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REVIEW ARTICLE

Algal lectins as promising biomolecules for biomedical research

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Abstract

Lectins are natural bioactive ubiquitous proteins or glycoproteins of non-immune response that bind reversibly to glycans of glycoproteins, glycolipids and polysaccharides possessing at least one non-catalytic domain causing agglutination. Some of them consist of several carbohydrate-binding domains which endow them with the properties of cell agglutination or precipitation of glycoconjugates. Lectins are rampant in nature from plants, animals and microorganisms. Among microorganisms, algae are the potent source of lectins with unique properties specifically from red algae. The demand of peculiar and neoteric biologically active substances has intensified the developments on isolation and biomedical applications of new algal lectins. Comprehensively, algal lectins are used in biomedical research for antiviral, antinociceptive, anti-inflammatory, anti-tumor activities, etc. and in pharmaceutics for the fabrication of cost-effective protein expression systems and nutraceutics. In this review, an attempt has been made to collate the information on various biomedical applications of algal lectins.

Keywords

Anti-HIV, antinociceptive, biomedical applications, cytokines, glycoproteins

History

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Introduction

Lectins are proteins/glycoproteins of non-immune origin that bind non-covalently and reversibly to aposing cells bearing specific sugars culminating their agglutination (Singh et al., 2011a). Stillmark (1888) enunciated first lectin (then called hemagglutinin) from seeds of *Ricinus communis*. After that thousands of lectins have been isolated from different sources including plant seeds and roots, bacteria, algae, fungi, body fluid of invertebrates, lower vertebrates and mammalian cell membranes (Singh et al., 1999). They are type cast with respect to carbohydrate-binding specificity, molecular structure, biochemical and biomedical properties. Among microbes, occurrence of lectins has been widely reported from algae and mushrooms (Singh et al., 2010).

Algae are amidst the most diverse organisms in the plant kingdom. They are photosynthetic, mainly aquatic organisms, devoid of vascular tissues, true roots, stems, leaves and possess simple reproductive structures. According to the latest system of classification based on ultra structure of the plastid, algae are classified into four groups which are further subdivided into eight divisions (Lee, 1999): group 1 – prokaryotic algae containing division (1) Cyanophyta; group 2 – eucaryotic algae containing divisions (2) Glaucophyta, (3) Rhodophyta, (4) Chlorophyta; group 3 – eucaryotic algae containing divisions (5) Euglenophyta and (6) Dinophyta; group 4 – eucaryotic algae containing division (7) Heterokontophyta and (8) Pyrmnesiophyta.

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The presence of agglutinins in marine algae was firstly reported by Boyd et al. (1966). Later on, lectins have been reported from a large number of algae. Algal lectins are generally referred to as phycolectins (Matsubara et al., 1996; Rogers et al., 1977) and they differ from plant lectins in a variety of physico-chemical characteristics. In general, marine algal lectins are monomeric, low molecular weight proteins, exhibiting high content of acidic amino acids, with isoelectric point (pI) in the range of 4–6, do not require metal ions for their biological activities and most of them show specificity for glycoproteins than monosaccharides (Hori et al., 1990; Rogers & Hori, 1993; Shiomi et al., 1981). Based on the binding properties to glycoproteins, algal lectins are categorized into three major categories, complex type *N*-glycan specific lectins, high mannose (HM) type *N*-glycan specific lectins and lectins with specificity to both the above types of *N*-glycans (Hori et al., 1990). Mannose binding lectins are considered essential as they interplay with cell-surface glycoconjugates. Due to their small size and presence of disulphide linkages, algal lectins are antigenic and highly stable. Furthermore, the peculiar small structure of algal lectins makes them more expedient for use as specific molecular diagnostic probes against the cell surface carbohydrates and in drug targeting (Nascimento et al., 2006). Recently, algal lectins have received greater attention due to their robust oligosaccharide-binding specificity (Okuyama et al., 2009).

Lectins are the most versatile group of proteins used in biological and biomedical research. They posses enormous potential as they play a major role in cell–cell recognition (Singh et al., 2011b) and are widely used in drug delivery

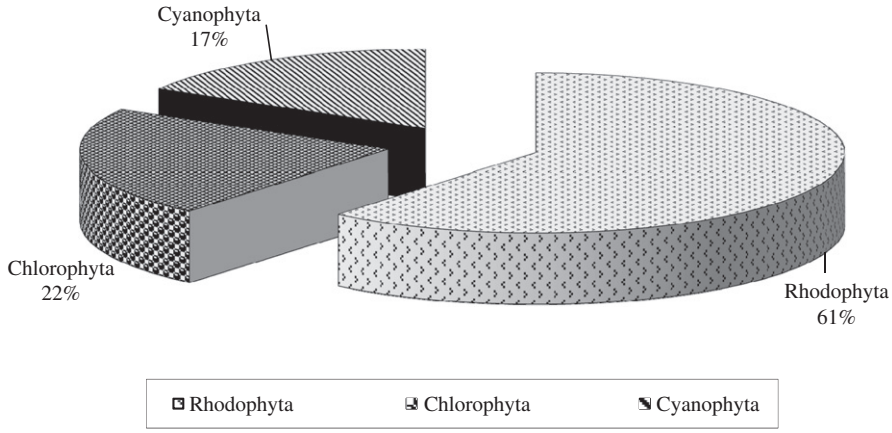

Figure 1. Distribution of biomedically important lectins in algae.

(Singh et al., 1999). Algal lectins have various biomedical properties such as anti-tumor, anti-HIV, anti-inflammatory, anti-fungal, anti-microbial, etc. (Nascimento et al., 2012; Swamy, 2011; Teixeira et al., 2012). The occurrence of biomedically important lectins among various divisions of algae is represented in Figure 1.

Biological action spectrum of biomedically important algal lectins

Lectins have the property of adherence to sugars on cell-membranes, thereby reforming the physiology of membrane which leads to agglutination and other biochemical changes in cells (Neves et al., 2007). Algal lectins have been detected using animal erythrocytes as well as human blood type erythrocytes. The susceptibility of erythrocytes to certain lectins increases upon mild treatment with proteolytic enzymes which leads to exposure of cryptic residues present on erythrocytes surface (Sharon & Lis, 1972). The biological action spectrum of biomedically important algal lectins is summarized in Table 1.

