboratory and glasshouse trials. *J. Insect Physiol.* **1996**, *42*, 1035–1045. [[CrossRef](#)]
240. Zhou, Y.; Tian, Y.; Wu, B.; Mang, K. Inhibition effect of transgenic tobacco plants expressing snowdrop lectin on the population development of *Myzus persicae*. *Chin. J. Biotechnol.* **1998**, *14*, 9–16.
241. Down, R.E.; Ford, L.; Woodhouse, S.D.; Davison, G.M.; Majerus, M.E.; Gatehouse, J.A.; Gatehouse, A.M. Tritrophic interactions between transgenic potato expressing snowdrop lectin (GNA), an aphid pest (peach-potato aphid; *Myzus persicae* (Sulz.) and a beneficial predator (2-spot ladybird; *Adalia bipunctata* L.). *Transgenic Res.* **2003**, *12*, 229–241. [[CrossRef](#)]
242. Luo, S.; Zhangsun, D.; Tang, K. Functional GNA expressed in *Escherichia coli* with high efficiency and its effect on *Ceratovacuna lanigera* Zehntner. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 184–191. [[CrossRef](#)] [[PubMed](#)]
243. Down, R.E.; Fitches, E.C.; Wiles, D.P.; Corti, P.; Bell, H.A.; Gatehouse, J.A.; Edwards, J.P. Insecticidal spider venom toxin fused to snowdrop lectin is toxic to the peach-potato aphid, *Myzus persicae* (Hemiptera: Aphidae) and the rice brown planthopper, *Nilaparvata lugens* (Hemiptera: Delphacidae). *Pest Manag. Sci.* **2006**, *62*, 77–85. [[CrossRef](#)] [[PubMed](#)]

244. Wang, Z.; Zhang, K.; Sun, X.; Tang, K.; Zhang, J. Enhancement of resistance to aphids by introducing the snowdrop lectin gene GNA into maize plants. *J. Biosci.* **2005**, *30*, 627–638. [[CrossRef](#)] [[PubMed](#)]
245. Hogervorst, P.A.; Ferry, N.; Gatehouse, A.M.; Wäckers, F.L.; Romeis, J. Direct effects of snowdrop lectin (GNA) on larvae of three aphid predators and fate of GNA after ingestion. *J. Insect Physiol.* **2006**, *52*, 614–624. [[CrossRef](#)] [[PubMed](#)]
246. Miao, J.; Wu, Y.; Xu, W.; Hu, L.; Yu, Z.; Xu, Q. The impact of transgenic wheat expressing GNA (snowdrop lectin) on the aphids *Sitobion avenae*, *Schizaphis graminum*, and *Rhopalosiphum padi*. *Environ. Entomol.* **2011**, *40*, 743–748. [[CrossRef](#)]
247. Qi, G.; Lan, N.; Ma, X.; Yu, Z.; Zhao, X. Controlling *Myzus persicae* with recombinant endophytic fungi *Chaetomium globosum* expressing *Pinellia ternata* agglutinin: Using recombinant endophytic fungi to control aphids. *J. Appl. Microbiol.* **2011**, *110*, 1314–1322. [[CrossRef](#)]
248. Xiao, Y.; Wang, K.; Ding, R.; Zhang, H.; Di, P.; Chen, J.; Zhang, L.; Chen, W. Transgenic tetraploid *Isatis indigotica* expressing Bt Cry1Ac and *Pinellia ternata* agglutinin showed enhanced resistance to moths and aphids. *Mol. Biol. Rep.* **2012**, *39*, 485–491. [[CrossRef](#)]
249. Duan, X.; Hou, Q.; Liu, G.; Pang, X.; Niu, Z.; Wang, X.; Zhang, Y.; Li, B.; Liang, R. Expression of *Pinellia pedatisecta* lectin gene in transgenic wheat enhances resistance to wheat aphids. *Molecules* **2018**, *23*, 748. [[CrossRef](#)]
250. Javaid, S.; Amin, I.; Jander, G.; Mukhtar, Z.; Saeed, N.A.; Mansoor, S. A transgenic approach to control hemipteran insects by expressing insecticidal genes under phloem-specific promoters. *Sci. Rep.* **2016**, *6*, 34706. [[CrossRef](#)]
251. Chakraborti, D.; Sarkar, A.; Mondal, H.A.; Schuermann, D.; Hohn, B.; Sarmah, B.K.; Das, S. Cre/lox system to develop selectable marker free transgenic tobacco plants conferring resistance against sap sucking homopteran insect. *Plant Cell Rep.* **2008**, *27*, 1623–1633. [[CrossRef](#)]
252. Chakraborti, D.; Sarkar, A.; Mondal, H.A.; Das, S. Tissue expression of potent insecticidal, *Allium sativum* leaf agglutinin (ASAL) in important pulse crop, chickpea (*Cicer arietinum* L.) to resist the phloem feeding *Aphis craccivora*. *Transgenic Res.* **2009**, *18*, 529–544. [[CrossRef](#)] [[PubMed](#)]
253. Sadeghi, A.; Broeders, S.; De Greve, H.; Hernalsteens, J.P.; Peumans, W.J.; Van Damme, E.J.M.; Smagghe, G. Expression of garlic leaf lectin under the control of the phloem-specific *Asus1* from *Arabidopsis thaliana* protects tobacco plants against the tobacco aphid (*Myzus nicotianae*). *Pest Manag. Sci.* **2007**, *63*, 1215–1223. [[CrossRef](#)]
254. Yao, J.; Zhao, X.; Qi, H.; Wan, B.; Chen, F.; Sun, X.; Yu, S.; Tang, K.X. Transgenic tobacco expressing an *Arisaema heterophyllum* agglutinin gene displays enhanced resistance to aphids. *Can. J. Plant Sci.* **2004**, *84*, 785–790.
