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Review

A review on the antimicrobial properties of lectins

Victor Juno Alencar Fonseca [a], Ana Lays Braga [a], Jaime Ribeiro Filho [b], Claudener Souza Teixeira [c], Gabriel C.A. da Hora [d], Maria Flaviana Bezerra Morais-Braga [a,*]

[a] Laboratório de Micologia Aplicada do Cariri – LMAC, Universidade Regional do Cariri – URCA, Crato, CE, Brazil
[b] Laboratório de Investigação em Genética e Hematologia Translacional, Instituto Gonçalo Moniz (IGM), Fundação Oswaldo Cruz (Fiocruz), Salvador, Brazil
[c] Centro de Ciências Agrárias e da Biodiversidade, Universidade Federal do Cariri, Crato, CE, Brazil
[d] Department of Chemistry, University of Utah, Salt Lake City, UT 84112-0850, USA

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ABSTRACT

Lectins are biologically versatile biomolecules with remarkable antimicrobial effects, notably against bacteria, fungi and protozoa, in addition to modulating host immunity. For this, the lectins bind to carbohydrates on the surface of the pathogen, which can cause damage to the cell wall and prevent the attachment of microorganisms to host cells. Thus, this study intends to review the biological activities of lectins, with an emphasis on antimicrobial activity. Lectins of plant stood out for its antimicrobial effects, demonstrating that they act against a variety of strains, where *in vitro* were able to inhibit their development and affect their morphology. *In vivo*, they modulated host immunity, signaling and activating defense cells. Some of these lectins were capable to modulate the action of antibiotics, indicating their potential to minimize the antibiotic resistance. The results suggest that lectins have antimicrobial activity with potential to be used in drug development.

1. Introduction

Lectins are proteins with a variety of biological functions, among which antimicrobial defense has been highlighted in the literature. These naturally occurring molecules are commonly secreted in response to invasive agents such as bacteria [1], binding to carbohydrates on the surface of both pathogens and leukocytes, which results in direct and indirect antimicrobial effects, respectively [2]. Since these proteins are produced by a great variety of living organisms, they are often categorized according to their natural source as animal lectins, plant lectins, fungal lectins, or bacterial lectins. Alternatively, lectins are classified according to their binding affinity to specific carbohydrates (ex. Galactose-binding lectin, fucose-binding lectin, N-glycan-binding lectin) [3]. In this context, lectin-carbohydrate binding is governed by attractive forces, which include hydrogen bonds, hydrophobic and electrostatic interactions [4]. In addition, the binding of some lectins to their specific carbohydrates requires the participation of certain ions, such as Ca^{2+} and Mg^{2+} [5].

Lectins also play important roles in the innate immunity of multicellular organisms, which can be due to their similarity with the epitopes of some glycans found on the cell surface of pathogens. Such similarity favors the activation of signaling pathways in a variety of cells, through the activation of surface receptors [6]. Especially in animals and plants, lectin-triggered signaling contributes to cell immobilization, as well as to cytotoxic mechanisms associated with growth inhibition and cell death [7,8].

Studies have identified a series of mechanisms through which lectins combat infectious agents. Research conducted by Zhang et al. [9] demonstrated that a lectin extracted from the fish species *Misgurnus anguillicaudatus* had significant agglutinating activity against Gram-negative bacteria, possibly due to its interaction with lipopolysaccharides (LPS) present in the outer membrane of these microorganisms. This mechanism seems to be common to most lectins and possibly explains how these molecules inhibit the formation of biofilms and bacterial aggregates [10]. On the other hand, evidence has indicated that the antifungal effects of lectins result from the interaction with chitin (a biopolymer found on the surface of these microorganisms), which may in incomplete development of spores [11]. Additionally, lectins have immunomodulatory activities, regulating the polarization of CD4+ lymphocytes, including Th1, Th2, and Th17 [12] and thus stimulating the production of cytokines such as IFN- γ, IL-6, TNF-α, IL-4, IL-2, and IL-10 [13], which contributes to the elimination of a variety of microbes

* Corresponding author at: Universidade Regional do Cariri—URCA, Centro de Ciências Biológicas e da Saúde—CCBS, Departamento de Ciências Biológicas - DCBio, Laboratório de Micologia Aplicada do Cariri – LMAC, Av. Cel. Antonio Luiz, 1161, Pimenta, CEP: 63105-000 Crato, CE, Brazil.
E-mail address: flaviana.morais@urca.br (M.F.B. Morais-Braga).

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and parasites.

Thus, this study intends to review the biological activities of lectins, with an emphasis on the advances and perspectives of targeted antimicrobial research.

2. Methodology

PubMed was consulted as a scientific literature database, and the general information did not specify a periodic window. As for applications and researches related to lectins, the period established was from 2000 to 2021. The following keywords were used in the search engines: "Lectin Antiprotozoal Activity", "Lectin Antifungal Activity", "Lectin Antibacterial Activity", totaling 1770 articles, of which, through a detailed analysis, 88 articles were selected, which was not included review articles, nor those that addressed lectins, but did not bring results regarding the intended biological activities. Cellular organisms were also prioritized, excluding viruses from the inclusion criteria. Both *in vivo* and *in vitro* studies were included, with or without description of mechanisms of action.

3. Antimicrobial activities of lectins

A summary of the antibacterial, antifungal, and antiparasitic activities of lectins is shown in Tables 1, 2, and 3, respectively. A total of 27 articles investigated the effects of lections on bacterial and fungal growth. In addition, the present search demonstrated the ability of lectins to modulate the activity of antimicrobial drugs (6 articles) and inhibit biofilm formation (12 articles), which significantly contributes to their antimicrobial effects, especially against bacteria.

With regard to the mechanisms underlying the antimicrobial activities of lectins, the search carried out in the present study found that lectins are capable of causing direct damage to bacterial, fungal, and protozoan cells (5 articles), in addition to acting as agglutinating agents (8 articles) and inhibiting spore germination (5 articles). Here, we discuss both the antimicrobial effects and potential mechanisms of actions of lectins of both plant and animal origin, emphasizing their potential use in antimicrobial drug development.