Animal erythrocytes especially from sheep and rabbit have been reported to be more suitable for lectin detection in marine algae than human erythrocytes (Freitas et al., 1997). The extracts of *Microcystis viridis* induced agglutination in hen, rabbit and horse erythrocytes, but no agglutination has been reported with human erythrocytes (Yamaguchi et al., 1999). Hori et al. (1988) screened a plethora of marine algae for hemagglutinins. They concluded that marine algal agglutinins are most sensitive to protease treated sheep erythrocytes followed by native rabbit and sheep erythrocytes, but not to human and chicken red blood cells. *Caulerpa cupressoides* lectin agglutinated trypsin treated sheep, rabbit and chicken erythrocytes (Ainouz & Sampaio, 1991). Lectin activity increased significantly when rabbit red blood cells were treated with trypsin, bromelain, papain and subtilisin, but chicken erythrocytes treated with only bromelain showed agglutination (Freitas et al., 1997). *Serraticardia maxima* lectin has been reported to agglutinate native, trypsin and papain treated erythrocytes of horse, cow, sheep, rabbit, guinea pig, mouse and chicken. Non-treated horse erythrocytes were most agglutinated, while non-treated cow erythrocytes were least agglutinated (Shiomi et al., 1980). Lectin from *Ulva rigida* promoted agglutination of sheep and rabbit erythrocytes (Bird et al., 1993), whereas lectin from *Ulva pertusa* specifically agglutinated rabbit erythrocytes (Wang et al., 2004).

Bryothamnion seaforthii lectin has been found to agglutinate both native and trypsin treated rabbit as well as trypsin treated chicken and cow erythrocytes (Ainouz & Sampaio 1991; Ainouz et al., 1995; Vieira et al., 2004). Lectin from *Bryothamnion triquetrum* has been shown to agglutinate enzyme treated erythrocytes from rabbit, chicken, goat and pig (Ainouz et al., 1992). Sheep and rabbit erythrocytes were found sensitive to *Gracilaria* sp. lectin (Bird et al., 1993; Chiles & Bird, 1990), while extracts from *Eucheuma serra* agglutinated both native and trypsin treated sheep erythrocytes as well as trypsin treated rabbit erythrocytes (Kawakubo et al., 1997). Trypsin treated rabbit and chicken erythrocytes were sensitive to crude extract of red algae *Gracilaria ornata,* whereas no agglutination has been reported against native and trypsin treated human erythrocytes (Leite et al., 2005). The extract of *Oscillatoria agardhii* agglutinated both trypsin treated red blood cells of rabbit and pronase treated erythrocytes of sheep (Sato et al., 2000; Sato & Hori, 2009).

The agglutination of blood type A, B and O erythrocytes occurs due to robust binding of lectins to the *N*-acetyl-D-galactosamine, D-galactose and L-fucose moieties, respectively present on their surface (Khan et al., 2002). The extracts of *Chlorella* sp. I, *Chlorella* sp. 21 and *Chlorella* sp. W have been reported to agglutinate blood type A, B and O erythrocytes (Chu et al., 2007). When native erythrocytes were used, both the crude extract and pure lectin of *Ptilota plumosa* was found to be specific towards human blood group B erythrocytes. After papain treatment, only the pure lectin showed blood type B specificity, whereas the crude extract also showed low agglutination with blood group A and O erythrocytes (Sampaio et al., 2002). Human A-type specific agglutinating activity has been reported from *Bryopsis plumosa* (Jung et al., 2010). Native, trypsin and bromelain treated erythrocytes from mouse, chicken and humans were used to determine the blood specificity of *Bryopsis hypnoides* lectin. The lectin exhibited a preference for trypsin treated human blood group O and chicken erythrocytes (Niu et al., 2009). Enzyme treated erythrocytes of human ABO blood type were agglutinated by *B. triquetrum* (Ainouz et al., 1992).

Table 1. Biological action spectrum of biomedically important algal lectins.