255. Kai, G.; Ji, Q.; Lu, Y.; Qian, Z.; Cui, L. Expression of *Monstera deliciosa* agglutinin (MDA) in tobacco confers resistance to peach-potato aphids. *Integr. Biol.* **2012**, *4*, 937–944. [[CrossRef](#)]
256. Al Atalah, B.; Smagghe, G.; Van Damme, E.J.M. Oryzata, a jacalin-related lectin from rice, could protect plants against biting-chewing and piercing-sucking insects. *Plant Sci.* **2014**, *221–222*, 21–28. [[CrossRef](#)] [[PubMed](#)]
257. Ye, S.H.; Chen, S.; Zhang, F.; Wang, W.; Tian, Q.; Liu, J.Z.; Chen, F.; Bao, J.K. Transgenic tobacco expressing *Zephyranthes grandiflora* agglutinin confers enhanced resistance to aphids. *Appl. Biochem. Biotechnol.* **2009**, *158*, 615–630. [[CrossRef](#)] [[PubMed](#)]
258. Chang, T.; Chen, L.; Chen, S.; Cai, H.; Liu, X.; Xiao, G.; Zhu, Z. Transformation of tobacco with genes encoding *Helianthus tuberosus* agglutinin (HTA) confers resistance to peach-potato aphid (*Myzus persicae*). *Transgenic Res.* **2003**, *12*, 607–614. [[CrossRef](#)]
259. Sauvion, N.; Nardon, C.; Febvay, G.; Gatehouse, A.M.; Rahbé, Y. Binding of the insecticidal lectin concanavalin A in pea aphid, *Acyrtosiphon pisum* (Harris) and induced effects on the structure of midgut epithelial cells. *J. Insect Physiol.* **2004**, *50*, 1137–1150. [[CrossRef](#)]
260. Shahidi-Noghabi, S.; Van Damme, E.J.; Mahdian, K.; Smagghe, G. Entomotoxic action of *Sambucus nigra* agglutinin I in *Acyrtosiphon pisum* aphids and *Spodoptera exigua* caterpillars through caspase-3-like-dependent apoptosis. *Arch. Insect. Biochem. Physiol.* **2010**, *75*, 207–220. [[CrossRef](#)]
261. Van Damme, E.J.M.; Barre, A.; Rougé, P.; Peumans, W.J. Cytoplasmic/nuclear plant lectins: A new story. *Trends Plant Sci.* **2004**, *9*, 484–489. [[CrossRef](#)]

262. Lannoo, N.; Van Damme, E.J.M. Nucleocytoplasmic plant lectins. *Biochim. Biophys. Acta* **2010**, *1800*, 190–201. [[CrossRef](#)] [[PubMed](#)]
263. Delporte, A.; Van Holle, S.; Lannoo, N.; Van Damme, E.J.M. The tobacco lectin, prototype of the family of Nictaba-related proteins. *Curr. Protein Pept. Sci.* **2015**, *16*, 5–16. [[CrossRef](#)] [[PubMed](#)]
264. Van Holle, S.; Rougé, P.; Van Damme, E.J.M. Evolution and structural diversification of Nictaba-like genes in food crops with focus on soybean (*Glycine max*). *Ann. Bot.* **2017**, *119*, 901–914. [[PubMed](#)]
265. Fouquaert, E.; Peumans, W.J.; Vandekerckhove, T.T.M.; Ongenaert, M.; Van Damme, E.J.M. Proteins with an *Euonymus*-like domain are ubiquitous in embryophyta. *BMC Plant Biol.* **2009**, *9*, 136. [[CrossRef](#)]
266. Esch, L.; Schaffrath, U. An update on jacalin-like lectins and their role in plant defense. *Int. J. Mol. Sci.* **2017**, *18*, 1592. [[CrossRef](#)] [[PubMed](#)]
267. Lannoo, N.; Peumans, W.J.; Pamel, E.V.; Alvarez, R.; Xiong, T.C.; Hause, G.; Mazars, C.; Van Damme, E.J.M. Localization and in vitro binding studies suggest that the cytoplasmic/nuclear tobacco lectin can interact in situ with high mannose and complex *N*-glycans. *FEBS Lett.* **2006**, *580*, 6329–6337. [[CrossRef](#)] [[PubMed](#)]
268. Al Atalah, B.; Fouquaert, E.; Vanderschaeghe, D.; Proost, P.; Balzarini, J.; Smith, D.F.; Rougé, P.; Lasanajak, Y.; Callewaert, N.; Van Damme, E.J.M. Expression analysis of the nucleocytoplasmic lectin ‘Orysata’ from rice in *Pichia pastoris*. *FEBS J.* **2011**, *278*, 2064–2079. [[CrossRef](#)] [[PubMed](#)]
269. Al Atalah, B.; Vanderschaeghe, D.; Bloch, Y.; Proost, P.; Plas, K.; Callewaert, N.; Savvides, S.N.; Van Damme, E.J.M. Characterization of a type D1A EUL-related lectin from rice expressed in *Pichia pastoris*. *Biol. Chem.* **2014**, *395*, 413–424. [[CrossRef](#)] [[PubMed](#)]
270. Van Holle, S.; Van Damme, E.J.M. Signaling through plant lectins: Modulation of plant immunity and beyond. *Biochem. Soc. Trans.* **2018**, *46*, 217–233. [[CrossRef](#)] [[PubMed](#)]
271. Van Hove, J.; De Jaeger, G.; De Winne, N.; Guisez, Y.; Van Damme, E.J.M. The *Arabidopsis* lectin EULS3 is involved in stomatal closure. *Plant Sci.* **2015**, *238*, 312–322. [[CrossRef](#)] [[PubMed](#)]
272. Van Holle, S.; Smagghe, G.; Van Damme, E.J.M. Overexpression of Nictaba-like lectin genes from *Glycine max* confers tolerance toward *Pseudomonas syringae* infection, aphid infestation and salt stress in transgenic *Arabidopsis* plants. *Front. Plant Sci.* **2016**, *7*, 1590. [[CrossRef](#)] [[PubMed](#)]
