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Antimicrobial and Antiparasitic Activity of Lectins

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Abstract: Antibiotic resistance is a major problem in current contemporary medicine and it has become a major concern of the 21st century. New resistance mechanisms developed by microorganisms spread greatly, threatening the ability to treat numerous infectious diseases, and increasing the number of nosocomial infections. Besides the role in immunology and glycobiology where they are used as hemaglutinine and identification of complex carbohydrates and glycoconjugates, lectins proved to mediate diversified biological functions like cytotoxicity, complement activation, cell-to-cell and host-pathogen communications, innate immune response, and cell-to-cell signalling. Recently, great interest has been developed for the research and applications of lectins in agriculture and medicine due to their antiparasitic and antimicrobial potentials. This review focuses on the recent data regarding the antimicrobial and antiparasitic activities of lectins, by presenting the role of lectins in host-pathogen interaction and also the cytotoxic effects on microorganisms and parasites. Identification and characterisation of new lectins with antimicrobial activity could serve as a natural alternative for the treatment of infections caused by antibiotic-resistant microorganisms and parasites.

Keywords: Antimicrobial activity, host-pathogen interaction, lectins, parasites.

INTRODUCTION

Lectins are carbohydrate-binding molecules that specifically recognise various glucidic structures and intervene in numerous biological mechanisms such as cell–to–cell communication, host–pathogen interactions, serum–glycoprotein turnover, and innate immunity [1-3]. Professor Richard Cummings said that "Plant lectins have been for glycobiology as oligonucleotides have been to genetics - except that plant lectins are practically free" [4]. Plant lectins, have been an example in the field of protein–carbohydrate interactions. Despite the lack of data on their *in vivo* activity, lectins demonstrated to be useful tools in the field of immunology and glycobiology, because of their large range of specificities for carbohydrates with complex structures. Their specificity for carbohydrate structures made them useful in various applications, such as purification and characterisation of complex glycoconjugates and carbohydrates, as well as in bone marrow transplantation [5, 6]. Lectins were first identified in plants and described by Stillmark in 1888, who observed that the crude extracts of castor beans (*Ricinus communis*) contained a toxic substance named ricin that agglutinated human red blood cells [7, 8]. Between 1940 and 1952 lectins were used to demonstrate that blood group antigens are glucidic structures and investigate the structures of the antigens; Boyd and Shyleigh (1954) proposed to replace the name of hemaglutinine to lectin. Furthermore, Nowell and Aub (1960) discovered the red kidney bean lectin and its mitogenic activity on lymphocytes. The numerous data accumulated so far revealed new function and applications such as antimicrobial and antiparasitic activity, apoptosis, phagocytosis, complement activation, cell-to-cell signalling, bacterial typing, mapping neuronal pathways, and defining glycosilation status of target glycoconjugates. Lectins are found in many organisms including bacteria, parasites, fungi, algae, plants and animals and also in viruses [4, 9]. Modern chemistry and biophysical techniques have permitted to isolate and purify the lectins and molecular biology assays have contributed to the identification of their functions.

LECTINS STRUCTURE AND CLASSIFICATION

Lectins are multivalent glycoproteins or proteins that present at least one or more carbohydrate binding domain (CBD) and bind reversibly and specific to a mono- or oligosaccharide. In general, they have the property to agglutinate cells and precipitate glycoconjugates. Lectins with only one CBD are not capable to agglutinate the red blood cells. Consequently, agglutination methods are frequently used for detection of lectins that presents more than one CBD. Affinity chromatography is the technique used for purification of majority of lectins which uses polymers like Sepharose, Dextrine, Sephadex or Chitin [10, 11]. According to the overall structures plant lectins are classified in merolectins, holoectins, superlectins and chimerolectins. *Merolectins* have a single CBD, so they are unable to precipitate glycoconjugates or agglutinate cells (e.g. *hevein* from the rubber tree *Hevea brasiliensi*, and monomeric mannose binding protein from orchis). *Hololectins* contain minimum two identical or much related carbohydrate binding domain. Because these lectins bind to more carbohydrate sites they can be assessed *in vitro* by agglutinate red blood cells or precipitate glyco-

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conjugates tests. Hololectins represent the most wide class of plant lectins. *Superlectins* present at least two CBD, but in contrast with hololectins, these domains do not have identical or similar features. Therefore, superlectins distinguish structurally different carbohydrates (e.g. tulip bulb lectin TxLCI recognizes N-acetyl-galactosamine and mannose residues). *Chimerolectins* are represented by fusion proteins that present two unrelated chains, one of them binds to sugars and the second chain presents other biological activity, such as catalytic activity. Examples of chimerolectins are type 2 ribosome-inactivating proteins RIPs [12-14]. Lectins can also be categorised according to their carbohydrate specificity in different families: legume lectins, RIP types 2, chitin binding lectins, jacalins and jacalin-like lectins, monocot mannose binding lectins and other lectins [13]. Animal lectins are a heterogeneous class of glycoproteins involved in numerous cellular processes such as: protein sorting (calnexin, calreticulin ERGIC-53, VIP36), cellular adhesion (selectins), protein degradation (EDEM 1, 2 and 3, NFB42, SKP2), immunity (ficolins, YKL-40, lactoferin receptor), and development (oviductin, intelectins 1 and 2, omentin) (Table **1**) [15-28].