Algae	Hemagglutination activity													Reference(s)
	Animal erythrocytes									Human erythrocytes				
	Sheep	Rabbit	Chicken	Rat	Horse	Goat	Pig	Cow	Mouse	A	B	AB	O	
Blue-green algae														
Chlorella sp.I	−	ND	ND	ND	ND	ND	−	−	ND	+	+	ND	+	Chu et al. (2007)
Chlorella sp. 21	+	ND	ND	ND	ND	ND	+	+	ND	+	+	ND	+	Chu et al. (2007)
Chlorella sp.W	−	ND	ND	ND	ND	ND	+	−	ND	+	+	ND	+	Chu et al. (2007)
Microcystis aeruginosa	ND	+	ND	ND	+	ND	ND	ND	ND	+	+	ND	+	Yamaguchi et al. (1998)
Microcystis aeruginosa	+	+	ND	+	ND	ND	ND	ND	+	+	−	ND	+	Watanabe et al. (1987)
M. viridis[a]	ND	+	ND	ND	+	ND	ND	ND	ND	−	−	ND	−	Yamaguchi et al. (1999)
Oscillatoria agardhii	H[a]	H[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Sato et al. (2000)
Green algae														
Boodlea coacta	ND	H[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Hori et al. (1986)
Bryopsis hypnoides	ND	ND	H[b]	ND	ND	ND	ND	ND	−	−	−	−	H[b]	Niu et al. (2009)
B. pennata	−	H[b]	H[b]	ND	ND	−	ND	H[b]	ND	−	H[b]	H[b]	H[b]	Ainouz & Sampaio (1991)
B. plumosa	+	ND	ND	ND	+	ND	ND	ND	ND	−	−	ND	−	Han et al. (2010)
	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	ND	ND	ND	Jung et al. (2010)
Caulerpa cupressoides	H[b]	H[b]	H[b]	ND	ND	−	ND	H[b]	ND	H[b]	H[b]	H[b]	H[b]	Ainouz & Sampaio (1991)
	−	H[d]	H[c]	ND	ND	ND	ND	ND	ND	H[d]	H[d]	ND	H[d]	Freitas et al. (1997)
	ND	H[b]	ND	ND	ND	ND	ND	ND	ND	H[b]	H[b]	ND	H[b]	Benevides et al. (2001)
Ulva pertusa	ND	+	−	ND	ND	ND	ND	ND	ND	−	−	ND	−	Wang et al. (2004)
U. rigida	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bird et al. (1993)
Red algae														
Bryothamnion seaforthii	−	H[b]	H[b]	ND	ND	−	ND	H[b]	ND	−	−	−	−	Ainouz & Sampaio (1991)
B. triquetrum	ND	H[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Ainouz et al. (1995)
Eucheuma serra	+	H[b]	ND	ND	−	ND	ND	ND	ND	ND	ND	ND	ND	Kawakubo et al. (1997)
	H[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Kawakubo et al. (1999)
Gracilaria cervicornis	−	H[b]	H[b]	ND	ND	−	ND	−	ND	−	−	−	−	Ainouz & Sampaio (1991)
G. cornea	−	−	H[b]	ND	ND	−	ND	−	ND	−	−	−	−	Ainouz & Sampaio (1991)
G. ornata	ND	H[b]	H[b]	ND	ND	ND	ND	ND	ND	−	−	ND	−	Leite et al. (2005)
G. tikvahiae	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bird et al. (1993)
	+	+	ND	ND	ND	ND	ND	ND	ND	+	+	ND	−	Chiles & Bird (1990)
G. tikvahiae G-3	+	+	ND	ND	ND	ND	ND	ND	ND	+	+	ND	+	Chiles & Bird (1989)
G. tikvahiae McLachlan (NC)	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bird et al. (1993)
G. verrucosa[b,c]	H[e]	−	H[b]	ND	ND	ND	ND	ND	ND	−	−	ND	−	Freitas et al. (1997)
	+	+	+	+	+	ND	+	+	ND	ND	ND	ND	ND	Kakita et al. (1999)
	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bird et al. (1993)
	+	+	+	ND	+	ND	ND	+	ND	ND	ND	ND	ND	Shiomi et al. (1981)
G. verrucosa G-16 S	+	+	ND	ND	ND	ND	ND	ND	ND	+	+	ND	−	Chiles & Bird (1989)
Hypnea cervicornis	−	H[b]	−	ND	ND	−	ND	H[b]	ND	−	−	−	−	Ainouz & Sampaio (1991)
H. japonica	+	+	+	ND	+	ND	ND	ND	ND	+	+	ND	+	Hori et al. (1986)
H. musciformis	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bird et al. (1993)
	H[b]	H[b]	−	ND	ND	−	ND	H[b]	ND	H[b]	H[b]	H[b]	H[b]	Ainouz & Sampaio (1991)
Kappaphycus alvarezii	H[g]	H[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Hung et al. (2009)
K. striatum	+	H[g]	−	ND	ND	ND	ND	ND	ND	−	−	ND	−	Hung et al. (2011)
Ptilota plumosa	ND	ND	ND	ND	ND	ND	ND	ND	ND	H[f]	+	ND	H[f]	Sampaio et al. (2002)
P. serrata	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	+	ND	+	Sampaio et al. (1999)
Serraticardia maxima[b]	H[h]	H[h]	H[h]	ND	H[h]	ND	ND	H[h]	H[h]	ND	ND	ND	ND	Shiomi et al. (1980)
Solieria robusta	ND	H[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Matsubara et al. (1996)
Tichocarpus crinitus	ND	+	ND	+	ND	ND	ND	ND	ND	+	+	ND	+	Molchanova et al. (2010)
	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	Chernikov et al. (2007)

+: positive haemagglutination; −: no haemagglutination; ND: haemagglutination not determined.
[a]Haemagglutination activity also with hen erythrocytes.
[b]Haemagglutination activity also with guinea pig erythrocytes.
[c]Haemagglutination activity also with carp erythrocytes.
[d]Haemagglutination activity also with goose erythrocytes.
H[a]: haemagglutination activity with pronase treated erythrocytes.
H[b]: haemagglutination activity with trypsin treated erythrocytes.
H[c]: haemagglutination activity with bromelain treated erythrocytes.
H[d]: haemagglutination activity with native, trypsin, bromelain, papain and subtilisin treated erythrocytes.
H[e]: haemagglutination activity with bromelain and papian treated erythrocytes.
H[f]: haemagglutination activity with native and papain treated erythrocytes.
H[g]: haemagglutination activity with native, trypsin and papain treated erythrocytes.
H[h]: haemagglutination activity with native, trypsin and protease treated erythrocytes.

Characteristics of biomedically important algal lectins

The binding specificity of lectins is established by the shape of binding site and the amino-acid residues to which the carbohydrate is linked. Alterations in the binding site can essentially change their specificity. Algal lectins display a considerable repertoire of carbohydrate specificities and physico-chemical characteristics. The carbohydrate specificity and characteristics profile of biomedically important algal lectins is summarized in Table 2. Most of the red algal lectins have high content of acidic and hydroxyl amino acids, but lower levels of basic amino acids. They have low molecular weight, show high affinity to glycoproteins and do not require divalent cations for their biological activity (Hori et al., 1990; Okamoto et al., 1990; Rogers & Hori, 1993; Sampaio et al., 1999).

Lectin (OAA) from *Oscillatoria agardhii* belongs to a new lectin family NIES-204 and arrayed high binding specificity for high-mannose *N*-glycans and gp120 (envelope protein of HIV) in picomolar range (Sato & Hori, 2009). Lectin (MVL) isolated from *M. viridis* shown inhibition activity with yeast mannan, whereas lectin (SVN) from *Scytonema varium* shown the specificity for $Man_8GlcNAc_2$/$Man_9GlcNAc_2$ (Li et al., 2008; Yamaguchi et al., 1999). Cyanovirin-N (CV-N) lectin of 11 kDa from *Nostoc ellipsosporum* showed specificity towards $Man_9GlcNAc_2$ (Ziolkowska & Wlodawer, 2006). The structural integrity of CV-N lectin has been reported to be highly resistant to degradation upon treatment with detergents, organic solvents, freezing and heating up to 100 °C (Boyd et al., 1997).

Green algae lectin isolated from *Bryopsis hypnoides* shown specificity for *N*-acetyl glucosamine, *N*-acetyl galactosamine and bovine submaxillary mucin and was of 27 kDa having pI 5–6 (Niu et al., 2009). The lectin was stable in a pH range of 4–8 and does not require metal ions for hemagglutination activity. The lectin from *U. pertusa* exhibited carbohydrate content of 1.2% with molecular weight of 23 kDa, thermal stability up to 70 °C for 30 min and carbohydrate specificities for *N*-acetyl-D-glucosamine and bovine thyroglobulin (Wang et al., 2004). *C. cupressoides* lectin (CcL) displayed specificity for simple sugars like raffinose, lactose, galactose and fructose, derivatives of galactose and porcine stomach mucin. The molecular weight of the lectin was 44.7 kDa and it had carbohydrate content of 11.05% (Benevides et al., 2001; Freitas et al., 1997).

