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Review

Cyanobacterial lectins characteristics and their role as antiviral agents

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ABSTRACT

Lectins are ubiquitous proteins/glycoproteins of non-immune origin that bind reversibly to carbohydrates in non-covalent and highly specific manner. These lectin-glycan interactions could be exploited for establishment of novel therapeutics, targeting the adherence stage of viruses and thus helpful in eliminating wide spread viral infections. Here the review focuses on the haemagglutination activity, carbohydrate specificity and characteristics of cyanobacterial lectins. Cyanobacterial lectins exhibiting high specificity towards mannose or complex glycans have potential role as anti-viral agents. Prospective role of cyanobacterial lectins in targeting various diseases of worldwide concern such as HIV, hepatitis, herpes, influenza and ebola viruses has been discussed extensively. The review also lays emphasis on recent studies involving structural analysis of glycan-lectin interactions which in turn influence their mechanism of action. Altogether, the promising approach of these cyanobacterial lectins provides insight into their use as antiviral agents.

Contents

Abbreviations: Cyt-CVNH, Cyanothece CVN homolog; M_r, molecular weight; MAL, *Microcystis aeruginosa* lectin; MVN, microvirin; MVL, *Microcystis viridis* lectin; CV-N, cyanovirin; LCV-N, linker cyanovirin; PEG-ALD-LCVN, PEGylated-aldehyde-linker cyanovirin; rCVN, recombinant cyanovirin; OAA, *Oscillatoria agardii* agglutinin; rOAA, recombinant *Oscillatoria agardii* agglutinin; SVN, scytovirin; NcCVNH, cyanovirin-N homologs (CVNHs) from *Neurospora crassa*; TbCVNH, cyanovirin-N homologs (CVNHs) from *Tuber borchii*; CrCVNH, cyanovirin-N homologs (CVNHs) from *Ceratopteris richardii*; PFA, *Pseudomonas fluorescens* agglutinin; MBHA, myxobacterium hemagglutinin; EC, effective concentration; IC, inhibitory concentration; CC, cytotoxic concentration; ELISA, enzyme linked immunosorbent assay; PCR, polymerase chain reaction; TSP, total secreted protein.

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1. Introduction

Lectins are versatile proteins/glycoproteins that possess characteristic attribute of specifically recognizing and binding to carbohydrates or glycoconjugates. They are non-immunogenic in origin and recognize various sugar structures with high degree of stereospecificity [1]. These multivalent proteins form reversible linkages upon interaction with sugars/glycoproteins linked to cell membrane or in solution [2]. They have atleast one non-catalytic domain and are involved in various cell–cell interactions. Through sugar specific binding sites, lectins agglutinate cells including erythrocytes, lymphocytes and microbial cells [3]. Thus, an emblematic attribute of lectin activity is erythrocyte agglutination, wherein lectins are routinely and easily visualised through haemagglutination assays [4]. However, a few lectins attach to cell surfaces but do not result in agglutination (non-agglutinating lectins), as lectin affinity to its receptor differs according to the disparity in their carbohydrate receptor [5]. Lectins are highly sought proteins due to their wide potential in many cellular and molecular recognition processes, pharmacology, biochemistry, medicine and clinical analysis [2]. A number of microbial lectins are implicated in many biomedical applications [6–9]. Microbial lectins also have potential roles in mycoparasitism and host-parasite interactions [10–13]. Mushroom lectins have antitumor, antiviral, mitogenic and immune stimulating potential [14]. A panorma of microfungal lectins have been attributed with various antimicrobial [15,16], immunomodulatory [17–19] and mitogenic [20–23] activities. Thus, due to their potential use and various applications, lectins are promising molecules in the field of biotechnology.