At the end of each session, figures with the suggested bioactivity performed by the lectins were added. In Section 3.1, Fig. 5 shows the mechanisms of agglutination, anti-adherent, anti-biofilm and drug synergism. In Section 3.2, Fig. 7 shows how the lectin prevents the adhesion of spores to a surface, as well as inhibiting the entry of extracellular carbohydrate into the fungal cell, interfering with spore germination. In Section 3.3, Fig. 8 shows the immunomodulatory role of lectins against protozoa.

3.1. Lectins with antibacterial activity

3.1.1. Lectins with immunomodulatory activity

Studies have demonstrated that lectins have a remarkable immunomodulatory activity, and therefore can stimulate the defense system against invading agents. In this context, C-type lectins are present in several organisms, where they play important roles in innate immunity. Accordingly, previous research demonstrated that OppCTL, a Ca^{2+}-dependent lectin extracted from the fish *Oplegnathus punctatus*, has its expression significantly increased (especially in the liver), during infectious processes. This lectin was found to present agglutinating activity in the presence of bacterial cell wall components such as lipopolysaccharide (LPS) and peptidoglycan (PGN), corroborating its increased production in response to invasive pathogens [2]. Similar findings were reported for PcLec6, another Ca^{2+}-dependent lectin extracted from the crustacean *Procambarus clarkii*. In addition to presenting high affinity to LPS and PGN, this lectin showed agglutinating activity in the presence of *Staphylococcus aureus* and *Vibrio alginolyticus*. Furthermore, the inoculation of the lectin into the crustacean facilitated the clearance of the bacterium *V. alginolyticus*, indicating a possible immune role in the crustacean [1].

Li et al. [14], investigating the antibacterial activity of LvCTL3, a recombinant lectin extracted from *Litopenaeus vannamei*, against Gram-negative and Gram-positive bacteria, showed agglutinating activity against *V. alginolyticus*, *Vibrio parahaemolyticus*, and *Bacillus subtilis in* the presence of Ca^{2+}. In addition, this lectin was capable of reducing the mortality of shrimps infected with *V. parahaemolyticus* when compared to the vehicle-treated group. Importantly, LvCTL3 was detected in all shrimp tissues, especially in hemocytes and gills, suggesting that this lectin may be involved in pathogen recognition and immune response. These findings are corroborated by the study of Sun et al. [15], who demonstrated that Fc-hsL, a lectin extracted from the shrimp *Fenneropenaeus chinensis*, had agglutinating activity and inhibited the growth of both Gram-positive (*Bacillus cereus*, *Bacillus megaterium*, *Bacillus thuringiensis*, *Micrococcus luteus*, and *S. aureus*) and Gram-negative (*Escherichia coli* and *Klebsiella pneumoniae*) bacteria. Importantly, during infection, FC-hsL was also detected in the hepatopancreas, one of the most important organs of the humoral response of shrimps.

Lectins with immunomodulatory activity participate in the immune response of invertebrate organisms. Studies have shown that they can opsonize invasive bacteria or foreign particles, increasing their phagocytosis. The expression of HSL lectins in the sea cucumber *Holothuria scabra*, was found to increase in response to artificial bacterial infection, reducing the number of colony-forming units from the first day of testing, reaching complete inhibition at the fifth day of inoculation. This lectin also inhibited bacterial growth *in vitro* in comparison with the control ampicillin [16].

A lectin extracted from the mussel *Mytilus trossulus* (MTL), which agglutinated in the presence of *Vibrio proteolyticus*, had its activity inhibited in the presence of D-galactose. Following the challenge with *V. proteolyticus*, the expression of MTL was significantly upregulated, suggesting that this lectin may also be involved in the immune response of mollusks to infections by pathogenic microorganisms in aquatic environments [17]. Accordingly, CGL, another mussel lectin extracted from *Crenomytilus grayanus* (Fig. 1), also inhibited the growth of Gram-positive and Gram-negative bacteria, strongly binding to *E. coli*, which was inhibited in the presence of D-galactose, indicating that mussel lectins may have similar antibacterial properties [18]. According to He et al. [19], PmCTL-1, a C-type lectin extracted from the oyster *Pinctada fucata* showed strong activity against Gram-positive bacteria such as *M. luteus*, *S. aureus* and *B. subtilis*.

Some animals produce venom as a defense mechanism, such as snakes. In relation to these animals, lectins with antibacterial activity can be isolated from their venom. About snake lectins, the fraction P8—I, extracted from the venom of *Bothriopsis oligolepis* showed antibacterial activity against *Salmonella choleraesuis*, *M. luteus*, and *S. aureus*, the latter being the most sensitive to the protein, which had inhibitory concentrations comparable to those obtained with the positive control ampicillin [20]. On the other hand, lectin BIL extracted from the snake venom *Bothrops leucurus* showed antibacterial activity against *S. aureus*, *Enterococcus faecalis*, and *B. subtilis*. However, a bactericidal effect was achieved only at high concentrations [21].

Two lectin fractions extracted from the skin of the wild frog *Bufo arenarum* (LBP1 and LBP2) were tested *in vitro* against microorganisms naturally present in the skin of the animal. The results showed that both fractions likewise suppressed the growth of bacteria in a solid medium. Additionally, when the fractions were removed, the bacteria grew back, indicating that the lectins present in the fraction present a bacteriostatic activity [22].

A lectin extracted from the fish *Misgurnus anguillicaudatus* (MaCTL) showed strong agglutinating activity in human and hare erythrocytes. However, this activity was only observed in the presence of Ca^{2+}, corroborating the evidence that C-type lectins have a Ca^{2+}-dependent activity. In this context, Zhang et al. [9] demonstrated that this lectin induced agglutination in the presence of the six different bacteria (*B. subtilis*, *M. luteus*, *S. aureus*, *A. hydrophila*, *E. coli*, and *Vibrio*

Table 1
Antibacterial activity of lectins reported in the literature. The concentrations mentioned are the lowest with relevant activity against the bacteria tested.