ANTIMICROBIAL ACTIVITY OF PLANT LECTINS

Recent studies have been researching the role of lectins in microbiology, since lectins represent valuable tools to study the interaction between the carbohydrates present in eukaryotic cells and pathogens for uncovering the infectious disease development. Many pathogens initiate adhesion followed by infection using cell surface carbohydrates as either receptors or ligands. For examples, it has been demonstrated that *Helicobacter pylori* infects human intestinal cells through an interaction comprising lectins [29]. *Galaxaura marginata* and *Eucheuma serra* are two red marine algae that produce lectin GMA and ESA respectively and have antimicrobial activity against *Vibrio* sp. *Bryothamnion triquetrum* lectin (BTL) and *Bryothamnion seaforth ii* lectin (BSL) were capable to reduce formation of dental plaque by avoiding streptococci adhesion in enamel pellicles. BTL presents a more pronounced potential in avoiding the adherence of *Streptoccocus mitis* and *S. sobrinus* and BSL was able to inhibit the adherence of *S. mutans*. Therefore, the use of this type of lectins can contribute to preventing formation of dental plaque at early stages [30]. Other pathogens such as *Escherichia coli* (*E.coli*) bind mannose residues in the host cells, while viruses like influenza virus interact to host sialic acids [31]. *Neisseria gonnorrhea* specifically binds Nacetyllactosamine (Gal-β-4-GlcNAc, LacNAc), *Streptococcus pneumonia* binds the pentasaccharide NeuAc-α-3-Gal-β-4-GlcNAc-β-3-Gal-β-4-Glc and other tetra- and trisaccharides, while *Pseudomonas aeruginosa* specifically binds to fucose [32]. Bacteria and viruses can distinguish between two identical carbohydrates even if they differ in only one hydroxyl group, based on this type of specificity of host–pathogen interactions strategies may be developed to prevent the bacteria adhesion [33]. Interaction of plant lectins with the bacterial cell wall through teichoic and teichuronic acids, lipopolysaccharides and peptidoglycans could explain the antibacterial activity of lectins in Gram-negative and Gram-positive bacteria. *Lathyrus ochrus* isolectin I from seeds have the capacity to bind to muramic acid and muramyl dipeptide from bacteria cell wall involving hydrogen bonds between ring of sugars and carbohydrate binding site of lectin and hydrophobic interactions with the side chains of isolectin I, especially at residues Tyr100 and Trp128 [34]. Recent data showed that lectin extract from *Artocarpus heterophyllus* presents greater antibacterial activity compared to *Canavalia ensiflora* lectin, *Pisum sativum* lectin and *Lens culinaris* lectin. The *A. heterophyllus* lectin extract has antibacterial activity as demonstrated by the effect against *Bacillus subtilis* and *Pseudomonas aeruginosa*, followed by Staphylococcus *aureus* and *E. coli.* The antibacterial activity of all plant lectin extracts used in this study was 1mg/ml [35]. In 2010, Petnual *et al*. reported the antimicrobial activity of *Curcuma longa* (turmenic) lectin for all the microbial species tested. *Pseudomonas aeruginosa* proved to be the most sensitive after treatment with curcuma lectin [36]. Another lectin with antibacterial activity against Gram-positive bacteria is lectin isolated from the seed of *Archidendron jiringa*. The interaction of lectins with N-acetylmuramic acid and muramic acid, the most commune carbohydrates existing in the bacterial cell wall, plays a key role in host-pathogen communications, permitting the recognition of bacteria. Almost all bacteria and parasites are expressed on the cell surface glycans. The glycans such as glycosylated teichoic acids and peptidoglycan are covalently bound, but in the case of capsular polysaccharides the bounds are non-covalent. Each surface-exposed glycan is a possible lectin-reactive situs. The capacity of lectins to form aggregates with microbial glycoconjugates could block the sites of bacteria for the interaction with host preventing infections [37]. Purified *Indigofera heterantha* lectin (500 µg/ml) exhibited a significant antibacterial effect on four microbial strains *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*, and no antifungal effect against *Fusarium oxysporum, Aspergillus oryzie*, and *Aspergillus niger* [38]. *Schinus terebinthifolius* lectin SteLL purified from leafs, a chitin-binding lectin, presents antimicrobial activity against many microorganisms and fungi [39]. Fabatin and thionin lectins from *Vicia faba* inhibit the growth and survival of *P. aeruginosa* and *E. coli,* and have no activity on yeast such as *Saccharomyces cerevisiae* and *Candida albicans* [40, 41]. The heartwood lectin isolated from *Artocarpus incisus* inhibited Gram-positive bacteria such as *Staphylococcus aureus, Corynebacterium callunae, Bacillus subtilis,* and *Streptococcus faecalis* and Gram-negative represented by *Klebsiella (K.) pneumonia, Escherichia coli*, and *Pseudomonas aeruginosa*. The antimicrobial activity was more active on Gram-positive bacteria, minimal inhibitory concentration (MIC) determined for *Staphylococcus aureus* was 0.58 µg/mL and the minimum bactericidal concentration (MBC) was 8.1 µg/mL. The Gram-negative bacterium *Klebsiella pneumoniae* presented an MIC of 9.37 µg/mL being the least sensitive microorganism. This lectin is a chitin-binding glycoprotein that also presents antifungal effect against *Fusarium* strains [42]. Lectin isolated from *Phthirusa pyrifolia* leaf has affinity for fructose-1-6-biphosphate residues and presents antibacterial activity against *Streptococcus faecalis, K. pneumoniae*, and *Staphylococcus epidermidis.* Minimum bactericidal concentration for *Bacillus subtilis* was established at 0.5 mg/mL, therefore this lectin is an agent more active for Gram-positive bacteria than for Gram-negative bacteria and it was proposed that the possible mechanism to