The three isolectins isolated from *Kappaphycus alvarezii* revealed their monomeric nature, having molecular weight of 28 kDa and moreover, displayed affinity for glycoproteins bearing high-mannose *N*-glycans (Hung et al., 2011). Lectin KAA-2 shared physico-chemical properties with ESA-2 lectin from *E. serra* (Sato et al., 2011a). Small-sized (9 kDa) isolectins (hypnin A1, A2, A3) from *Hypnea japonica* belonged to a new lectin family and showed no affinity for monosaccharides. These isolectins have been reported to bind only to core (α1-6) fucosylated *N*-gycans which makes them a valuable tool for cancer diagnosis and quality control of medicinal antibodies (Okuyama et al., 2009). Amansia lectin of 26.9 kDa isolated from *Amansia multifida* contained 2.9% neutral carbohydrates and showed specificity for avidin (Costa et al., 1999; Neves et al., 2007). *Tichocarpus crinitus* lectin (TCL) is an acidic glycoprotein with pI 4.93, containing 6.9% carbohydrate content and its amino acid content revealed the presence of aspartic acid and glutamic acid residues (Molchanova et al., 2010). Thermostable fetuin, avidin and mucin specific lectins have been reported from *B. seaforthii* and *B. triquetrum* with molecular weight of 4.5 kDa and 3.5 kDa, respectively (Ainouz et al., 1995). The sugar inhibition studies on lectins having molecular weight 41 kDa and 25 kDa purified from *S. maxima* and *Gracilaria verrucosa*, respectively, revealed that both are not inhibited by simple sugars (Shiomi et al., 1980; 1981).

Biomedical applications of algal lectins

Several bioactivities have been attributed to algal lectins which include anti-inflammatory, anti-adhesion, anti-HIV, antinociceptive, antibiotic, mitogenic and human platelet aggregation inhibition activities (Harnedy & FitzGerald, 2011). The ability of these lectins to stimulate lymphocytes as well as other cells has made them important tools for experiments and diagnostics. Biomedical potential of various algal lectins is depicted in Figure 2. The most abeyant biomedical applications of algal lectins are summarized in Table 3.

Antinociceptive

A wide variety of mephitic stimuli are known to bring about powerful inhibition of pain sensation at a remote region of body; nociceptors are sensitized by tissue injury and inflammation. Kurihara et al. (2003) reported that primary nociceptor which is known as hyperalgesia in humans and nociception in animal models, which is common for all inflammatory pain types. Currently, opioids and non-steroidal anti-inflammatory drugs are used as analgesic. But due to their side-effects and low potency there is a need for an alternative. Therefore, the hunt for new compounds for controlling pain and inflammation with low side effects has switched to marine algae. Specific binding of lectins with carbohydrates acts an integral part of host defense system. This has opened up a new component of the immune system with both fundamental and practical implications (Ahmadiani et al., 1998; Vanderlei et al., 2010).

Antinociceptive effect of lectins from marine alga *A. multifida*, *B. seaforthii* and *B. triquetrum* has been reported both at central and peripheral levels of the nervous system (Neves et al., 2007; Viana et al., 2002). *A. multifida* lecin (Amansin/LEC) has also been indicated as a potential analgesic drug (Neves et al., 2007). Agglutinin from *Hypnea cervicornis* (HCA) showed antinociceptive activity via interaction of the lectin carbohydrate-binding site. Lectin HCA was able to reduce writhings which suggests inhibition of the release of mediators in response to acetic acid. But formalin-induced nociception suggested that inflammatory pain is mainly responsible for antinociceptive effect; however, the hot plate test postulated peripheral acting mechanism of antinociception (Bitencourt et al., 2008). Significant antinociceptive effects have also been demonstrated by *Chlorella stigmatophora* and *Phaeodactylum tricornutum* lectins which

Table 2. Characteristics of biomedically important algal lectins.

Algae	Inhibitory sugars/Glycoproteins*	Lectin characteristics	Reference(s)
Blue-green algae			
Microcystis aeruginosa	*N*-acetyl-D-galactosamine	Monomer, M_r 57 kDa, pI 6.4, rich in Asx & Arg, carbohydrate content 7.8%	Yamaguchi et al. (1998)
M. viridis	Yeast mannan, oligomannosides such as $Man_9GlcNAc_2$	Homodimer in solution, 113 amino acid residues, M_r 13 kDa, pH stability 5–8	Yamaguchi et al. (1999); Ziolkowska & Wlodawer (2006)
Nostoc ellipsosporum	$Man_9GlcNAc_2$	Monomer, M_r 11 kDa, 101 amino acid residues	Boyd et al. (1997); Ziolkowska & Wlodawer (2006)
Oscillatoria agardhii	High-mannose (HM)-type *N*-glycans	M_r 13.9 kDa, belongs to new lectin family NIES-204	Sato et al. (2007)
Scytonema varium	$Man_8GlcNAc_2/Man_9GlcNAc_2$, α (1–2), α (1–6)Man	Monomeric, M_r 9.7 kDa, 95 amino acid residues	Li et al. (2008); Ziolkowska & Wlodawer (2006)
Green algae			
Boodlea coacta	High-mannose *N*-glycans	M_r 13.8 kDa	Sato et al. (2011b)
Bryopsis hypnoides	*N*-acetyl galactosamine, *N*-acetyl glucosamine, bovine submaxillary mucin	M_r 27 kDa, pI∼5–6, pH stability 4–10, hemagglutination activity independent of divalent cations	Niu et al. (2009)
B. plumosa	D-mannose, α-methyl-D-mannose, L-fucose *N*-acetyl-D-galactosamine, *N*-acetyl-D-glucosamine	Monomer, M_r 17 kDa, pI 7.3, hemagglutination activity independent of divalent cations, thermal stability upto 70 °C for 30 min	Han et al. (2010)
Caulerpa cupressoides	Raffinose, lactose, galactose and fructose, derivatives of galactose, porcine stomach mucin	Homodimer, M_r 44.7 kDa, carbohydrate content 11.05%	Freitas et al. (1997); Vanderlei et al. (2010)
Ulva pertusa	*N*-acetyl-D-glucosamine, bovine thyroglobulin	M_r 23 kDa, pH stability 6–8, thermal stability upto 70 °C for 30 min, hemagglutination activity dependent on divalent cations, carbohydrate content 1.2%	Wang et al. (2004)
Red algae			
Amansia multifida	Avidin	Monomer, M_r 26.9 kDa, carbohydrate content 2.9%	Neves et al. (2007)
Bryothamnion seaforthii	Feutin, avidin, mucin	Monomeric, M_r 4.5 kDa, hemagglutination activity independent of divalent cations, thermal stability upto 90 °C for 30 min	Ainouz et al. (1995)
B. triquetrum	Feutin, avidin, mucin	Monomeric, M_r 3.5 kDa, 91 amino acid residues, hemagglutination activity independent of divalent cations, thermal stability upto 90 °C for 30 min	Ainouz et al. (1995); Calvete et al. (2000)
Eucheuma serra	Yeast mannan, IgM (mouse), tyroglobulin, high-mannose (HM)-type *N*-glycans	Monomeric, M_r 29 kDa, pH stability 2.5–10.5, pI 4.95, thermal stability upto 60 °C for 1 h, no carbohydrate content	Kawakubo et al. (1997)
Gracilaria cornea	Feutin, porcine stomach mucin	Monomeric, M_r 60 kDa, pI 4.3, hemagglutination activity independent of divalent cations, thermal stability upto 40 °C for 20 min, carbohydrate content 52.5%	Lima et al. (2005)
G. ornata	Porcine stomach mucin, lactotransferrin, asialofetuin, bovine & porcine thyroglobulins	Monomeric, M_r 17 kDa, pI 5.4, rich in Asx, Glx, Ser, Glu, Ala, Cys, thermal stability upto 50 °C for 60 min, carbohydrate content 2.9%	Leite et al. (2005)
G. tikvahiae	*N*-acetylneuraminic acid, glycoconjugates containing *N*-acetylneuraminic acid	M_r 29.7 kDa, hemagglutination activity independent of divalent cations	Chiles & Bird (1990)
G. verrucosa	No inhibition activity with simple sugars	Tetramer, M_r 41 kDa, subunit M_r 12 kDa & M_r 10.5 kDa, pH 4–12, pI 4.8, hemagglutination activity independent of divalent cations, thermal stability upto 40 °C for 30 min, rich in Gly & hydroxyl amino acids	Shiomi et al. (1981)
Griffithsia sp.	Glucose, mannose, *N*-acetylglucosamine	Dimeric, M_r 12.7 kDa, 121 amino acid residues	Mori et al. (2005); Ziolkowska & Wlodawer (2006)
Hypnea cervicornis	*N*-acetyl-D-galactosamine, bovine submaxillary mucin, desialylated ovine submaxillary mucin, porcine stomach mucin, asialofetuin	M_r 9.1 kDa	Nagano et al. (2005)
H. japonica			