Species	Lectin	Bioactivity	Bioactivity concentration	Affected microorganisms	References
Vatairea macrocarpa (Benth.) Ducke	VML	Modulation + penicillin; Modulation + gentamicin; Modulation + norfloxacin	14.94 μM; 1.18 μM; 4.71 μM.	*Staphylococcus aureus*; *Staphylococcus aureus*; *Staphylococcus aureus*.	[31]
Dioclea violacea Benth.	DVL	Modulation + gentamicin	0.39 μM; 0.49 μM.	*Staphylococcus aureus*; *Echerichia coli*.	[29]
Pinctada fucata martensii (Dunker, 1880)	PmCTL-1	Growth inhibition	11.18 μM; 11.18 μM; 11.18 μM.	*Micrococcus luteus*; *Staphylococcus aureus*; *Bacillus subtilis*.	[19]
Misgurnus anguillicaudatus (Cantor, 1842)	rMaCTL	Agglutinating	0.04 μM; 0.08 μM; 0.04 μM; 0.08 μM.	*Aeromonas hydrophila*; *Escherichia coli*; *Vibrio anguillarum*; *Staphylococcus aureus*.	[9]
Canavalia ensiformis (L.) DC.	ConA	Modulation + gentamicin	0.50 μM; 0.78 μM.	*Staphylococcus aureus*; *Escherichia coli*.	[30]
Lantana camara L.	LCL	Growth inhibition	10 μg (7.1 mm); 10 μg (7.3 mm); 10 μg (6,9 mm).	*Klebsiella pnumoniae*; *Pseudomonas aeruginosa*; *Escherichia coli*.	[55]
Vicia faba L.	ND[a]	Growth inhibition	0.87 μM; 0.87 μM; 3.47 μM.	*Staphylococcus aureus*; *Klebsiella pneumonia*; *Pseudomonas aeruginosa*.	[49]
Lens culinaris Medik.	ND[a]	Growth inhibition	0.14 μM; 0.28 μM; 1.09 μM.	*Staphylococcus aureus*; *Klebsiella pneumonia*; *Pseudomonas aeruginosa*.	[49]
Pisum sativum L.	ND[a]	Growth inhibition	7.35 μM; 3.68 μM; 7.35 μM.	*Staphylococcus aureus*; *Klebsiella pneumonia*; *Pseudomonas aeruginosa*.	[49]
Penaeus semisulcatus De Haan, 1844 [in De Haan, 1833–1850]	Semisulcatus lectin	Antibiofilm	1.52 μM; 1.52 μM; 1.52 μM; 1.52 μM.	*Aeromonas hydrophila*; *Vibrio parahaemolyticus*; *Staphylococcus aureus*; *Enterococcus fecalis*.	[41]
Portulaca elatior Mart. ex Rohrb	PeRoL	Growth inhibition	0.25 μM; 0.12 μM; 0.98 μM.	*Enterococcus faecalis*; *Pseudomonas aeruginosa*; *Staphylococcus aureus*.	[24]
Punica granatum L.	PgTeL	Growth inhibition	0.24 μM; 0.48 μM;	*Staphylococcus aureus* 8325-4; *Staphylococcus aureus* LAC USA300;	[38]
Aplysina fulva (Pallas, 1766)	AFL	Antibiofilm	0.52 μM; 8.33 μM; 16.67 μM.	*Staphylococcus aureus*; *Staphylococcus epidermidis*; *Escherichia coli*.	[42]
Oplegnathus punctatus (Temminck & Schlegel, 1844)	rOppCTL	Agglutinating	5.19 μM; 5.19 μM; 5.19 μM; 5.19 μM; 5.19 μM; 5.19 μM.	*Bacillus subtilis*; *Staphylococcus aureus*; *Escherichia coli*; *Vibrio anguillarum*; *Edwardsiella tarda*; *Aeromonas hydrophila*.	[2]
Parkia platycephala Benth.	PPL	Modulation + gentamicin	0.51 μM; 0.40 μM.	*Staphylococcus aureus*; *Escherichia coli*.	[33]
Canavalia ensiformis (L.) DC.	ConA	Antibiofilm	3.92 μM; 3.92 μM.	*Escherichia coli*; *Listeria monocytogenes*.	[40]
Procambarus clarkii (Girard, 1852)	PcLec6	Agglutinating	2.58 μM; 2.58 μM.	*Staphylococcus aureus*; *Vibrio alginolyticus*.	[1]
Stenopsyche kodaikanalensis Swegman & Coffman, 1980	*Stenopsyche kodaikanalensis* lectin	Agglutinating; Bacteriolytic	1.67 μM; 1.67 μM.	*Bacillus subtilis*; *Bacillus flexus*.	[25]
Chondrilla caribensis f. hermatypica Rützler, Duran & Piantoni, 2007	CCL	Antibiofilm	7.35 μM; 0.92 μM; 29.41 μM.	*Staphylococcus aureus*; *Staphylococcus epidermidis*; *Escherichia coli*.	[43]
Aplysia dactylomela Rang, 1828	ADEL	Antibiofilm	0.26 μM.	*Staphylococus aureus*.	[10]
Calliandra surinamensis Benth.	Casul	Antibiofilm	0.13 μM; 1.04 μM; 0.26 μM; 0.13 μM.	*Staphylococcus aureus*; MRSA; *Escherichia coli*; *Staphylococcus saprophyticcus*.	[45]
Mytilus trossulus Gould, 1850	MTL	Agglutinating	2.8 μM.	*Vibrio proteolyticus*.	[17]
Moringa oleifera Lam.	WSMoL	Growth inhibition	0.54 μM; 17.27 μM.	*Staphylococcus aureus*; *Escherichia coli*.	[26]
Bauhinia variegata L.	nBVL	Anti-adhesive	6.25 μM; 6.25 μM.	*Streptococcus mutans*; *Streptococcus sanguinis*.	[37]
Artocarpus heterophyllus Lam.	Artocarpine	Growth inhibition	0.97 μM; 0.97 μM; 3.89 μM.	MRSA; *Escherichia coli*; *Pseudomonas aeruginosa*.	[32]
Sparassis latifolia Y.C. Dai & Zheng Wang 2006	*Sparassis latifolia* lectin	Growth inhibition			[47]