Table 1. Lectins classification and role in plants and animals [1-28].

Plant Lectins	Animal Lectins
I. Structurally: **1. Merolectins** - single CBD - e.g.: hevein, mannose binding protein from orchis **2. Hololectins** - two or more identical or similar CBD - e.g.: most plant lectins **3. Superlectins** - two or more different CBD - e.g.: tulip bulb lectin TxLCI **4. Chimerolectins** - fusion proteins with one CBD and one catalytic/other function domain - e.g.: RIPs type 2, class I chitinase	**I. Calnexin type** - localisation: ER - role: protein sorting - e.g.: calnexin, calreticulin, calmegin
	II. C-type lectins - **selectins:** cellular adhesion - **collectins:** innate immunity - e.g.: E-selectin, P-selectin, L-selectins, SP-A, SP-D, conglutinin
	III. M-types lectins - localisation: type II TM proteins - role: ERAD protein degradation pathway - e.g.: EDEM 1, 2 and 3
	IV. L-types lectins - localisation: ER, Golgi Apparatus - role: protein sorting - e.g.: ERGIC-53, ERGL, VIP36, VIPL
II. Specificity **1. Legume lectins** - specificity: manose, GalNAc, galactose - e.g.: concanavalin A, Lathyrus ochrus LOL-1, Grifonia simplicifolia GS-1, Dioclea grandiflora DGL, Peanut PNA, Phaseolus vulgaris PHA, Soybean SBA, Ulex europaeus UEA **2. Chitin binding lectins** - specificity: N-acetylglucosamine, chitotetrose - e.g.: hevein, pokeweed lectin, Urtica dioica UDA, wheat germ WGA **3. Monocot mannose binding lectins** - specificity: manose - e.g.: garlic bulbs lectin, amaryllis, snowdrop lectin **4. Jacalins and jacalin-like lectins** - specificity: manose -artocarpin, jacalin, heltuba, calsepa, Maclura pomifera MPA **5. Type 2 ribosome-inactivating proteins** - e.g.: trichosanthin, ricin, abrin, saponin, pokeweed antiviral protein, barley translation inhibitor (Hordeum vulgare), JIP60 **6. Other lectins**	**V. P-type lectins** - localisation: lysosome - role: trafficking of lysosomal enzymes - e.g.: manose-6P receptor (Man6P)
	VI. Galectins - localisation: cytosol, ECM - role: cell-to-cell and cell–matrix interactions, transmembrane signalling - e.g.: galectin 1, 2,3, 4,7, 8, 9, 10, 12, and 13
	VII. I-type lectins (siglecs) - localisation: TM proteins - role: cell adhesion - e.g.: CD33, siglecs5-12, MAG, sialoadesin
	VIII. F-box lectins - localisation: cytosol - role: protein degradation - e.g.: NFB42, SKP2, OCP1
	IX. R-type lectins - localisation: membrane - role: transmembrane signalling - e.g: mannose receptor (MR) family, EW29, pierisin 1
	X. Ficolins - localisation: cytosol, membrane, ECM - role: immunity - e.g.: ficolin M, ficolin L
	XI. F-type lectins (fucolectins) - localisation: only in fish - role: hemaglutinin - e.g.: AAA (Anguilla Anguilla aglutinin)
	XII. Chitinase-like lectin - localisation: ECM - role: immunity, fertility, development - e.g.: YKL-40, oviductin
	XIII. Intelectins (x-lectins) - localisation: membrane - role: immunity, fertility, development - e.g.: intelectins 1 and 2, omentin, lactoferin receptor

(ER- endoplasmic reticulum, TM- transmembranar, ECM- extracellular matrix, CBD- carbohydrate binding domain, RIPs- ribosome-inactivating proteins, GalNAc- N-acetilglucosamine).

be correlated with the levels of peptidoglycans on the envelopment [43]. Bark of *Sebastiania jacobinensis*, used by people for treating infections, hold antifungal lectins. The influence of lectin on growth and survival of *Colletotrichum gloeosporioides, Candida albicans*, *Aspergillus niger*, *Fusarium moniliforme, Fusarium oxysporum*, and *Trichoderma viride* was studied and it appeared that the lectin was effective only on *Fusarium* species [44].