(*continued*)

Table 2. Continued

Algae	Inhibitory sugars/Glycoproteins*	Lectin characteristics	Reference(s)
	Complex *N*-glycans (transferrin, fetuin, α-acid glycoprotein), *O*-glycans (feutin & mucin), asialofeutin, asialomucin, glycopeptides prepared from asialofeutin, core (α1-6) fucosylated glycans	Small-sized isolectins, M_r 9.1 kDa (hypnin-1 & hypnin-2)	Hori et al. (2000); Okuyama et al. (2009)
H. musciformis	Porcine stomach mucin, bovine submaxillary mucin, desialylated ovine submaxillary Mucin	M_r 9.3 kDa	Nagano et al. (2005)
Kappaphycus alvarezii	Porcine thyroglobulin, bovine thyroglobulin, asialo-porcine thyroglobulin, asialo bovine thyroglobulin, yeast mannan	Monomeric, M_r 28 kDa, hemagglutination activity independent of divalent cations, pH stability 3–10, thermal stability upto 50 °C for 30 min, no carbohydrate content	Hung et al. (2009)
K. striatum	Glycoproteins bearing high-mannose-type *N*-glycans, porcine and bovine thyroglobulins, their asialo-derivatives and yeast mannan	Monomeric, M_r 28 kDa, pH stability 3–10, thermal stability upto 60 °C for 30 min, hemagglutination activity independent of divalent cations	Hung et al. (2011)
Pterocladiella capillacea	Avidin, porcine stomach mucin	Monomeric, M_r 5.8 kDa, hemagglutination activity independent of divalent cations, pH stability 7–10, thermal stability upto 60 °C for 30 min	Oliveira et al. (2002)
Ptilota filicina	*p*-nitrophenyl-*N*-acetyl-α-and-β-D-galactosaminide, porcine stomach mucin, bovine submaxillary gland mucin, asialo bovine mucin	Homotrimer, M_r 56.9 kDa, rich in acidic & hydroxyl amino acids, hemagglutination activity dependent on divalent cations, thermal stability upto 50 °C for 30 min	Sampaio et al. (1998)
P. plumosa	Galactose, glucose and their derivatives with *p*-nitrophenyl-α-D-galactoside	Homotrimer, M_r 52.5 kDa, rich in acidic amino acids.	Sampaio et al. (2002)
P. serrata	*o*-nitrophenyl-*N*-acetyl-α-D-galactoside, *p*-nitrophenyl-*N*-acetyl-β-D-galactoside, lactose, porcine stomach mucin, asialo bovine mucin and asialofetuin	Homotrimer, M_r 55.4 kDa, rich in acidic & hydroxyl amino acids.	Sampaio et al. (1999)
Serraticardia maxima	No inhibition activity with simple sugars	M_r 25 kDa, pH stability 4–10, hemagglutination activity independent of divalent cations	Shiomi et al. (1980)
Solieria filiformis	Mannan, avidin, ovalbumin, egg white	M_r 29 kDa	Benevides et al. (1996)
Tichocarpus crinitus	Porcine stomach mucin (type VII), feutin	Monomeric, M_r 41 kDa, pI 4.93, rich in acidic amino acids, hemagglutination activity independent of divalent cations, carbohydrate content 6.9%	Molchanova et al. (2010)

*Only most specific are enlisted.