(*continued on next page*)

Table 1 (*continued*)

Species	Lectin	Bioactivity	Bioactivity concentration	Affected microorganisms	References
			8.33 μM; 4.17 μM; 2.08 μM.	*Staphylococcus aureus*; *Escherichia coli*; *Pseudomonas aeruginosa*.	
Andrias davidianus (Blanchard, 1871)	ADL	Respiration inhibition	735.29 μM; 735.29 μM; 735.29 μM; 735.29 μM; 735.29 μM.	*Escherichia coli*; *Enterobacter aerogenes*; *Staphylococcus aureus*; *Bacillus subtilis*; *Shewanella* sp.	[28]
Apuleia leiocarpa (Vogel) J.F.Macbr.	ApulSL	Growth inhibition	0.81 μM; 0.81 μM; 1.62 μM; 3.23 μM; 0.81 μM; 1.62 μM; 3.23 μM; 3.23 μM; 3.23 μM; 3.23 μM; 0.20 μM; 0.40 μM; 0.40 μM.	*Bacillus subtilis*; *Bacillus cereus*; *Enterococcus faecalis*; *Escherichia coli*; *Klebsiella pneumoniae*; *Micrococcus luteus*; *Pseudomonas aeruginosa*; *Salmonella enteritidis*; *Staphylococcus aureus*; *Streptococcus pyogenes*; *Xanthomonas campestris* pv. *peasants*; *Xanthomonas campestris* pv. *malvacearum*; *Xanthomonas campestris* pv. *viticola*.	[48]
Aspergillus gorakhpurensis Kamal & Bhargava 1969	*A. gorakhpurensis* lectin	Growth inhibition	50.14 μM; 50.14 μM; 50.14 μM.	*Bacillus cereus*; *Staphylococcus aureus*; *Escherichia coli*.	[27]
Kaempferia rotunda L.	KRL	Growth inhibition	1.72 μM; 1.72 μM.	*Staphylococcus aureus*; *Escherichia coli*.	[86]
Solanum tuberosum L.	StL-20	Growth inhibition	1.25 μM; 0.50 μM; 0.50 μM; 1.25 μM.	*Escherichia coli*; *Listeria monocytogenes*; *Salmonella enteritidis*; *Shigella boydii*.	[46]
Litopenaeus vannamei (Boone, 1931)	LvCTl3	Agglutination	5.56 μM; 5.56 μM; 5.56 μM.	*Vibrio alginolyticus*; *Vibrio parahaemolyticus*; *Bacillus subtilis*	[14]
Sterculia foetida L.	SFL	Growth inhibition	7.53 μM; 15.06 μM; 7.53 μM; 15.06 μM; 7.53 μM; 15.06 μM.	*Bacillus subtilis* CCT 0516; *Escherichia coli* ATCC 2536; *Pseudomonas aeruginosa* ATCC 23243; *Staphylococcus aureus* ATCC 25619; *Pseudomonas aeruginosa* ATCC 8027; *Staphylococcus aureus* ATCC 25925.	[52]
Schinus terebinthifolius Raddi - synonymy of Schinus terebinthifolia Raddi	Stell	Growth inhibition	0.13 μM; 2.05 μM; 0.26 μM; 0.13 μM; 0.26 μM; 0.03 μM.	*Pseudomonas aeruginosa*; *Escherichia coli*; *Klebsiella pneumoniae*; *Staphylococcus aureus*; *Proteus mirabilis*; *Salmonella enteritidis*.	[7]
Moringa oleifera L.	WSMoL	Growth inhibition	69.06 μM; 69.06 μM.	*Staphylococcus aureus*; *Escherichia coli*.	[51]
Bothrops leucurus (Wagler, 1824)	BIL	Growth inhibition	1.05 μM; 2.08 μM; 4.17 μM.	*Staphylococcus aureus*; *Enterococcus faecalis*; *Bacillus subtilis*.	[21]
Kaempferia rotunda L.	KRL	Growth inhibition	2.59 μM; 2.59 μM; 2.59 μM; 2.59 μM; 20.69 μM; 20.69 μM.	*Shigella Sonnei*; *Bacillus cereus*; *Bacillus subtilis*; *Bacillus megaterium*; *Klebsiella* sp.; *Sarcina lutea*.	[50]
Eugenia uniflora L.	EuniSL	Growth inhibition	0.02 μM; 0.25 μM; 0.25 μM; 0.02 μM; 0.02 μM; 0.25 μM; 0.25 μM.	*Staphylococcus aureus*; *Streptococcus* sp.; *Bacillus subtilis*; *Klebsiella* sp.; *Pseudomonas aeruginosa*; *Corinebacterium bovis*; *Escherichia coli*.	[53]
Holothuria (Metriatyla) scabra Jaeger, 1833	HSL	Growth inhibition	0.01 μM; 0.03 μM; 0.04 μM; 0.05 μM;	*Staphylococcus* sp.; *Streptococcus* sp.; *Shigella* sp.; *Klebsiella* sp.;	[16]

(*continued on next page*)

Table 1 (*continued*)