273. Eggermont, L.; Stefanowicz, K.; Van Damme, E.J.M. Nictaba homologs from *Arabidopsis thaliana* are involved in plant stress responses. *Front. Plant Sci.* **2018**, *8*, 2218. [[CrossRef](#)] [[PubMed](#)]
274. Stewart-Jones, G.B.; Soto, C.; Lemmin, T.; Chuang, G.Y.; Druz, A.; Kong, R.; Thomas, P.V.; Wagh, K.; Zhou, T.; Behrens, A.J.; et al. Trimeric HIV-en structures define glycan shields from clades A, B, and G. *Cell* **2016**, *165*, 813–826. [[CrossRef](#)] [[PubMed](#)]
275. Lifson, J.; Coutré, S.; Huang, E.; Engleman, E. Role of envelope glycoprotein carbohydrate in human immunodeficiency virus (HIV) infectivity and virus-induced cell fusion. *J. Exp. Med.* **1986**, *164*, 2101–2106. [[CrossRef](#)] [[PubMed](#)]
276. Robinson, W.E., Jr.; Montefiori, D.C.; Mitchell, W.M. Evidence that mannosyl residues are involved in human immunodeficiency virus type 1 (HIV-1) pathogenesis. *AIDS Res. Hum. Retrovir.* **1987**, *3*, 165–182. [[CrossRef](#)] [[PubMed](#)]
277. Müller, W.E.; Renneisen, K.; Kreuter, M.H.; Schröder, H.C.; Winkler, I. The D-mannose-specific lectin from *Gerardia savaglia* blocks binding to human immunodeficiency virus type I to H9 cells and human lymphocytes in vitro. *J. Acquir. Immune Defic. Syndr.* **1988**, *1*, 453–458. [[PubMed](#)]
278. Hansen, J.E.; Nielsen, C.M.; Nielsen, C.; Heegaard, P.; Mathiesen, L.R.; Nielsen, J.O. Correlation between carbohydrate structures on the envelope glycoprotein gp120 of HIV-1 and HIV-2 and syncytium inhibition with lectins. *AIDS* **1989**, *3*, 635–641. [[CrossRef](#)]
279. Hammar, L.; Eriksson, S.; Morein, B. Human immunodeficiency virus glycoproteins: Lectin binding properties. *AIDS Res. Hum. Retrovir.* **1989**, *5*, 495–506. [[CrossRef](#)]
280. Houlès Astoul, C.; Peumans, W.J.; Van Damme, E.J.M.; Rougé, P. Accessibility of the high-mannose glycans of glycoprotein gp120 from human immunodeficiency virus type 1 probed by in vitro interaction with mannose-binding lectins. *Biochem. Biophys. Res. Commun.* **2000**, *274*, 455–460. [[CrossRef](#)]
281. Boyd, M.R.; Gustafson, K.R.; McMahan, J.B.; Shoemaker, R.H.; O’Keefe, B.R.; Mori, T.; Gulakowski, R.J.; Wu, L.; Rivera, M.I.; Laurencot, C.M.; et al. Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: Potential applications to microbicide development. *Antimicrob. Agents Chemother.* **1997**, *41*, 1521–1530. [[CrossRef](#)]

282. Dey, B.; Lerner, D.L.; Lusso, P.; Boyd, M.R.; Elder, J.H.; Berger, E.A. Multiple antiviral activities of cyanovirin-N: Blocking of human immunodeficiency virus type 1 gp120 interaction with CD4 and coreceptor and inhibition of diverse enveloped viruses. *J. Virol.* **2000**, *74*, 4562–4569. [[CrossRef](#)] [[PubMed](#)]
283. Bewley, C.A.; Cai, M.; Ray, S.; Ghirlando, R.; Yamaguchi, M.; Muramoto, K. New carbohydrate specificity and HIV-1 fusion blocking activity of the cyanobacterial protein MVL: NMR, ITC and sedimentation equilibrium studies. *J. Mol. Biol.* **2004**, *339*, 901–914. [[CrossRef](#)] [[PubMed](#)]
284. Férirn, G.; Huskens, D.; Noppen, S.; Koharudin, L.M.; Gronenborn, A.M.; Schols, D. Broad anti-HIV activity of the *Oscillatoria agardhii* agglutinin homologue lectin family. *J. Antimicrob. Chemother.* **2014**, *69*, 2746–2758. [[CrossRef](#)] [[PubMed](#)]
285. Bokesch, H.R.; O'Keefe, B.R.; McKee, T.C.; Pannell, L.K.; Patterson, G.M.; Gardella, R.S.; Sowder, R.C., 2nd; Turpin, J.; Watson, K.; Buckheit, R.W., Jr.; et al. A potent novel anti-HIV protein from the cultured cyanobacterium *Scytonema varium*. *Biochemistry* **2003**, *42*, 2578–2584. [[CrossRef](#)]
286. Robinson, J.E.; Holton, D.; Liu, J.; McMurdo, H.; Murciano, A.; Gohd, R. A novel enzyme-linked immunosorbent assay (ELISA) for the detection of antibodies to HIV-1 envelope glycoproteins based on immobilization of viral glycoproteins in microtiter wells coated with concanavalin A. *J. Immunol. Methods* **1990**, *132*, 63–71. [[CrossRef](#)]
287. Gattegno, L.; Ramdani, A.; Jouault, T.; Saffar, L.; Gluckman, J.C. Lectin-carbohydrate interactions and infectivity of human immunodeficiency virus type 1 (HIV-1). *AIDS Res. Hum. Retrovir.* **1992**, *8*, 27–37. [[CrossRef](#)] [[PubMed](#)]