Eugenia uniflora lectin revealed an extraordinary non-selective antibacterial activity. This lectin isolated from the seed of cayenne cherry inhibited the growth and survival of *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Klebsiella* sp. The MIC for these bacteria was 1.5 μg/mL while for *E. coli, Bacillus subtilis*, *Streptococcus* sp. was less effective in inhibiting the growth with an MIC of 16.5 μg/mL. This data recommended the use of lectin as antibacterial agent for therapeutic purposes and clinical microbiology [45].

The effect of lectins may vary according to bacteria growth. The lectins from *Canavalia brasiliensis* (ConBr), *Canavalia gladiata* (CGL), *Canavalia maritima* (ConM), *Canavaliaensi formis* (ConA) and *Canavalia boliviana* (ConBol) present inhibitory activity against planktonic bacteria. The results showed that ConBol, ConBr and ConM present inhibitory effect on *Streptococcus mutans*. Interestingly all lectins, except ConA, stimulated significantly the growth and survival of *Streptococcus oralis*. The inhibitory activity on *S. mutans* biofilm was obseved in ConBol, ConM and ConA. Regarding the bacteria that grow in biofilms, no effects were found on *Streptococcus oralis* [46]. *Cladonia verticillaris* is a lichen of cosmopolitan distribution and represents a rich source of lectins. The protocol established for isolation of *C. verticillaris* lichen lectin (ClaveLL) is simple and yields milligram quantities of protein. Also, the *C. verticillaris* produces bioactive secondary metabolites, such as fumarprotocetraric and protocetraric acids. The fumarprotocetraric acid has demonstrated biological actions, such as expectorant, antioxidant, and allelopathic effect. ClaveLL showed the best inhibitory activity against the Gram-negative bacteria *E. coli* with MIC value of 7.18 μg mL−1 and the best bactericidal activity against Gram-positive *B. subtilis* and *E. faecalis* with MBC value of 57.4 μg mL−1 [47]. *Solanum tuberosum* contains a variety of lectins with the molecular mass between 45 - 65 kDa. These lectins prevent the formation of mucose-like components such as biofilms consisting proteins and GlcNAc oligomers that are secreted by microorganisms for maintaining the microbial ecology. StL-20 lectin from *Solanum tuberosum* exhibits antimicrobial activity for *E. coli* O157:H18, *Listeria monocytogenes, S. enteridis,* and *S. boydii* and antifungal activity for *Rhizopus sp., Penicillium sp.,* and *Aspergillus niger* [48]. A major problem in treating microbial infections is the formation of microbial complex communities related with an extracellular matrix made by many types of glycans. This association is named biofilm and confer to microorganisms resistance to antibiotics. Microbial community that grows in biofilms can form on biotic and abiotic surfaces, such as human tissues, medical prosthetic devices or water piping systems and marine environments. Infections with bacteria capable to form biofilm are usually chronic and require a complex scheme of treatment for long period of time [49]. Their eradication becomes extremely difficult or impossible because the growth and survival of bacteria inside the biofilm avoid the penetration of various antibiotics [49-53]. For some antimicrobial agents, the concentration necessary to remove the biofilm can be up to a thousand times higher than that required for planktonic bacteria of the same species [54]. Formation of bacterial biofilm is a stadial process starting with changes in bacteria phenotype, and it goes from the unicellular state in suspension to a multicellular state and then attach to substrate where a community forms. Cell adhesion molecules that exist in the pili and/or flagella permit anchor the cells to each other and substrate [55]. The founder colonies enable the adherence of other bacterial cells through adhesion sites and started to build the glycoproteic matrix that will form the biofilm. The polymeric matrix called EPS (*Extracellular Polymeric Substances*) maintain the aggregated cells and is a component of great importance in biofilm-forming [56]. Thus, carbohydrate residues act as mediators for the binding between microorganism and the substrate, and also represent the site of interaction between bacteria to form cellular aggregates which prove the essential role in formation and maintenance of bacterial biofilms [57-59]. Investigating the molecules that are able to bind specifically to carbohydrates could contribute to the development of new strategies against microbial biofilms. Therefore, lectins could be used as important tools to investigate the glucidic structures of those glycan polymers from microbial origin. Studying the interaction of lectins with microbial biofilms has two main objectives: (i) identification and characterisation of *Extracellular Polymeric Substances* made by diverse species of bacteria [60], (ii) blocking the bacterial binding sites present in glycoproteins and / or carbohydrates and inhibition of biofilm development [61]. Wheat germ agglutinin named WGA is used for highlighting *Staphylococcus epidermidis* microcolonies, particularly in the experiments involved in bacterial organisation in biofilms during the formation of the bacteria aggregates [62]. The same authors, Sanford *et al*. used the WGA to quantify the production of GlcNAcβ-1,4 a carbohydrate component of the extracellular matrix that contributes to biofilm formation [63]. Lectins may be suitable anti-adhesion agents for streptococci, since it has been shown that a lectin-dependent mechanism is involved in its adhesion [64]. Plant lectins can be used as a novel approach to decrease the development of dental plaque by inhibiting the early adherence and subsequent formation of microbial biofilm [65].