Species	Lectin	Bioactivity	Bioactivity concentration	Affected microorganisms	References
			0.11 μM; 0.11 μM.	*Serratia* sp; *Escherichia coli*.	
Fenneropenaeus chinensis (Osbeck, 1765)	rFc-hsL	Growth inhibition	5 μM; 5 μM; 2.5 μM; 2.5 μM; 5 μM; 10 μM; 20 μM; 20 μM.	*Bacillus subtilis*; *Bacillus cereus*; *Bacillus megaterium*; *Bacillus thuringiensis*; *Micrococcus luteus*; *Staphylococcus aureus*; *Escherichia coli*; *Klebsiella pneumoniae*.	[15]
Fenneropenaeus chinensis (Osbeck, 1765)	rmFc-hsL	Growth inhibition	0.6 μM; 2.4 μM; 0.6 μM; 0.6 μM; 4.8 μM; 0.6 μM; 4.8 μM; 1.2 μM.	*Bacillus subtilis*; *Bacillus cereus*; *Bacillus megaterium*; *Bacillus thuringiensis*; *Micrococcus luteus*; *Staphylococcus aureus*; *Escherichia coli*; *Klebsiella pneumoniae*.	[15]
Bufo arenarum Hensel, 1867 - synonymy of *Rhinella arenarum* (Hensel, 1867)	LBP1	Growth inhibition	25 μg/11 ± 0.8; 25 μg/16 ± 0.8; 25 μg/20 ± 0.7; 25 μg/12 ± 0.7.	*Escherichia coli* K12 strain 4100; *Escherichia coli*; *Proteus morganii*; *Enterococcus faecalis*	[22]
Bufo arenarum Hensel, 1867 - synonymy of *Rhinella arenarum* (Hensel, 1867)	LBP2	Growth inhibition	25 μg/12 ± 0.5; 25 μg/17.5 ± 0.8; 25 μg/19 ± 0.7; 25 μg/12.5 ± 0.7.	*Escherichia coli* K12 strain 4100; *Escherichia coli*; *Proteus morganii*; *Enterococcus faecalis*	[22]
Myracrodruon urundeuva Allemão	MuLL	Growth inhibition	3.57 μM; 1.79 μM.	*Staphylococcus aureus* LAC USA300; *Staphylococcus aureus* 8325-4.	[56]
Myracrodruon urundeuva Allemão	MuBL	Growth inhibition	1.79 μM; 0.89 μM.	*Staphylococcus aureus* LAC USA300; *Staphylococcus aureus* 8325-4.	[56]
Myracrodruon urundeuva Allemão	MuHL	Growth inhibition	1.79 μM; 1.79 μM.	*Staphylococcus aureus* LAC USA300; *Staphylococcus aureus* 8325-4.	[56]

[a] ND: not determined.

anguillarum). However, this effect was achieved exclusively in the presence of Ca^{2+}. The lectin also inhibited the growth of 4 of the 6 bacteria (*A. hydrophila*, *E. coli*, *V. anguillarum*, and *S. aureus*), demonstrating significant activity against Gram-negative strains, which can be explained by the strong affinity of lectins to LPS. This type of bonding can cause damage to the membrane, leading to the generation of pores, which results in cell death [9].

While some lectins specifically recognize a particular type of sugar, others can recognize monosaccharides, disaccharides, oligosaccharides, and polysaccharides, although the affinity for each type of sugar may vary significantly. This is the case of PeRoL, a lectin extracted from the roots of *Portulaca elatior*, which can bind to sugars such as trehalose mannose, glucose, galactose and *N*-acetylglycosamine. Importantly, antimicrobial studies demonstrated its bacteriostatic activity against *E. faecalis*, *P. aeruginosa*, and *S. aureus*. With regard to the mechanism of action, bacteriostatic agents usually inhibit one of the following vital processes: cell wall synthesis, membrane functions, and proteins and nucleic acid synthesis [24].

Another non-selective lectin can be extracted from the serum of the larvae of the aquatic insect *Stenopsyche kodaikanalensis*. Studies demonstrated that this lectin agglutinated in the presence of lactose, galactose, laminarin, and fetuin. With regard to the biological activity, antimicrobial tests demonstrated its agglutinating and bacteriolytic activities against activity *B. subtilis* and *Bacillus flexus*, respectively [25]. The ability of lectins to agglutinate bacteria results in microbial mass concentration, which may require less biocide to achieve the effects on the cells [26].

A lectin extracted from the mycelium of *Aspergillus gorakhpurensis* was found to specifically bind to mucin and other complex carbohydrates such as *N*-acetyl-D-galactosamine, chondroitin-6-sulfate, fetine, N-glycolil neuramine, D-mannitol, and dihydrate D-trehalose. This lectin was significantly effective against Gram-positive bacteria such as *Bacillus cereus*, with an inhibition zone of 20 ± 0.25 mm at a lower concentration than that obtained with the control drug ampicillin [27].

ADL, a lectin extracted from the skin of salamander *Andrias davidianus*, showed antibacterial activity against *E. coli*, *Enterobacter aerogenes*, *S. aureus*, *B. subtilis*, and *Shewanella* sp. The mechanism of action by which this protein acts seems to be related to the inhibition of cell respiration. In fact, ADL inhibited glucose degradation pathways in different bacteria, including TCAC in *E. coli* and *S. aureus*, and HMP in *E. aerogenes*, *Shewanella* sp. and *B. subtilis*, which interrupts the vital processes of these organisms resulting in cell death [28].

3.1.2. Potentiation of antibiotic action

The species *Dioclea violacea* synthesizes a lectin with some specificity to mannose and glucose. This lectin showed no relevant antibacterial activity against multidrug-resistant bacteria such as *S. aureus*, *E. coli*, and *P. aeruginosa*. However, it was capable of potentiating the antibacterial effect of gentamicin, reducing the minimum inhibitory concentration (MIC) of the antibiotic against *S. aureus* and *E. coli* by 80.1% and 60.3%, respectively. The authors proposed that the lectin acts by delivering the drug to target cells through the recognition of carbohydrates in the membrane, which leads to the release of gentamicin, facilitating the entry of the antibiotic into the bacterial cytoplasm [29]. Similar findings were observed in a study conducted with a lectin obtained from *Canavalia ensiformis* (ConA), which had no significant antibacterial effect, but potentiated the activity of gentamicin against *S. aureus* and *E. coli* [30].

The antibiotic-potentiating activity of lectins has been consistently demonstrated. In this context, *Vatairea macrocarpa* lectin (VML) was able to reduce the MIC of norfloxacin, penicillin, and gentamicin against *S. aureus* [31]; Artocarpin, isolated from the heartwood of *Artocarpus heterophyllus*, showed moderate antibacterial activity against

Table 2
Antifungal activity of lectins reported in the literature. The concentrations mentioned are the lowest with relevant activity against the tested fungi.