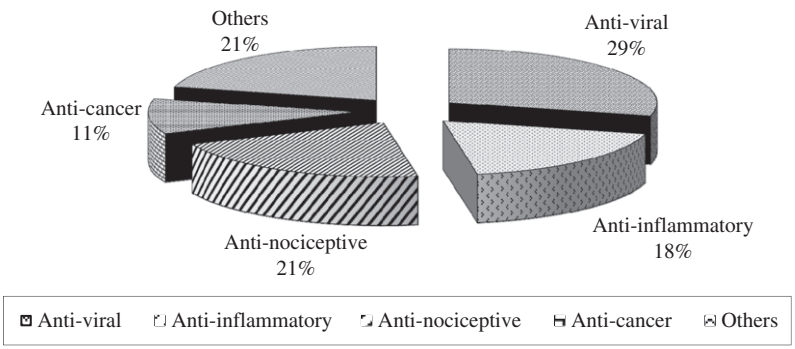

Figure 2. Biomedical applications of algal lectins.

reduce neutrophil migration to peritoneal cavity (Guzman et al., 2001). Lectin from green algae *C. cupressoides* produces antinociceptive and anti-inflammatory response in models of nociception in mice and inflammation in rats which attributes peripheral antinociception action against the release of mediators in response to acetic acid (Vanderlei et al., 2010).

Anti-inflammatory

Inflammation is a body's defense reaction caused by injury or damage, which is characterized by rubor (redness), tumor (swelling), calor (heat) and dolar (pain). The first phase of inflammation and edema is marked by the release of histamine and serotonin, second phase involves the release

Table 3. Biomedical applications of algal lectins.

Algae	Lectin designated	Biomedical application(s)	Reference(s)
Blue-green algae			
Microcystis viridis	MVL	Antiviral activity ($EC_{50} = 30$ mM, IC_{50} 30 nM).	Bewley et al. (2004)
Nostoc ellipsosporum	Cyanovirin-N (CV-N)	Anti-HIV activity *in vitro* ($IC_{50} = 1.8$ nM) ($EC_{50} = 0.1$ nM). Antiviral activity against Ebola virus ($EC_{50} = 100$ nM). Antiviral activity against Influenza A and B virus ($EC_{50} = 0.004$–0.5 μg/ml).	Barrientos et al. (2003); Boyd et al. (1997); O'Keefe et al. (2003)
Oscillatoria agardhii	OAA	Inhibits HIV replication in MT-4 cells ($EC_{50} = 44.5$ nM).	Sato et al. (2007)
Scytonema varium	SVN	Neutralizes both laboratory-adapted strains and primary isolates of HIV1 activity ($EC_{50} = 0.3$ & $IC_{50} = 20.1$).	Alexandre et al. (2010)
Green algae			
Boodlea coacta	BCA	Anti-HIV activity *in vitro* in MT-4 cells ($EC_{50} = 8.2$ nM) & Anti-influenza activity inhibiting replication of influenza virus in MDCK cells	Sato et al. (2011b)
Bryopsis hypnoides	–	Mediates protoplast regeneration.	Niu et al. (2009)
B. plumosa	Bryohealin	Wound-healing properties.	Jung et al. (2010)
Caulerpa cupressoides	CcL	Antinociceptive & anti-inflammatory effect.	Vanderlei et al. (2010)
Ulva rigida	–	Stimulated mitogenesis in murine splenocytes	Bird et al. (1993)
Brown algae			
Laminaria diabolica	Diabolin	Causes the development of fertilization envelope around unfertilized eggs of sea urchin (*Hemicentrotus pulcherrimus*).	Smit (2004)
Red algae			
Amansia multifida	LEC	Antinociceptive properties.	Neves et al. (2007)
	Amansin	Stimulated dose dependent proliferation of human PBMC (peripheral blood mononuclear cells). Induces interferon (IFN-γ) production and neutrophil migration *in vivo* & *in vitro.*	Lima et al. (1998); Neves et al. (2001)
Bryothamnion seaforthii	BSL	Differentiate human colon carcinoma cell variants.	Pinto et al. (2009)
	BSL	Antinociceptive activity.	Vieira et al. (2004); Viana et al. (2002)
	BSL	Block adherence of *Streptococci* to acquired pellicle *in vitro*.	Teixeira et al. (2007)
B. triquetrum	BTL	Differentiate human colon carcinoma cell variants	Pinto et al. (2009)
	BTL	Vasorelaxant effect.	Lima et al. (2004)
	BTL	Antinociceptive activity.	Viana et al. (2002)
Eucheuma serra	ESA	Cytotoxic against cancer cell lines. ESA-immobilized lipid vesicles effectively bind to cancer cell lines.	Sugahara et al. (2001)
	ESA	ESA-immobilized onto span80 vesicles shows anti-tumor activity *in vitro* and *in vivo*	Omokawa et al. (2010)
Gracilaria cornea	GCL	Acaricidal activity.	Lima et al. (2005)
G. verrucosa HBOI strain G-16 S	–	Mitogenic for murine splenocytes.	Bird et al. (1993)
G. tikvahiae HBOI strain G-3	–	Mitogenic for human lymphocytes & murine splenocytes.	Bird et al. (1993)
G. tikvahiae HBOI strain G-5	–	Mitogenic for murine splenocytes.	Bird et al. (1993)
Griffithsia sp.	Griffithsin (GRFT)	Inhibit HIV-1 virus ($IC_{50} = 0.4$ nM).	Alexandre et al. (2010)
	GRFT	Potent antiviral activity against T- &-M- tropic HIV-1 ($EC_{50} = 0.043$–0.63). Inhibitor of coronavirus.	Mori et al. (2005); Ziolkowska et al. (2006)
Hypnea cervicornis	HCA	Bactericidal activities.	Siddqiui et al. (1993)
	HCA	Anti-inflammatory activity & antinociceptive effects.	Bitencourt et al. (2008)
	HCA	Anti-hypernociceptive effect	Figueiredo et al. (2010)
H. japonica	Hypnin A	Toxicity to tumor cells. Inhibition of normal embryonic development of marine invertebrates. Specific binding to fucosylated *N*-glycans making it valuable tool for cancer diagnosis.	Okuyama et al. (2009)
		Inhibits ADP-induced platelet aggregation.	Matsubara et al. (1996)
Kappaphycus alvarezii	KAA-2	Inhibits influenza virus infection.	Sato et al. (2011a)
Phaeodactylum tricornutum	–	Anti-inflammatory, analgesic & free radical scavenging activity	Guzman et al. (2001)
Solieria filiformis	–	Stimulates the growth of Gram +ve species *Bacillus cereus* & inhibited the growth of Gram –ve species (*Serratia marcescens, Salmonella typhi, Klebsiella pneumonia, Pseudomonas aeruginosa, Enterobacter aerogenes, Proteus* sp).	Holanda et al. (2005)
Tichocarpus crinitus	TCL	Stimulate synthesis of pro-inflammatory cytokinies TNF-α, IFN-γ, IL-6 by human whole-blood cells.	Molchanova et al. (2010)

–: Lectin not designated.

of cytokines followed by prostaglandins (Vanderlei et al., 2010). HCA lectin isolated from *H. cervicornis* induces anti-inflammatory effects in models of paw edema and peritonitis which is elicited by a reduction in leukocyte migration to the peritoneal cavity of the animals. Thus, the anti-inflammatory effects occur via competition of mucins of cell glycoproteins with selectins which results in neutrophil reduction and blockade of leukocyte adhesion to the endothelium (Neves et al., 2007). Anti-inflammatory effects have also been demonstrated by lectins from *C. cupressoides, C. stigmatophora, P. tricornutum* and *A. multifid*a which results in neutrophil migration to peritoneal cavity and carrageenan-induced paw-edema of rats (Guzman et al., 2001; Neves et al., 2007; Vanderlei et al., 2010).