ANTIVIRAL ACTIVITY OF PLANT LECTINS

Numerous lectins present antiviral activity, the best characterised is the lectin isolated from the fruit banana, *Musa acuminata.* This lectin was named BanLec and is a jacalin-related lectin. BanLec interacts with viruses such as human immunodeficiency virus type-1 (HIV-1) due to the specificity of the lectin to mannose carbohydrate structures. The antiviral activity of BanLec anti-HIV is very robust with IC50 values in the nanomolar to picomolar range. BanLec bind to gp120 glycoprotein by recognizing the high mannose structures. Moreover, temperature-sensitive viral entry studies showed that BanLec is able to block HIV-1 cellular entry to lymphocytes. These studies were also confirmed by the

Table 2. Antimicrobial activity of some plant lectins [29-65].

Plant	Lectin specificity	Antimicrobial activity
Araucaria angustifolia	GlcNAc	*Clavibacter michiganensis*, *Xanthomonas axonopodis*
Archidendron jiringa	Muramic acid, N-acetylmuramic acid	*Gram-positive bacteria*
Artocarpus incisa	GlcNAc	*Saccharomyces cerevisiae, Fusarium moniliforme*
Artocarpus integrifolia	GlcNAc	*Saccharomyces cerevisiae, Fusarium moniliforme*
Artocarpus heterophyllus	GlcNAc	*B. subtilis*, *P. aeruginosa*, *E. coli, S. aureus*
Astragalus mongholicus	Lactose/D-Gal	*Fusarium oxysporum, Botrytis cincerea, Drechslera turcia, Colletorichum* sp.
Bryothamnion seaforthii	Mucin	*Streptoccocus mutans*
Bryothamnion triquetrum	Mucin	*Streptoccocus sobrinus, S. mitis*
Canavalia boliviana	Man	*S. mutans, S. oralis*
Cladonia verticillaris	α-1,4-Polygalactoside	*E.coli, B. subtilis, E. faecalis*
Curcuma longa	Glc	*P. aeruginosa, Staphylococcus aureus, Fusarium oxysporum, Bacillus subtilis, Colectrotrichum cassiicola, Escheriehia coli, Candida albicans, Exserohilum turicicum*
Eugenia uniflora	Carbohydrate complex	*Bacillus subtilis, Klebsiella* sp., *Corynebacterium bovis, Streptococcus sp., E. coli, P. aeruginosa, Staphylococcus aureus*
Eucheuma serra	Man	*Vibrio vulnificus*
Galaxaura marginata	Man	*Vibrio sp.*
Gastrodia data	α-Man/ GlcNAc	*Bacillus cinerea, Valsa ambiens*, *Gibberella zeae*, *Rhizoctonia solani*, *Ganoderma lucidum*
Hevea brasiliensis	Chitotriose	*Bacillus. cinerea, F. oxysporum* f. sp. *pisi, Fusarium culmorum, Septoria nodorum, Phycomyces blakesleeanus, Pyricularia oryzae, Trichoderma hamatum, Pyrenophora triticirepentis*
Indigofera heterantha	Muramic acid	*Klebsiella pnuemoniae, S. aureus, E. coli, B. subtilis*
Lathyrus ochrus	Muramic acid, muramyl dipeptide	*B. subtilis*, *P. aeruginosa*, *E. coli, S. aureus*
Lens culinaris	Glc/Man	*S. aureus, B. subtilis, P. aeruginosa, E. coli,*
Myracrodruon urundeuva	GlcNAc	*Klebsiella pneumoniae, B. subtilis, E. coli, Corynebacterium callunae, S. aureus, P. aeruginosa, Fusarium sp., Streptococcus faecalis*
Ophiopogon japonicus	Man	*R. solani, Gibberella saubinetii*
Opuntia ficus indica	Glc/Man	*Candida albicans, Colletrotrichum gloesporioides*, *Fusarium oxysporum, Fusarium solani*
Phaseolus coccineus	Sialic acid	*Sclerotinia sclerotiorum, Helminthosporium maydis*, *R. solani*, *Gibberalla sanbinetti*
Phthirusa pyrifolia	Fru-1,6P	*Staphylococcus epidermidis*, *S. faecalis*, *B. subtilis*, *K. pneumoniae*, *F. lateritium, R. solani*
Pisum sativum	Man	*Trichoderma viride, Fusarium oxysporum, Aspergillus flavus*
Sebastiania jacobinensis	Carbohydrate complex	*Fusarium moniliforme, Fusarium oxysporum*
Solanum tuberosum	Chitin	*E. coli O157:H18, Listeria monocytogenes, S. enteridis, S. boydii, Rhizopus sp., Penicillium sp., Aspergillus niger*
Schinus terebinthifolius	Chitin	*Candida albicans, Fusarium sp., Aspergilum sp.*
Triticum vulgaris	GlcNAc, Sialic acid	*Staphylococcus epidermidis, Strepococcus sp.*
Urtica dioica	GlcNAc	*Septoria nodorum, B. cinerea, T. viride C. lindemuthianum, Phycomyces blakesleeanus, Trichoderma hamatum, Phoma betae*
Vicia faba	Sialic acid, Glc	*E. coli, P. aeruginosa*