288. Hart, T.K.; Klinkner, A.M.; Ventre, J.; Bugelski, P.J. Morphometric analysis of envelope glycoprotein gp120 distribution on HIV-1 virions. *J. Histochem. Cytochem.* **1993**, *41*, 265–271. [[CrossRef](#)]
289. Pal, R.; DeVico, A.; Rittenhouse, S.; Sarngadharan, M.G. Conformational perturbation of the envelope glycoprotein gp120 of human immunodeficiency virus type 1 by soluble CD4 and the lectin succinyl Con A. *Virology* **1993**, *194*, 833–837. [[CrossRef](#)]
290. Yeh, J.C.; Seals, J.R.; Murphy, C.I.; van Halbeek, H.; Cummings, R.D. Site-specific N-glycosylation and oligosaccharide structures of recombinant HIV-1 gp120 derived from a baculovirus expression system. *Biochemistry* **1993**, *32*, 11087–11099. [[CrossRef](#)]
291. Gram, G.J.; Hemming, A.; Bolmstedt, A.; Jansson, B.; Olofsson, S.; Akerblom, L.; Nielsen, J.O.; Hansen, J.E. Identification of an N-linked glycan in the V1-loop of HIV-1 gp120 influencing neutralization by anti-V3 antibodies and soluble CD4. *Arch. Virol.* **1994**, *139*, 253–261. [[CrossRef](#)]
292. Gu, J.J.; Harriss, J.V.; Ozato, K.; Gottlieb, P.D. Induction by concanavalin A of specific mRNAs and cytolytic function in a CD8-positive T cell hybridoma. *J. Immunol.* **1994**, *153*, 4408–4417. [[PubMed](#)]
293. Akashi, M.; Niikawa, T.; Serizawa, T.; Hayakawa, T.; Baba, M. Capture of HIV-1 gp120 and virions by lectin-immobilized polystyrene nanospheres. *Bioconj. Chem.* **1998**, *9*, 50–53. [[CrossRef](#)] [[PubMed](#)]
294. Hayakawa, T.; Kawamura, M.; Okamoto, M.; Baba, M.; Niikawa, T.; Takehara, S.; Serizawa, T.; Akashi, M. Concanavalin A-immobilized polystyrene nanospheres capture HIV-1 virions and gp120: Potential approach towards prevention of viral transmission. *J. Med. Virol.* **1998**, *56*, 327–331. [[CrossRef](#)]
295. No, T.B.; Chan, Y.S.; Ng, C.C.; Wong, J.H. Purification and characterization of a lectin from green split peas (*Pisum sativum*). *Appl. Biochem. Biotechnol.* **2015**, *177*, 1374–1385.
296. Balzarini, J.; Neyts, J.; Schols, D.; Hosoya, M.; Van Damme, E.; Peumans, W.; De Clercq, E. The mannose-specific lectins from *Cymbidium* hybrid and *Epipactis helleborine* and the (N-acetylglucosamine)n-specific plant lectin from *Urtica dioica* are potent and selective inhibitors of human immunodeficiency virus and cytomegalovirus replication in vitro. *Antivir. Res.* **1992**, *18*, 191–207. [[PubMed](#)]
297. Balzarini, J.; Schols, D.; Neyts, J.; Van Damme, E.; Peumans, W.J.; De Clercq, E. α -(1-3)- and α -(1-6)-D-mannose-specific plant lectins are markedly inhibitory to human immunodeficiency virus and cytomegalovirus infections in vitro. *Antimicrob. Agents Chemother.* **1991**, *35*, 410–416. [[CrossRef](#)] [[PubMed](#)]
298. Mahmood, N.; Hay, A.J. An ELISA utilizing immobilized snowdrop lectin GNA for the detection of envelope glycoproteins of HIV and SIV. *J. Immunol. Methods* **1992**, *151*, 9–13. [[CrossRef](#)]
299. Gilljam, G. Envelope glycoproteins of HIV-1, HIV-2, and SIV purified with *Galanthus nivalis* agglutinin induce strong immune responses. *AIDS Res. Hum. Retrovir.* **1993**, *9*, 431–438. [[CrossRef](#)]
300. Hammar, L.; Hirsch, I.; Machado, A.; De Mareuil, J.; Baillon, J.; Chermann, J.C. Lectin effects on HIV-1 infectivity. *Ann. N. Y. Acad. Sci.* **1994**, *724*, 166–169. [[CrossRef](#)]

301. Hammar, L.; Hirsch, I.; Machado, A.A.; De Mareuil, J.; Baillon, J.G.; Bolmont, C.; Chermann, J.C. Lectin-mediated effects on HIV type 1 infection *in vitro*. *AIDS Res. Hum. Retroviruses* **1995**, *11*, 87–95. [[CrossRef](#)]
302. Balzarini, J.; Hatse, S.; Vermeire, K.; Princen, K.; Aquaro, S.; Perno, C.-F.; De Clercq, E.; Egberink, H.; Vanden Mooter, G.; Peumans, W.; et al. Mannose-specific plant lectins from the amaryllidaceae family qualify as efficient microbicides for prevention of human immunodeficiency virus infection. *Antimicrob. Agents Chemother.* **2004**, *48*, 3858–3870. [[CrossRef](#)] [[PubMed](#)]
303. Weiler, B.E.; Schröder, H.C.; Stefanovich, V.; Stewart, D.; Forrest, J.M.; Allen, L.B.; Bowden, B.J.; Kreuter, M.H.; Voth, R.; Müller, W.E. Sulphoevernan, a polyanionic polysaccharide, and narcissus lectin potently inhibit human immunodeficiency virus infection by binding to viral envelope protein. *J. Gen. Virol.* **1990**, *71*, 1957–1963. [[CrossRef](#)] [[PubMed](#)]