Species	Lectin	Bioactivity	Bioactivity concentration	Microorganisms	References
ND[a]	Dectin-1-Fc (IgG2a)	Germination inhibition	0.20 μM.	*Aspergillus fumigatus*	[65]
ND[a]	Dectin-1-Fc (IgG2b)	Germination inhibition	0.20 μM.	*Aspergillus fumigatus*	[65]
Triticum aestivum L.	WGA-Fc (IgG2a)	Germination inhibition	0.20 μM.	*Aspergillus fumigatus*	[65]
Machaerium acutifolium Vogel	MaL	Growth inhibition	18 μM; 9 μM.	*Candida albicans*; *Candida parapsilosis*;	[68]
Vicia faba L.	ND[a]	Growth inhibition	1.74 μM.	*Candida albicans*.	[49]
Lens culinaris Medik.	ND[a]	Growth inhibition	0.28 μM.	*Candida albicans*.	[49]
Pisum sativum L.	ND[a]	Growth inhibition	14.71 μM.	*Candida albicans*.	[49]
Moringa oleifera Lam.	WSMoL	Growth inhibition	1.38 μM; 1.38 μM; 1.38 μM; 1.38 μM.	*Candida albicans*; *Candida glabrata*; *Candida krusei*; *Candida parapsilosis*.	[62]
Portulaca elatior Mart. ex Rohrb	PeRoL	Fungicide	0,48 μM; 0,48 μM; 0,48 μM; 0,48 μM.	*Candida albicans*; *Candida parapsilosis*; *Candida krusei*; *Candida tropicalis*.	[24]
Helianthus annuus L.	Helja	Growth inhibition	0.6 μM^{-7}.	*Candida Albicans*	[67]
Solanum integrifolium Lam.	CBL	Growth inhibition	1.52 μM.	*Rhizoctonia solani*;	[63]
Calliandra surinamensis Benth.	Casul	Growth inhibition	2.60 μM.	*Candida Krusei*	[45]
Phaseolus lunatus L.	Lunatin	Growth inhibition	4.12 μM; 4.12 μM; 4.12 μM; 4.12 μM;	*Pythium aphanidermatum*; *Fusarium solani*; *Fusarium oxysporum*; *Botrytis cinerea*.	[75]
Mytilus trossulus Gould, 1850	MTL	Germination inhibition	28 μM; 28 μM; 28 μM; 28 μM.	*Trichoderma*; *Haematonectria*; *Haematonectria*; *Alternaria*.	[17]
Sparassis latifolia Y.C. Dai & Zheng Wang	*Sparassis latifolia* lectin	Growth inhibition	4.17 μM; 1.04 μM; 4.17 μM; 2.08 μM; 8.33 μM; 4.17 μM.	*Candida albicans*; *Candida catenulate*; *Candida glabrata*; *Candida rugosa*; *Candida albicans* 14001; *Candida albicans* 14007.	[47]
Crenomytilus grayanus Dunker	CGL	Germination inhibition	55.56 μM; 55.56 μM; 55.56 μM.	*Aspergillus*; *Penicillium*; *Trichoderma*.	[66]
Phaseolus vulgaris L.	CPBL	Growth inhibition	30 μM.	*Valsa mali*	[74]
Helianthus annuus L.	Helja	Growth inhibition	12.50 μM; 12.50 μM; 12.50 μM; 12.50 μM.	*Candida albicans*; *Candida tropicalis*; *Candida parapsilosis*; *Pichia membranifaciens*.	[70]
Canavalia brasiliensis Benth.	ConBr	Growth inhibition	0.08 μM.	*Candida parapsilosis*.	[60]
Mucuna pruriens (L.) DC.	*Mucuna pruriens* lectin	Growth inhibition	0.03 μM.	*Candida parapsilosis*.	[60]
Clitoria fairchildiana R.A. Howard	*Clitoria fairhcildiana* lectin	Growth inhibition	0.02 μM.	*Candida parapsilosis*.	[60]
Dioclea virgata (Rich.) Amshoff	*Dioclea virgate* lectin	Growth inhibition	0.15 μM.	*Candida parapsilosis*.	[60]
Bauhinia variegata L.	BVL	Growth inhibition	3.91 μM.	*Candida parapsilosis*.	[60]
Abelmoschus esculentus (L.) Moench	*Abelmoschus esculentus* lectin	Growth inhibition	0.05 μM.	*Candida parapsilosis*.	[60]
Dioclea violacea Benth.	DVL	Growth inhibition	0.61 μM; 1.23 μM; 1.23 μM; 1.23 μM; 1.23 μM; 4.90 μM; 1.23 μM; 1.23 μM; 0.31 μM; 1.23 μM; 0.31 μM;	*Candida albicans* URM4987; *Candida albicans* URM4986; *Candida URM4979 azyma*; *Candida guilliermondii* URM4975; *Marine candida* URM4976; *Candida membranaefaciens* URM4983; *Candida obtusa URM4982*; *Candida robusta* URM4972; *Candida shehatae* URM4978; *Candida tropicalis URM6090*; *Candida tropicalis* URM4989; *Kloeckera apiculata* URM5002; *Rhodotorula glutinis* URM5092.	[87]

(*continued on next page*)

Table 2 (*continued*)