(Glc- glucose, GlcNAc- N-acethylglucosamine, Gal- galactose, Man- manose).

decreased levels of products of early reverse transcription in the presence of BanLec. The Anti-HIV action of BanLec was compared positively with two anti-HIV drugs presently used in the clinic, Maraviroc and T-20 and to other anti-HIV lectins, such as griffithsin and snowdrop lectin [66]. A new lectin isolated from red marine alga *Kappaphycus alvarezii* named KAA-2 (with specificity to mannose type *N*-glycans) presented antiviral effect against H1N1 virus [67]. Another lectin isolated from the red alga *Griffithsia* sp. called griffithsin (GRFT) blocks the access of HIV virus to target cells by binding to mannose specific carbohydrates present in the virus envelop [68]. Furthermore, GRFT is active in other viruses such as coronaviruses that give the severe acute respiratory syndrome (SARS) [69]. Lectin from *Gerardia savaglia* (D-mannose–specific) was described to prevent infection of H9 cells with HIV virus. The lectin interacted with glucidic side chain of gp120 envelop molecules and inhibited syncytium formation in the infected H9 and Jurkat cells and human lymphocytes. The lectins concanavalin A, Lens culinaris agglutinin, *Vicia faba* agglutinin, wheat germ agglutinin, *Pisum sativum* agglutinin were also found to interact with HIV virus by binding to mannose specific residues of the gp120 glycoprotein. These lectins inhibit the interaction of HIV virus with CD4+ cells by blocking the linkage site of the virus, and also by agglutinating the virus [70]. Other plant lectins, especially mannose-binding lectins displayed anti-coronaviral activity in SARS syndrome. They interfered with the attachment of viruses in early stage of replication cycle and blocked the multiplication and proliferation of viruses [71]. The therapy of AIDS with lectins is being studied by many researchers. Diverse lectins have different anti-HIV mechanisms of action. Recently, it was seen that polychaete worm *Chaetopterus variopedatus* produced a lectin that inhibited the viral p24 antigen of HIV-1, as demonstrated by lack of cytopathic effect on target cells. The sea worm (*Serpula vermicularis*) lectin presents the same effect as lectin from polychaete worm, suggesting that these sea worms present some lectins that are conserved between species [72]. *Polygonatum cyrtonema* lectin inhibited cytophatic effect in MT-4 and CEM cells infected with both HIV-1 and HIV-2 [73]. The snowdrop *Galanthus nivalis* and *Hippeastrum* hybrid produce lectins named GNA and HHA respectively, which inhibit a variety of HIV-1 and HIV-2 strains and clinical CXCR4- and CCR5- isolates in diverse human cell types. Furthermore, these lectins proved their efficiency in inhibiting a variety of mutant virus strains in T lymphocytes. HHA and GNA clearly inhibit syncytium formation in infected HuT-78/HIV T lymphocytes [74]. Different lectin molecules like MAP30 from bitter melon and GAP31 from *Suregada multiflora* show antiviral activity [75]. In wild mushroom *Russula delica* was identified as a dimeric lectin with two identical subunits, with a molecular weight of 60 kDa and high hemagglutinating activity. This lectin presents a strong antiviral activity, but lacks mitogenic activity towards mouse splenocytes. *Russula delica* lectin inhibited the proliferation of HepG2 hepatoma cells and MCF7 breast cancer cells, with the half maximal inhibitory concentration value of 0.88 μM and 0.52 μM, respectively. Also, dimeric lectin inhibited an IC50 of 0.26 μM the HIV-1 reverse transcriptase activity [76]. From the mushroom *Hericium erinaceum* a lectin was isolated which was designated as *Hericium erinaceum* agglutinin (HEA) with a mass approximated to 51 kDa. Inulin assay showed that the hemagglutinating activity of HEA was inhibited at the concentration of 12.5 mM inulin. HEA presents mitogenic activity and inhibits HIV-1 reverse transcriptase activity with an IC50 of 31.7 μM, but lacks of antifungal activity [77].