Anti-cancer

Lectins in oncology can be used as diagnostic probes and biological response modifiers. Due to their small size and several disulphide bridges, marine algal lectins possess greater stability and specificity for complex carbohydrates and glycoconjugates. Therefore, they are thought to induce immunogenicity. Many algal lectins are reported to possess anti-tumor activity against human cancer cells (Karasaki et al., 2001; Timoshenko et al., 2001; Wang et al., 2000). Tumor-specific ''active targeting'' is often practiced which is achieved by immobilizing tumor-specific ligands (antibodies, peptides or saccharides) onto drug-carrier systems (Forssen & Wills, 1998; Peer et al., 2007; Trochilin, 2005). *E. serra* agglutinin (ESA) induced cell-death of colon cancer Colo201 cells and cervix cancer HeLa cells (Sugahara et al., 2001). ESA lectin had strong mitogenic activity against human and mouse lymphocytes due to affinity for glycoproteins bearing high-mannose type *N*-glycans. When immobilized onto span 80 (sorbitan monooleate) vesicles, ESA drastically decreased the viability of Colo201cancer cells *in vitro*, whereas normal cells remained unaffected. The vesicles also manifested inhibition of cancer cell growth in nude mice and diminished tumor growth after intravenous administration to nude mice having an implanted Colo201 tumor (Kawakubo et al., 1997).

Lectins BSL and BTL from *B. seaforthii* and *B. triquetrum*, respectively, were capable of differentiating human colon carcinoma cell variants with respect to their cell membrane glycoreceptors and could be used for structural modifications of cell membrane glycoconjugates in cancer cell systems (Pinto et al., 2009). The binding of both lectins to carcinoma cells results in internalization which could be used for drug delivery.

Antiviral

Lectins derived from marine algae are a rich source of antiviral products (Triveleka et al., 2003). Antiviral activity depends on the ability to bind mannose-containing oligosaccharides present on surface of viral envelope glycoproteins. Lectins from cyanobacteria and other marine macro-algae are specific for high-mannose which makes them promising candidates for the prevention of transmission of various enveloped viruses such as human immunodeficiency virus (HIV), influenza virus, hepatitis C virus (HCV), Ebola virus and severe acute respiratory syndrome coronavirus (SARS-CoV) (Ziolkowska & Wlodawer, 2006). The specific interaction of algal lectins with target glycans on virus surfaces suppresses virus infection (Balzarini, 2007).

Boodlea coacta lectin (BCA) has been reported to be the first HIV- and influenza virus-inhibiting protein from green algae. BCA revealed potent antiviral activity against most of the influenza virus strains tested by binding to the envelope HA (a trimeric glycoprotein expressed on influenza virus membrane) including a clinical isolate of pandemic H1N1-2009 virus (Sato et al., 2011b). Lectin isolated from *K. alvarezii* (KAA-2) exhibited strong antiviral activity against broad range of influenza virus strains including Swine-origin H1N1 influenza virus; regardless of the virus subtype and strain. Inhibition of influenza virus propagation occurred due to the blocking of viral entry into the host cell by binding to HM glycans on the surface envelope glycoprotein HA. This clearly indicates that KAA-2 completely inhibits yeast mannan bearing HM glycans and binds strongly to HA via HM glycans. The strain-independent inhibition by KAA-2 might be more effective than antibody-based medicines that are more prone to antigenic shift/drift. KAA-2 can be used as novel antiviral agent (Sato et al., 2011a).

In a recent groundbreaking study, griffithsin from *Griffithsia* sp. has been reported to be a potent inhibitor of the life-cycle of the coronavirus which is responsible for SARS. The antiviral potency of griffithsin is due to presence of multiple, sugar binding sites that provide robust attachment points for complex carbohydrate molecules present on viral envelopes. Such broad antiviral activity of this lectin makes it a promising candidate for the development of a novel antiviral agent (Ziolkowska & Wlodawer, 2006). Lectin CV-N showed an inclusive variety of antiviral activity for influenza viruses (A and B), Ebola virus, human herpes virus 6, HCV and measles virus (Barrientos et al., 2003; Dey et al., 2000; Helle et al., 2006; O'Keefe et al., 2003).

Algal proteins with antiviral activities have now ''emerged'' in the anti-HIV battlefield displaying immense dormant applications as topical agents (Feizi et al., 2011). Most of the research on anti-HIV activity of marine algae has converged upon red and brown macroalgae (Schaeffer & Krylov, 2000). High-mannose binding nature of algal lectins makes them expedient candidates for inhibiting HIV (Botos & Woldawer, 2005). They interact with glycans and cells of the host, thus disturbing proteins of viral envelope and cells of the host. A number of lectins isolated from red algae exhibit inhibitory activity against HIV. Griffithsin/GRFT isolated from *Griffithsia* sp. is a completely novel protein with no homology to any of the proteins listed in BLAST database. GRFT displays potent antiviral activity against both laboratory-adapted strains and primary isolates of HIV-1 (Alexandre et al., 2010; Charan et al., 2000; Giomarelli et al., 2006; Ziolkowska & Wlodawer, 2006) at subnanomolar concentrations ($IC_{50} = 0.4$ nm and $EC_{50} = 0.043$–0.63) which inhibits cell fusion and cell-to-cell HIV transmission (Emau et al., 2007) in contrast to several other monosaccharide-specific lectins from same structural family. GRFT is not only the strongest HIV inhibitor manifesting broad spectrum activity against various clades of HIV, but also acts as an initiation point for the design of smaller peptide-based antiviral