304. Gao, Z.; Zheng, B.; Wang, W.; Li, Q.; Yuan, Q. Cloning and functional characterization of a GNA-like lectin from Chinese narcissus (*Narcissus tazetta* var. *Chinensis* Roem). *Physiol. Plant.* **2011**, *142*, 193–204. [[CrossRef](#)] [[PubMed](#)]
305. An, J.; Liu, J.Z.; Wu, C.F.; Li, J.; Dai, L.; Van Damme, E.; Balzarini, J.; De Clercq, E.; Chen, F.; Bao, J.K. Anti-HIV I/II activity and molecular cloning of a novel mannose/sialic acid-binding lectin from rhizome of *Polygonatum cyrtoneuma* Hua. *Acta Biochim. Biophys. Sin. (Shanghai)* **2006**, *38*, 70–78. [[CrossRef](#)] [[PubMed](#)]
306. Swanson, M.D.; Winter, H.C.; Goldstein, I.J.; Markovitz, D.M. A lectin isolated from bananas is a potent inhibitor of HIV replication. *J. Biol. Chem.* **2010**, *285*, 8646–8655. [[CrossRef](#)] [[PubMed](#)]
307. Hoorelbeke, B.; Van Damme, E.J.; Rougé, P.; Schols, D.; Van Laethem, K.; Fouquaert, E.; Balzarini, J. Differences in the mannose oligomer specificities of the closely related lectins from *Galanthus nivalis* and *Zea mays* strongly determine their eventual anti-HIV activity. *Retrovirology* **2011**, *8*, 10. [[CrossRef](#)] [[PubMed](#)]
308. Huang, X.; Jin, W.; Griffin, G.E.; Shattock, R.J.; Hu, Q. Removal of two high-mannose N-linked glycans on gp120 renders human immunodeficiency virus 1 largely resistant to the carbohydrate-binding agent griffithsin. *J. Gen. Virol.* **2011**, *92*, 2367–2373. [[CrossRef](#)]
309. Hirahyama, M.; Shibata, H.; Imamura, K.; Sakaguchi, T.; Hori, K. High-mannose specific lectin and its recombinants from a carrageenophyta *Kappaphycus alvarezii* represent a potent anti-HIV activity through high-affinity binding to the viral envelope glycoprotein gp120. *Mar. Biotechnol.* **2016**, *18*, 215–231. [[CrossRef](#)]
310. Witvrouw, M.; Fikkert, V.; Hantson, A.; Pannecouque, C.; O’Keefe, B.R.; McMahon, J.; Stamatatos, L.; de Clercq, E.; Bolmstedt, A. Resistance of human immunodeficiency virus type 1 to the high-mannose binding agents cyanovirin N and concanavalin A. *J. Virol.* **2005**, *79*, 7777–7784. [[CrossRef](#)]
311. Balzarini, J.; Van Laethem, K.; Peumans, W.J.; Van Damme, E.J.; Bolmstedt, A.; Gago, F.; Schols, D. Mutational pathways, resistance profile, and side effects of cyanovirin relative to human immunodeficiency virus type 1 strains with N-glycan deletions in their gp120 envelopes. *J. Virol.* **2006**, *80*, 8411–8421. [[CrossRef](#)]
312. Balzarini, J.; Van Laethem, K.; Hatse, S.; Vermeire, K.; De Clercq, E.; Peumans, W.; Van Damme, E.; Vandamme, A.-M.; Böhlstedt, A.; Schols, D. Profile of resistance of human immunodeficiency virus to mannose-specific plant lectins. *J. Virol.* **2004**, *78*, 10617–10627. [[CrossRef](#)] [[PubMed](#)]
313. Pancera, M.; Zhou, T.; Druz, A.; Georgiev, I.S.; Soto, C.; Gorman, J.; Huang, J.; Acharya, P.; Chuang, G.-Y.; Ofek, G.; et al. Structure and immune recognition of trimeric prefusion HIV1 Env. *Nature* **2014**, *514*, 455–461. [[CrossRef](#)] [[PubMed](#)]
314. Balzarini, J.; Van Laethem, K.; Hatse, S.; Froeyen, M.; Peumans, W.; Van Damme, E.; Schols, D. Carbohydrate-binding agents cause deletions of highly conserved glycosylation sites in HIV gp120: A new therapeutic concept to hit the Achilles heel of HIV. *J. Biol. Chem.* **2005**, *280*, 41005–41014. [[CrossRef](#)] [[PubMed](#)]
315. Balzarini, J.; Van Laethem, K.; Hatse, S.; Froeyen, M.; Van Damme, E.; Bolmstedt, A.; Peumans, W.; De Clercq, E.; Schols, D. Marked depletion of glycosylation sites of HIV-1 gp120 under selective pressure by the mannose-specific plant lectins of *Hippeastrum* hybrid. and *Galanthus nivalis*. *Mol. Pharmacol.* **2005**, *67*, 1556–1565. [[CrossRef](#)] [[PubMed](#)]
316. Balzarini, J. Carbohydrate-binding agents: A potential future cornerstone for the chemotherapy of enveloped viruses? *Antivir. Chem. Chemother.* **2007**, *18*, 1–11. [[CrossRef](#)] [[PubMed](#)]
317. Balzarini, J. The $\alpha(1,2)$ -mannosidase I inhibitor 1-deoxymannojirimycin potentiates the antiviral activity of carbohydrate-binding agents against wild-type and mutant HIV-1 strains containing glycan deletions in gp120. *FEBS Lett.* **2007**, *581*, 2060–2064. [[CrossRef](#)] [[PubMed](#)]