ANTIPARASITIC ACTIVITY OF PLANT LECTINS

A large body of data exists regarding the interaction of lectins with a relatively broad spectrum of parasites ranging from the protozoa through the metazoan. Although Concanavalin A was used by many investigators as a lectin probe for these organisms, many other lectins have been used to study the cell surface molecules, and identification and differentiation of the parasites. In some instances, pathogenesis of protozoa seems to be correlated to their surface properties, as revealed by interactions with lectins. Thus, several investigators consider the comparison of surface saccharides of parasites very important for knowing the differences in virulence traits. It has been assumed that the virulence of the trophozoite form of *Entamoeba histolytica* may depend, in part, on its surface properties. The data that have been presented until now indicate that only strains isolated from cases of amoebic dysentery agglutinate with Concanavalin A, strains isolated from asymptomatic cases of amoebic dysentery, however, do not agglutinate with this lectin [78]. Marla *et al*. studied the cytotoxic activity of ten lectins (*Scheffera odorta, Swietenia macrophylla, Carica papaya, Artocarpus blancoi, Phaseolus vulgaris, Lenzites* sp., *Polyporus* sp., *Holothuria atra*) against *Acanthamoeba* sp. and *Tetrahymena pyriformis*. *Acanthamoeba* sp. is an amoeba that caused keratitis, a serious and potentially devastating corneal infection generally seen in soft contact lens wearers, while the ciliated *Tetrahymena pyriformis* is widely used as a test organism in the assessment of the cytotoxicity of different compounds and therapeutic agents. All lectins, with the exception of those from marine invertebrates (*Holoturia atra*), showed activity against the protozoans at 500 ppm. The growth of both protozoans upon exposure to the lectins was inhibited after 24 h of incubation. *Lenzites* sp. lectin was found to be active against both protozoans after one hour of incubation. These were also observed in the two seed lectins, where *C. papaya* lectin exhibited activity against *Tetrahymena pyriformis* while *A. blancoi* lectin showed activity against Acanthamoeba. It has been also reported that Concanavalin A can bind both to the plasma membrane and intracellular structures of *Tetrahymena pyriformis*. Binding of lectins with some sugars in the protozoans could cause interference in chemical or biological processes that eventually lead to the death of these parasites [79]. Mello *et al*. showed that lectin isolated from *Rhodnius prolixus* could be effective on the life cycle of *Trypanosoma rangelii*. It was expressed that carbohydrates on the surface of *T. rangelii* and *T. cruzi* cells, interact with *Glycine maxima* and *Ricinus communis* lectins, suggesting that they could be used in the determination of *T. cruzi* from the faeces of *Rhodnius prolixus,* one of the most important vector of the Chagas parasite [80]. It was further reported that con-A killed the procyclic forms of *T. brucei*, by attaching itself to N-glycans on their surfaces [81]. It was reported that WGA intensely agglutinated *Giardia intesti-*

nalis trophozoites and cycts and stopped their *in vitro* reproduction. Accordingly, it was concluded that food lectins could affect the course of giardiosis [82-84]. Dietary supplementation with *Curcuma longa* extract rich in lectins improved coccidiosis resistance as proved by stimulating body weight gains, reduced faecal oocyst, and reduced intestinal lesions compared with non-supplemented control diet. The chickens nourished Curcuma longa-supplemented diet presented an improved cellular immune response, as assessed by concanavalin A-induced spleen cell proliferation assay and also a stimulation of humoral immunity, as demonstrated by the high levels of serum antibodies to an Eimeria protein, MIC2. In the gut tissues, molecular biology techniques such as microarray assay identified 601 different transcripts, 287 were upregulated and 314 downregulated compared with non-supplemented controls. Analysing this gene it showed that mostly are associated with inflammatory processes [85]. The phytohaemagglutinin lectin extracted from *Phaseolus vulgaris* (PHA) has been shown to inhibit the feeding of *Trichostrongylus colubriformis* and *Teladorsagia circumcincta* L1 larvae. While the worms load were similar, animals treated with PHA lectin presented a nematode egg concentration in the faeces significantly lower compared with non-lectin treated nematode, suggesting that PHA lectin may presents an direct effect on parasite fecundity [86]. The ability of the plant lectins such as *Artocarpus heterophyllus* jacalin lectin (JAC), *Robinia pseudoacacia* agglutinin (RPA), concanavalin A (Con A), phytohemagglutinin L4 (PHA-L4), phytohemagglutinin E2L2 (PHA-E2L2), phytohemagglutinin E3L (PHA-E3L), wheat germ agglutinin (WGA), kidney bean albumin (KBA), *Maackia amurensis* lectin (MAL), *Maclura pomifera* agglutinin (MPA), *Dolichos biflorus* agglutinin (DBA), and *Galanthus nivalis* agglutinin (GNA) to block the feeding of nematodes *Teladorsagia circumcincta*, *Haemonchus contortus* and *Trichostrongylus colubriformis* in the first stage larvae L(1) from the sheep gastro-intestinal was assessed using a larval feeding inhibition test (LFIT). Only Con A, WGA and PHA-E3L, had a powerful effect on blocking larval feeding for all three species of gastro-intestinal nematodes [87]. Cyanobacteria lectin named cyanovirin-N is well known for antiretroviral activity, but recent studies show that this lectin binds to well-known *Entamoeba histolytica* and promotes phagocytosis [88]. *Giardia lamblia* is a flagellated protozoan parasite that colonizes and reproduces in the small intestine, causing giardiasis, a waterborne disease spreading worldwide. Different doses of wheat germ agglutinin (WGA) inhibit *Giardia lamblia* excystation and trophozoite growth *in vitro*. In mice infected with *Giardia muris* WGA decreased cyst passage. A double-blind study on 63 human subjects with giardiasis whose diet was supplemented with WGA lectin showed significant differences. The subjects were divided based on their symptoms in 25 asymptomatic patients with passing cysts and 38 patients with symptoms. They received 2g of WGA lectin 3 times a day or placebo (corn-starch) for 10 days, followed by metronidazole for 7 days. Stool specimens were collected every day for 10 days and microscopic examination and coproantigen determination was employed. In asymptomatic subjects, both coproantigen levels and cyst passage were reduced by 50% in those taking WGA compared with the placebo group. In symptomatic subjects, coproantigen levels and cyst passage was reduced in response to metronidazole. In the presence of WGA lectin the symptoms appear to resolve more rapidly than in patients taking metronidazole alone. A possible explanation of this effect is that the components of WGA single or in combination with metronidazole block the parasites to attach to the gastrointestinal tract and stop the course of giardiasis [89]. The possible mechanisms that could affect the survival of Giardia growth *in vitro* may be: (i) the lectin could be cytotoxic to the parasite, as it is to a number of mammalian cell lines, (ii) WGA could agglutinate trophozoites and prevent them from multiplying, (iii) WGA interferes with the function of surface glycoproteins involved in Giardia attachment, as is the case with other cell types [90].