Lectins have been isolated from various sources including bacteria, algae, plants, fungi, body fluid of invertebrates, lower vertebrates and mammalian cell membrane [24]. Percentile distribution of lectins from various microbial groups is given in Fig. 1. Based on the overall structure, Peumans and Van Damme [25,26] have classified plant lectins into merolectins (having single carbohydrate-binding domain), hololectins (having atleast two identical carbohydrate-binding domain), superlectins (having atleast two non-identical carbohydrate-binding domain) and chimerolectins (fusion proteins with two varied chains). Algal lectins are also called as phycolectins, however, they differ from plant lectins in their physico-chemical characteristics or properties [27,28]. Marine algal lectins are low molecular weight monomeric proteins which usually show specificity for glycoproteins than monosaccharides [29–31]. Thus these properties of algal lectins vary from most of the plant lectins which have affinity towards monosaccharides and usually consist of oligomeric forms [26]. Algal lectins do not require metal ions for their biological activities and exhibit high content of acidic amino acids, with isoelectric point (pI) in the range of 4–6 [29–31]. Further, algal lectins are categorized into three major categories based on their carbohydrate binding properties; high mannose (HM) type N-glycan specific lectins, complex type N-glycan specific lectins and lectins having specificity towards both the above types of N-glycans [29].

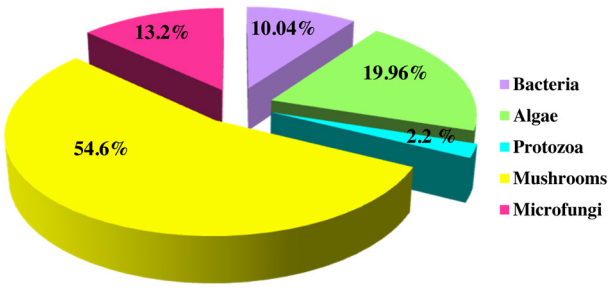

Fig. 1. Percentile distribution of lectins among various microbial groups. Data survey from various internet sources.

Amongst fungi, large number of lectins have been reported from higher fungi (mushrooms) having intracellular lectin activity usually in the fruiting bodies and show high specificity towards mucins and GalNAc residues [14]. Majority of microfungal lectins are also intracellular and usually dimeric with an isoelectric point in the range of 7.5–9.3 [10]. An array of microfungal lectins such as *Aspergillus* [21–23,32], *Penicillium* [15,33] and *Fusarium* [16] exhibit broad carbohydrate specificity, however they are highly specific towards mucins specifically porcine submaxillary mucin (PSM). Around 26 varied fungal lectins have been structurally characterized representing 8.5% of all lectin structures in lectin 3D database [34]. Further, ten different folds have been identified and due to divergent evolution, fungal lectins possess some similarity and fold convergence with bacterial lectins [34]. Bacterial lectins are often called adhesions owing to their primary function being facilitating attachment of bacteria to host [35]. Amongst bacterial lectins, the type 1 fimbrial lectins (FimH) of *Escherichia coli* are the best characterized and requires α-D-mannose and α-D-mannosides for binding and thus mediates adhesion [36]. *Ralstonia solanacearum* lectin (RSL) exhibits fucose specificity, consists of 90 amino acid subunits [37], display a strong sequence similarity to one third of the mushroom *Aleuria aurantia* Fuc-binding lectin (AAL) and forms six-bladed β propeller fold similar to that in AAL [38]. *Pseudomonas aeruginosa* lectin (PA-IL and PA-IIL) exhibits carbohydrate specificities similar to that of animal and plant lectins such as *Erythrina corallodendron* lectin, *Maclura pomifera* lectin, peanut agglutinin, the mannophilic ConA, and the fucophilic *Ulex europaeus* agglutinin-I [39].

The potential of lectins extracted from various microbial and plant sources as antiviral agents having role in future HIV therapy has been reviewed recently [40,41]. Owing to the presence of varied glycans on the virus cell surface, an array of glycan-binding lectins from various marine organisms play an important role as anti-viral agents [42]. Further role of various algal lectins as potential HIV microbicide candidate [43] and their use in biomedical research [44] has been reviewed. Members of all algal divisions are eukaryotic except division Cyanophyta, which are prokaryotic cells having neither an organized nucleus nor mitochondria or chloroplasts [43]. Information on lectins from cyanobacterial species is scarce as compared to other algal counterparts (Fig. 2). Amongst lectin possessing algal species, only 4.2% of cyanobacterial species has been