Species	Lectin	Bioactivity	Bioactivity concentration	Microorganisms	References
			0.61 μM; 9.81 μM.		
Dioclea rostrata Benth.	DRL	Growth inhibition	4.98 μM; 2.49 μM; 0.16 μM; 2.49 μM;	*Candida guilliermondii* URM4975; *Candida membranaefaciens* URM4983; *Candida shehatae* URM4978; *Kloeckera apiculata* URM5002.	[87]
Canavalia brasiliensis Benth.	ConBr	Growth inhibition	0.31 μM; 0.31 μM; 0.31 μM; 0.08 μM; 0.31 μM; 0.08 μM; 0.31 μM; 9.87 μM; 0.08 μM.	*Candida albicans* URM4987; *Candida URM4979 azyma*; *Candida guilliermondii* URM4975; *Candida membranaefaciens* URM4983; *Candida obtusa* URM4982; *Candida shehatae* URM4978; *Candida tropicalis URM4989*; *Kloeckera apiculata* URM5002; *Trichosporon cutaneum* URM4973.	[87]
Sophora alopecuroides L.	SAL	Growth inhibition	3.125 μM; 3.338 μM.	*Penicillium digitatum*; *Alternaria alternata*	[72]
Dioclea guianensis Benth.	Dgui	Germination inhibition	3.85 μM.	*Collectotrichum gloesporioides*.	[58]
Curcuma amarissima Roscoe	*Curcuma amarissima* lectin	Growth inhibition	0.54 μM; 1.08 μM; 1.08 μM.	*Collectrotrichum cassiicola*; *Exserohilum turicicum*; *Fusarium oxysporum*.	[71]
Talisia esculenta (A. St.-Hil.) Radlk.	TEL	Growth inhibition	2.08 μM.	*Microsporum canis*.	[11]
Phaseolus coccineus L.	PCL	Growth inhibition	8.33 μM; 8.33 μM; 8.33 μM; 8.33 μM.	*Gibberella sanguinetti*; *Sclerotinia sclerotiorum*; *Helminthosporium maydis*; *Rhizoctonia solani*.	[76]
Capsicum frutescens L.	*Capsicum frutescens* lectin	Inhibition of hyphae growth	33.90 μM; 33.90 μM.	*Fusarium moniliforme*; *Aspergillus flavus*.	[73]
Amaranthus viridis L.	AVL	Growth inhibition	100 μg/disc; 200 μg/disc.	*Botrytis cincerea*; *Fusarium oxysporum*.	[77]
Artocarpus integrifolius L.f.	Jackin	Inhibition of germination.	160.71 μM.	*Fusarium moniliforme*.	[88]
Artocarpus incisa	Frutackin	Inhibition of germination.	160.71 μM.	*Fusarium moniliforme*.	[88]
Astragalus mongholicus Bunge	AMML	Growth inhibition	20 μg/well; 100 μg/well; 100 μg/well; 100 μg/well.	*Botrytis cincerea*; *Fusarium oxysporum*; *Collectorichum* sp.; *Drechslera turcia*.	[57]
Phaseolus vulgaris L.	*Phaseolus vulgaris* lectin	Growth inhibition	60 μg/disc; 60 μg/disc; 60 μg/disc.	*Coprinus comatus*; *Fusarium oxysporum*; *Rhizoctonia solani*.	[61]

[a] ND: not determined.

Table 3
Antiprotozoal activity of lectins reported in the literature. The concentrations mentioned are the lowest with relevant activity against the protozoa tested.

Species	Lectin	Bioactivity	Bioactivity concentration	Microorganisms	References
Canavalia ensiformis (L.) DC.	ConA	Immunomodulation	0.39 μM.	*Leishmania amazonensis*	[13]
Synadenium carinatum Boiss.	ScLL	Immunomodulation	0.01 μM.	*Toxoplasma gondii*	[12]
Artocarpus heterophyllus Lam.	ArtinM	Immunomodulation	0.01 μM.	*Toxoplasma gondii*	[12]
Phaseolus vulgaris L.	*Phaseolus vulgaris* lectin	Direct damage to the structure of the microorganism	3.97 μM.	*Trichomonas vaginalis*	[83]
Bothrops pauloensis AMARAL	BpLec	Immunomodulation	0.13 μM.	*Toxoplasma gondii*	[81]
Phaseolus vulgaris L.	PHA	Direct damage to the structure of the microorganism	1.59 μM.	*Leishmania donovani*	[85]
Cliona varians (Duchassaing & Michelotti, 1864)	CvL	Agglutination	8.77 μM.	*Leishmania chagasi*	[84]
Bothrops leucurus (Wagler, 1824)	BLL	Immunomodulation	1.55 μM. 1.3 μM.	*Leishmania amazonensis*; *Leishmania brasiliensis*.	[80]
Chondrilla caribensis (Rützler, Duran & Piantoni)	CCL	Direct damage to the structure and induction of ROS	1.2 μM.	*Leishmania infantum*	[78]
Parkia pendula (Willd.) Benth. Ex Walp	PpeL	Inhibition of promastigote development.	10.5 μM.	*Leishmania infantum*	[79]

methicillin-resistant *S. aureus* (MRSA) *and E. coli* and weak antibacterial activity against *P. aeruginosa*. However, the lectin increased the antibacterial activities of antibiotics, producing synergistic effects when associated with norfloxacin against MRSA, *P. aeruginosa* and *E. coli*, as well as with tetracycline against MRSA and *P. aeruginosa* and with ampicillin against MRSA. These findings indicate that lectins may be useful in the management of antibacterial resistance, a major current public health problem [32].

According to Silva et al. [33], bacteria become resistant to antibiotics through multiple mechanisms, including structural changes in the cell wall, efflux pump expression, ribosome mutations, and antibiotic inactivation by enzymatic activity. A study by these authors demonstrated that *Parkia platycephala* lectin (Fig. 2) (PPL) modulated the antibacterial activity of gentamicin, reducing the MIC of the multiple drug resistance (MDR) bacteria *S. aureus* and *E. coli* by 61% and 36.9%, respectively. However, PPL was not able to modulate the activity of gentamicin against *P. aeruginosa*, which may be due to differences in the polysaccharides that form the extracellular wall of *P. aeruginosa*.