318. Férir, G.; Huskens, D.; Palmer, K.E.; Boudreaux, D.M.; Swanson, M.D.; Markovitz, D.M.; Balzarini, J.; Schols, D. Combinations of griffithsin with other carbohydrate-binding agents demonstrate superior activity against HIV type 1, HIV type 2, and selected carbohydrate-binding agent-resistant HIV type 1 strains. *AIDS Res. Hum. Retrovir.* **2012**, *28*, 1513–1523. [[CrossRef](#)] [[PubMed](#)]
319. Lam, Y.W.; Ng, T.B. A monomeric mannose-binding lectin from inner sheaths of the edible chive (*Allium tuberosum*). *J. Protein Chem.* **2001**, *20*, 361–366. [[CrossRef](#)]
320. Wang, H.X.; Ng, T.B. Examination of lectins, polysaccharopeptide, polysaccharide, alkaloid, coumarin and trypsin inhibitors for inhibitory activity against human immunodeficiency virus reverse transcriptase and glycohydrolases. *Planta Med.* **2001**, *67*, 669–672. [[CrossRef](#)]
321. Pollicita, M.; Schols, D.; Aquaro, S.; Peumans, W.J.; Van Damme, E.J.; Perno, C.F.; Balzarini, J. Carbohydrate-binding agents (CBAs) inhibit HIV-1 infection in human primary monocyte-derived macrophages (MDMs) and efficiently prevent MDM-directed viral capture and subsequent transmission to CD4+ T lymphocytes. *Virology* **2008**, *370*, 382–391. [[CrossRef](#)]
322. Alexandre, K.B.; Gray, E.S.; Mufhandu, H.; McMahon, J.B.; Chakauya, E.; O’Keefe, B.R.; Chikwamba, R.; Morris, L. The lectins griffithsin, cyanovirin-N and scytovirin inhibit HIV-1 binding to the DC-SIGN receptor and transfer to CD4(+) cells. *Virology* **2012**, *423*, 175–186. [[CrossRef](#)] [[PubMed](#)]
323. Hoorelbeke, B.; Xue, J.; LiWang, P.J.; Balzarini, J. Role of the carbohydrate-binding sites of griffithsin in the prevention of DC-SIGN-mediated capture and transmission of HIV-1. *PLoS ONE* **2013**, *8*, e64132. [[CrossRef](#)] [[PubMed](#)]
324. Mitchell, C.A.; Ramessar, K.; O’Keefe, B.R. Antiviral lectins: Selective inhibitors of viral entry. *Antivir. Res.* **2017**, *142*, 37–54. [[CrossRef](#)] [[PubMed](#)]
325. Lafont, V.; Dornand, J.; Covassin, L.; Liautard, J.P.; Favero, J. The lectin jacalin triggers CD4-mediated lymphocyte signaling by binding CD4 through a protein-protein interaction. *J. Leukoc. Biol.* **1996**, *59*, 691–696. [[CrossRef](#)] [[PubMed](#)]
326. Gordts, S.C.; Renders, M.; Férir, G.; Huskens, D.; Van Damme, E.J.; Peumans, W.; Balzarini, J.; Schols, D. NICTABA and UDA, two GlcNAc-binding lectins with unique antiviral activity profiles. *J. Antimicrob. Chemother.* **2015**, *70*, 1674–1685. [[CrossRef](#)]
327. Poiroux, G.; Barre, A.; Van Damme, E.J.M.; Benoist, H.; Rougé, P. Plant lectins targeting O-glycans at the cell surface as tools for cancer diagnosis, prognosis and therapy. *Int. J. Mol. Sci.* **2017**, *18*, 1232. [[CrossRef](#)] [[PubMed](#)]
328. Li, W.W.; Yu, J.Y.; Xu, H.L.; Bao, J.K. Concanavalin A: A potential anti-neoplastic agent targeting apoptosis, autophagy and anti-angiogenesis for cancer therapeutics. *Biochem. Biophys. Res. Commun.* **2011**, *414*, 282–286. [[CrossRef](#)] [[PubMed](#)]
329. Wu, L.; Bao, J.K. Anti-tumor and anti-viral activities of *Galanthus nivalis* agglutinin (GNA)-related lectins. *Glycoconj. J.* **2013**, *30*, 269–279. [[CrossRef](#)]
330. Jiang, Q.L.; Zhang, S.; Tian, M.; Zhang, S.Y.; Xie, T.; Chen, D.Y.; Chen, Y.J.; He, J.; Liu, J.; Ouyang, L.; et al. Plant lectins, from ancient sugar-binding proteins to emerging anti-cancer drugs in apoptosis and autophagy. *Cell Prolif.* **2015**, *48*, 17–28. [[CrossRef](#)]
331. Islam, F.; Gopalan, V.; Lam, A.K.; Kabir, S.R. Pea lectin inhibits cell growth by inducing apoptosis in SW480 and SW48 cell lines. *Int. J. Biol. Macromol.* **2018**, *117*, 1050–1057. [[CrossRef](#)]
332. Kabir, S.R.; Nabi, M.M.; Hague, A.; Uz Zaman, R.; Mahmud, Z.H.; Reza, M.A. Pea lectin inhibits growth of Ehrlich ascites carcinoma cells by inducing apoptosis and G2/M cell cycle arrest *in vivo* in mice. *Phytomedicine* **2013**, *20*, 1288–1296. [[CrossRef](#)] [[PubMed](#)]
333. Asaduzzaman, A.K.M.; Hasan, I.; Chakraborty, A.; Zaman, S.; Islam, S.S.; Ahmed, F.R.S.; Kabir, K.M.A.; Nurujjaman, M.; Uddin, M.B.; Alam, M.T.; et al. *Moringa oleifera* seed lectin inhibits Ehrlich ascites carcinoma cell growth by inducing apoptosis through the regulation of Bak and NF- κ B gene expression. *Int. J. Biol. Macromol.* **2018**, *107*, 1936–1944. [[CrossRef](#)] [[PubMed](#)]