The therapeutic effect of WGA as a lectin either alone or in combination with Nitazoxanide (NTZ) was also evaluated experimentally on cryptosporidial infection using immuno-

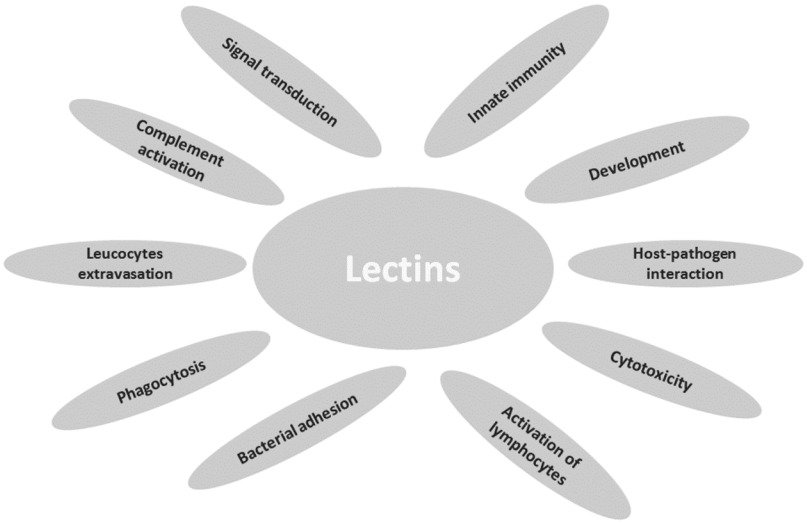

Fig. (1). Schematic representation of major processes mediated by lectins.

suppressed mice. A total of 100 mice were immunosuppressed and infected with 106 purified Cryptosporidium oocysts. The oocysts count in stool using modified Ziehl-Neelsen technique on the days post infection (p.i), and the histopathological examination of ileum sections and the IFN-g serum level were assessed for the drug evaluation. The use of WGA alone or with NTZ showed significant reduction of excreted oocysts count started on day 7, while the use of NTZ showed significant reduction started on day 10 in comparison to control group. The combined therapy showed significant reduction of oocysts in comparison to NTZ alone. The histopathological examination of mice receiving WGA alone or with NTZ showed increased inflammatory reaction and infiltrating inflammatory cells with multiple foci of enterocyte exfoliation along the villi. The IFN-g serum level was significantly higher than control in NTZ received groups. In conclusion, the combined therapy of NTZ and WGA showed earlier and better therapeutic effect against cryptosporidium infection [91].

CONCLUSIONS

Antimicrobial resistance is increasing across the world by development of new resistance mechanisms that spread globally leading to ever-increasing range of infections caused by viruses, bacteria, fungi and parasites. Antibiotic-resistant bacteria cause common infections and a high percentage of hospital-acquired infections where methicillin-resistant *Staphylococcus aureus* or multidrug-resistant bacteria come first. Discovery of the lectins with antimicrobial and antiparasitic activity could be used as adjuvant therapy for improving antibiotic therapy. Lectins can become part of diet and inhibit the attachment of microorganisms and parasites by blocking their carbohydrate sites required for interaction with host cells or even acting in the survival and growth of parasites. Investigation of lectin molecular mechanism of host-pathogen interaction can lead to develop novel ecological strategies for the treatment of infectious diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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