minilectins which can be directed against high-mannose sugars (Micewicz et al., 2010). CV-N lectin purified from *N. ellipsosporum* shares no similarity with other protein sequences which are deposited so far in public protein databases. CV-N is a potential inhibitor of both laboratory adapted and clinically isolated strains of HIV-1, HIV-2 and simian immunodeficiency virus (Bewley et al., 1998; Dey et al., 2000). Furthermore, CV-N prevents *in vitro* fusion and transmission of HIV-1 between infected and non-infected cells (Boyd et al., 1997). CV-N is highly resistant to physicochemical denaturations which are caused by various denaturants, detergents, organic solvents, multiple freeze thaw cycles and heat up to 100 °C with no loss of antiviral activity. These characteristics further boost its potential as an anti-HIV microbicide (Bewley et al., 1998; Boyd et al., 1997). GRFT, CV-N and SVN are mannose specific lectins found interacting with mannose-rich glycans present on the viral envelope and blocking HIV-1 entry *in vitro.* This supports their potential as microbicides or topical virucide to prevent sexual transmission of HIV and AIDS (Alexandre et al., 2010; Mori et al., 2005).

The envelope glycoprotein of HIV (gp120) is among the most heavily glycosylated proteins known so far. Up to 50% of this 120-kDa glycoprotein is contributed by *N*-linked carbohydrates. In particular, HIV gp120 contains 20–29 *N*-glycosylation sites depending on the nature of the viral isolate and the type of virus clade. Highly dense carbohydrate shield on gp120 has been found to be responsible for its low antigenicity and low immunogenicity. It also protects the virus against the immune system (Balzarini et al., 2005). Envelope glycoprotein gp120 and gp 41 of HIV-1 forms a trimer complex that mediates virus entry into target cells through receptor binding events. As demonstrated in studies, gp120 is composed of variable region (V_1–V_5) and constant regions (C_1–C_5). V_3 loop acts as the major determinant of viral entry. Carbohydrate moieties are affirmed to act as shields for gp120 which is highly glycosylated. Thus, carbohydrate-binding agents including CV-N and griffithsin inhibit HIV-1 infection (Hu et al., 2007).

Miscellaneous applications

Algae are promising organisms to furnish novel biochemically active compounds which are of potential importance to pharmaceutical sector and general public health. Lectin from *A. multifida* (Amansin) possesses the ability to induce interferon (INF-γ) production, neutrophil migration and is also a powerful stimulant of quiescent peripheral blood lymphocytes which can induce blast transformation heading for mitosis in cells in vitro. Low molecular weights of algal lectins play a vital role in the study of neutrophil migration as this prevents steric problems (Neves et al., 2001). Lectin bryohealin from *B. plumosa* has the potential of wound-healing (Jung et al., 2010). Similarly, lectin diabolin isolated from *Laminaria diabolica* initiates the development of a fertilization envelope around unfertilized eggs of sea urchin *Hemicentrotus pulcherrimus* which prevents its cleavage (Smit, 2004).

TCL stimulates the synthesis of pro-inflammatory cytokines TNF-α, INF-γ and interleukin-6 by human whole blood cells (Molchanova et al., 2010). TCL has also been reported to be a potent mitogen for human lymphocytes. The bacteriostatic and stimulatory effects on the growth of several Gram negative bacteria (*Serratia marcescens*, *Salmonella typhi, Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Proteus* sp) and Gram positive bacteria (*Bacillus cereus*) have been reported from *Solieria filiformis* lectin (Holanda et al., 2005).

H. japonica lectin (Hypnin A) inhibits human platelet aggregation induced by ADP or collagen in a dose-dependent manner (Matsubara et al., 1996). This lectin exhibits potent mitogenic activity against both lymphocytes from mouse and human. It also induces toxicity to tumor cells by inhibition of embryonic development of marine invertebrates (Hori et al., 2000; Matsubara et al., 1996). *Gracilaria cornea* lectin through multimechanistic approach showed acaricidal and antifeedant activity against *Anagasta kuehniella* (flour moth), which may be important for controlling pests from a new natural source (Lima et al., 2005). Interestingly, algal lectins are also used in antiadhesion trials. Lectins BTL and BSL have been shown to block adhesion of *Streptococci* to their mucin receptors in acquired pellicle via competition mechanism (Teixeira et al., 2007). These lectins interfere both with bacterial adhesion and aggregation. Thus, antiadhesion lectin therapy is a promising solution to the problems of caries. Lectins are widely used in lectinosorbent assays which characterize cell-binding patterns (Smit, 2004).

Future perspectives

Algae studied for lectins comprise only a negligible expanse of the total number of algal species and, therefore, a comprehensive province remains to be scrutinized. Lectins isolated from marine resources are highly diversified not only in terms of structure, but also functional aspects including specific and unique carbohydrate specificities. The research upshot concerns the evolution of powerful tools for the study of cancer, HIV and other diseases. The ultimate goal is to develop emphatic microbicides that not only stymie the transmission of cell-free viruses but also the transmission of donar-HIV infected T-cells and guards against other STDs (Huskens & Schols, 2012). The sugar binding specificity of lectins towards glycoconjugates has made them captivating proteins. This property enables them to fabricate useful tools for various therapeutic applications including cancer diagnosis and prognosis, pathological markers of diseases, glycan profiling, cell-communication, bioadhesion and for controlling a variety of infections.

Significant research on algal lectins during past few decades has accelerated the understanding of molecular-mechanism entangling adherence and recognition. The specific coupling and greater pH stability of algal lectins showed reversible linkage of algal lectins to drug enhancing penetration of drugs which can be used for targeting drugs to tumor tissue and for oral drug delivery. A number of lacunae still persist which need to be filled. Even though an invigorative role of many lectins has been evident, further pharmacokinetic studies need to be endeavored before their introduction as clinical tools. Distinct sources should be traversed to confine avant-grade lectins with dormant dupable properties.

Sanguinely, further groundwork is required to endow *in vivo* succor of these algal lectins equivalent to their *in vitro* effects and can be carried forward for the development of oral drug delivery systems, mucoadhesive formulations, lectinosorbent assays and development of efficient, safe and affordable microbicides. In case of anti-HIV drugs what is now needed is to determine precisely the distinctive features among numerous lectins that confer antiviral activity. Thus, it would be possible to engineer proteins with multiple binding sites recognizing different motifs for use as anti-HIV drugs with enhanced potencies (Feizi et al., 2011). The author realizes that the need of the hour is to characterize and overcome the shortcomings in purification of algal lectins for exploring immense empire of algal lectins for biomedical applications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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