334. De Andrade Luz, L.; Rossato, F.A.; Costa, R.A.P.E.; Napoleão, T.H.; Paiva, P.M.G.; Coelho, L.C.B.B. Cytotoxicity of the coagulant *Moringa oleifera* lectin (cMOL) to B16-F10 melanoma cells. *Toxicol In Vitro* **2017**, *44*, 94–99. [[CrossRef](#)] [[PubMed](#)]
335. Gondim, A.C.S.; Romero-Canelón, I.; Sousa, E.H.S.; Blindauer, C.A.; Butler, J.S.; Romero, M.J.; Sanchez-Cano, C.; Sousa, B.L.; Chaves, R.P.; Nagano, C.S.; et al. The potent anti-cancer activity of *Dioclea lasiocarpa* lectin. *J. Inorg. Biochem.* **2017**, *175*, 179–189. [[CrossRef](#)] [[PubMed](#)]

336. Luan, V.V.; Qian, Y.; Ni, X.; Chandra, T.K.; Xia, Y.; Wang, J.; Yan, Y.; Xu, B. *Polygonatum odoratum* lectin promotes *BECN1* expression and induces autophagy in malignant melanoma by regulation of miR1290. *OncoTargets Ther.* **2017**, *10*, 4569–4577. [[CrossRef](#)] [[PubMed](#)]
337. Wu, L.; Liu, T.; Xiao, Y.; Li, X.; Zhu, Y.; Zhao, Y.; Bao, J.; Wu, C. *Polygonatum odoratum* lectin induces apoptosis and autophagy by regulation of microRNA-1290 and microRNA-15a-3p in human lung adenocarcinoma A549 cells. *Int. J. Biol. Macromol.* **2016**, *85*, 217–226. [[CrossRef](#)] [[PubMed](#)]
338. Ouyang, L.; Chen, Y.; Wang, X.Y.; Lu, R.F.; Zhang, S.Y.; Tian, M.; Xie, T.; Liu, B.; He, G. *Polygonatum odoratum* lectin induces apoptosis and autophagy via targeting EGFR-mediated Ras-Raf-MEK-ERK pathway in human MCF-7 breast cancer cells. *Phytomedicine* **2014**, *21*, 1658–1665. [[CrossRef](#)] [[PubMed](#)]
339. Li, C.; Chen, J.; Lu, B.; Shi, Z.; Wang, H.; Zhang, B.; Zhao, K.; Qi, W.; Bao, J.; Wang, Y. Molecular switch of Akt in *Polygonatum odoratum* lectin-induced apoptosis and autophagy in human non-small cell lung cancer A549 cells. *PLoS ONE* **2014**, *9*, e101526. [[CrossRef](#)]
340. Liu, B.; Zhang, B.; Min, M.W.; Bian, H.J.; Chen, L.F.; Liu, Q.; Bao, J.K. Induction of apoptosis by *Polygonatum odoratum* lectin and its molecular mechanisms in murine fibrosarcoma L929 cells. *Biochim. Biophys. Acta* **2009**, *1790*, 840–844. [[CrossRef](#)]
341. Naik, S.; Rawat, R.S.; Khandai, S.; Kumar, M.; Jena, S.S.; Vijayalakshmi, M.A.; Kumar, S. Biochemical characterisation of lectin from Indian hyacinth plant bulbs with potential inhibitory action against human cancer cells. *Int. J. Biol. Macromol.* **2017**, *105*, 1349–1356. [[CrossRef](#)]
342. Sindhura, B.R.; Hegde, P.; Chachadi, V.B.; Inamdhar, S.R.; Swamy, B.M. High mannose *N*-glycan binding lectin from *Remusatia vivipara* (RVL) limits cell growth, motility and invasiveness of human breast cancer cells. *Biomed. Pharmacother.* **2017**, *93*, 654–665. [[CrossRef](#)] [[PubMed](#)]
343. Liu, T.; Wu, L.; Wang, D.; Wang, H.; Chen, J.; Yang, C.; Bao, J.; Wu, C. Role of reactive oxygen species-mediated MAPK and NF- κ B activation in *Polygonatum cyrtonema* lectin-induced apoptosis and autophagy in human lung carcinoma A549 cells. *J. Biochem.* **2016**, *160*, 315–324. [[CrossRef](#)] [[PubMed](#)]
344. Liu, B.; Wu, J.M.; Li, J.; Liu, J.J.; Li, W.W.; Li, C.Y.; Xu, H.L.; Bao, J.K. *Polygonatum cyrtonema* lectin induces murine fibrosarcoma L929 cell apoptosis and autophagy via blocking Ras-Raf and PI3K-Akt signaling pathways. *Biochimie* **2010**, *92*, 1934–1938. [[CrossRef](#)] [[PubMed](#)]
345. Liu, B.; Cheng, Y.; Bian, H.J.; Bao, J.K. Molecular mechanisms of *Polygonatum cyrtonema* lectin-induced apoptosis and autophagy in cancer cells. *Autophagy* **2009**, *5*, 253–255. [[CrossRef](#)] [[PubMed](#)]
346. Liu, B.; Cheng, Y.; Zhang, B.; Bian, H.J.; Bao, J.K. *Polygonatum cyrtonema* lectin induces apoptosis and autophagy in human melanoma A375 cells through a mitochondria-mediated ROS-p38-p53 pathway. *Cancer Lett.* **2009**, *275*, 54–60. [[CrossRef](#)]
347. Feng, L.X.; Sun, P.; Mi, T.; Liu, M.; Liu, W.; Yao, S.; Cao, Y.M.; Yu, X.L.; Wu, W.Y.; Jiang, B.H.; et al. Agglutinin isolated from *Arisema heterophyllum* Blume induces apoptosis and autophagy in A549 cells through inhibiting PI3K:Akt pathway and inducing ER stress. *Clin. J. Nat. Med.* **2016**, *14*, 856–864.
348. Chan, Y.S.; Yu, H.; Xia, L.; Ng, T.B. Lectin from green speckled lentil seeds (*Lens culinaris*) triggered apoptosis in nasopharyngeal carcinoma cell lines. *Chin. Med.* **2015**, *10*, 25. [[CrossRef](#)]
349. Kumar, S.; Jitendra, K.; Singh, K.; Kappor, V.; Sinha, M.; Xess, I.; Das, S.N.; Sharma, S.; Singh, T.P.; Dey, S. Biological properties and characterization of ASL50 protein from aged *Allium sativum* bulbs. *Appl. Biochem. Biotechnol.* **2015**, *176*, 1914–1927. [[CrossRef](#)]
350. Shi, Z.; Chen, J.; Li, C.Y.; An, N.; Wang, Z.J.; Yang, S.L.; Huang, K.E.; Bao, J.K. Antitumor effects of concanavalin A and *Sophora flavescens* lectin *in vitro* and *in vivo*. *Acta Pharmacol. Sin.* **2014**, *35*, 248–256. [[CrossRef](#)]
351. Faheina-Martins, G.V.; da Silveira, A.L.; Cavalcanti, B.C.; Ramos, M.V.; Moraes, M.O.; Pessoa, C.; Araújo, D.A. Antiproliferative effects of lectins from *Canavalia ensiformis* and *Canavalia brasiliensis* in human leukemia cell lines. *Toxicol. In Vitro* **2012**, *26*, 1161–1169. [[CrossRef](#)]
352. Pratt, J.; Roy, R.; Annabi, B. Concanavalin-A-induced autophagy biomarkers requires membrane type-1 metalloproteinase intracellular signaling in glioblastoma cells. *Glycobiology* **2012**, *22*, 1245–1255. [[CrossRef](#)] [[PubMed](#)]
353. Amin, A.R.; Thakur, V.S.; Gupta, K.; Jackson, M.W.; Harada, H.; Agarwal, M.K.; Shin, D.M.; Wald, D.N.; Agarwal, M.L. Restoration of p53 functions protects cells from concanavalin A-induced apoptosis. *Mol. Cancer Ther.* **2010**, *9*, 471–479. [[CrossRef](#)]

354. Liu, B.; Min, M.W.; Bao, J.K. Induction of apoptosis by concanavalin A and its molecular mechanisms in cancer cells. *Autophagy* **2009**, *5*, 432–433. [[CrossRef](#)] [[PubMed](#)]
355. Silva, F.O.; Santos, P.N.; Figueirôa, E.O.; de Melo, C.M.; de Andrade Lemoine Neves, J.K.; Arruda, F.V.; Cajazeiras, J.B.; do Nascimento, K.S.; Teixeira, E.H.; Cavada, B.S.; et al. Antiproliferative effect of *Canavalia brasiliensis* lectin on B16F10 cells. *Res. Vet. Sci.* **2014**, *96*, 276–282. [[CrossRef](#)] [[PubMed](#)]
356. Zhou, W.; Gao, Y.; Xu, S.; Yang, Z.; Xu, T. Purification of a mannose-binding lectin *Pinellia ternata* agglutinin and its induction of apoptosis in Bel-7404 cells. *Protein Expr. Purif.* **2014**, *93*, 11–17. [[CrossRef](#)] [[PubMed](#)]
357. Hayashi, K.; Walde, P.; Miyazaki, T.; Sakayama, K.; Nakamura, A.; Kameda, K.; Masuda, S.; Umakoshi, H.; Kato, K. Active targeting to osteosarcoma cells and apoptotic cell death induction by the novel lectin *Eucheuma serra* agglutinin isolated from a marine red alga. *J. Drug Deliv.* **2012**, *2012*, 842785. [[CrossRef](#)] [[PubMed](#)]
358. Fukuda, Y.; Sugahara, T.; Ueno, M.; Fukuta, Y.; Ochi, Y.; Akiyama, K.; Miyazaki, T.; Masuda, S.; Kawakubo, A.; Kato, K. The anti-tumor effect of *Eucheuma serra* agglutinin on colon cancer cells in vitro and in vivo. *Anticancer Drugs* **2006**, *17*, 943–947. [[CrossRef](#)] [[PubMed](#)]
359. Yau, T.; Dan, X.; Ng, C.C.W.; Ng, T.B. Lectins with potential for anti-cancer therapy. *Molecules* **2015**, *20*, 3791–3810. [[CrossRef](#)] [[PubMed](#)]
360. Estrada-Martínez, L.E.; Moreno-Celis, U.; Cervantes-Jiménez, R.; Ferriz-Martínez, R.A.; Blanco-Labra, A.; García-Gasca, T. Plant lectins as medical tools against digestive system cancers. *Int. J. Mol. Sci.* **2017**, *18*, 1403. [[CrossRef](#)] [[PubMed](#)]
361. Lagarda-Dias, I.; Guzman-Partida, A.M.; Vazquez-Moreno, L. Legume lectins: Proteins with diverse applications. *Int. J. Mol. Sci.* **2017**, *18*, 1242. [[CrossRef](#)] [[PubMed](#)]
362. Poiroux, G.; Barre, A.; Rougé, P.; Benoist, H. Targeting glycosylation aberrations to improve the efficiency of cancer phototherapy. *Curr. Cancer Drug Targets* **2018**. [[CrossRef](#)] [[PubMed](#)]
363. François, K.O.; Balzarini, J. Potential of carbohydrate-binding agents as therapeutics against enveloped viruses. *Mol. Res. Rev.* **2012**, *32*, 349–387. [[CrossRef](#)] [[PubMed](#)]
364. Mahalingam, A.; Geonnotti, A.R.; Balzarini, J.; Kiser, P.F. Activity and safety of synthetic lectins based on benzoboroxole-functionalized polymers for inhibition of HIV entry. *Mol. Pharm.* **2011**, *8*, 2465–2475. [[CrossRef](#)] [[PubMed](#)]



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