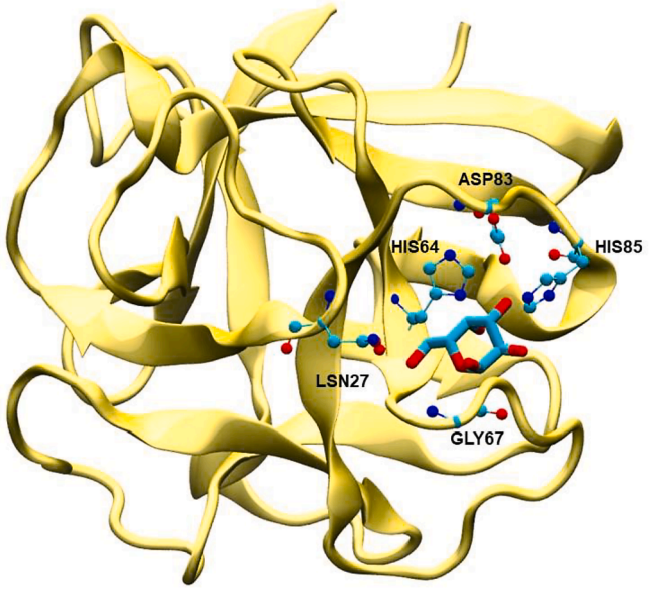

Fig. 1. Image of the *Crenomytilus grayanus* lectin (cartoon) crystal structure forming a complex with D-galactose (stick). The residues closest to the galactose are shown in ball-and-stick representation. Oxygens are colored in red, carbons in cyan, and nitrogen atoms in blue. PDB ID: 5F8W [23].

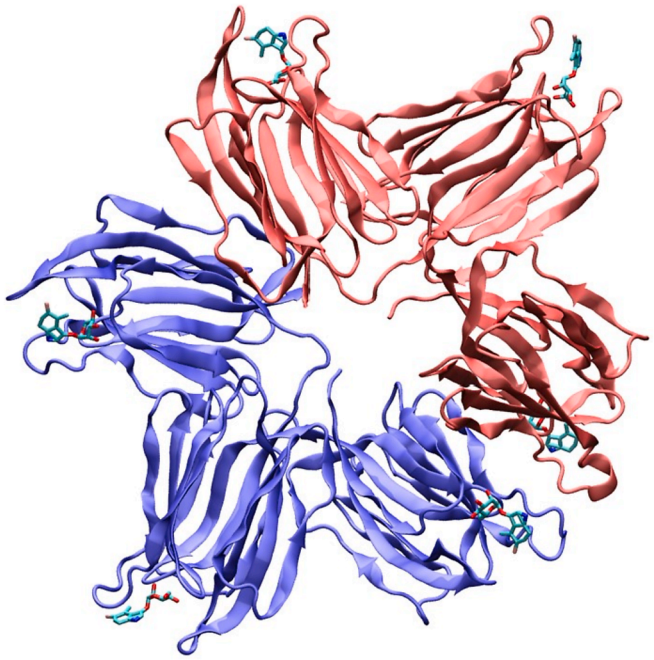

Fig. 2. Structural representation of the *Parkia platycephala* seed lectin showing the quaternary arrangement of the domain with chains A (blue) and B (red). The lectin is complexed with 5-Bromo-4-chloro-3-indolyl-a-D-mannose (in cyan stick) (PDB ID: 1ZGS) [35].

Community and hospital infections caused by β-lactamase-producing bacteria have increased worldwide. Hydrolysis of the β-lactam ring represents the most common mechanism of resistance of Gram-negative bacteria against third-generation cephalosporins. *Punica granatum* sarcotesta lectin (PgTeL) showed antibacterial activity against clinical and MDR isolates of *E. coli* expressing β-lactamases, exerting harmful effects on growth, cell structure and biofilm formation. In addition, the lectin showed synergistic effects when associated with the antibiotics such as ampicillin, carbenicillin, cefotaxime, cephalexin, and cefuroxime [34].

3.1.3. Action of lectins by binding to the bacterial surface

Lectins can also prevent microorganisms from sticking to a surface, which can affect biofilm formation, since adhesion is the first step in this process [36]. The lectin extracted from *Bauhinia variegata* (BVL—I) seeds, as well as its recombinant form (rBVL-1), was found to inhibit the adhesion of oral bacteria such as *Streptococcus mutans* and *Streptococcus sanguinis* in about 86%. While the mechanisms underlying the mechanism of action by rBVL-I have not yet been elucidated, evidence suggests that BVL-I binds to carbohydrates present on the bacterial surface, occupying the binding site for the adhesion of microorganisms to the oral cavity [37].

Biofilm formation is an important mechanism of bacterial resistance, representing a significant cause of persistent and recurrent bacterial infections. Like aggregation induction, biofilm formation has been associated with increased mutation frequency and lower susceptibility to antibiotics. In a study conducted by da Silva et al. [38], the lectin PgTeL, showed strong antibacterial activity against non-resistant and resistant isolates (MRSA) of *S. aureus*, causing structural damage in both strains. Curiously, while biofilm formation by the non-resistant isolate was inhibited by more than 50% at a concentration of 200 μg/mL, this phenomenon was stimulated at lower concentrations. The author suggested that this stimulus may be due to a defense mechanism of the bacterium after coming into contact with the lectin at concentrations unable to affect its growth. However, the resistant strain inhibited biofilm formation at all tested concentrations.

The binding affinity of lectins to carbohydrates, make them attractive as inhibitors of the adhesion of bacteria to specific surfaces by competitiveness, as reported for LecA, a lectin produced by *P. aeruginosa* as a virulence factor associated with bacterial adhesion and biofilm formation. In research conducted by Palmioli et al. [39] it was possible to inhibit the formation of *P. aeruginosa* biofilm by using a galactose-based dendrimer (Gal18) at a concentration of 250 μM. The legume *Canavalia ensiformis* produces a specific lectin of mannose (Fig. 3) (ConA) with remarkable antibiofilm activity against enterohemorrhagic *E. coli* (EHEC) and *Listeria monocytogenes*. It is remarkable that ConA was also able to reduce EHEC's mobility by 37% [40].

Preetham et al. [41] demonstrated that a lectin extracted from the shrimp *Penaeus semisulcatus* inhibited biofilm formation by

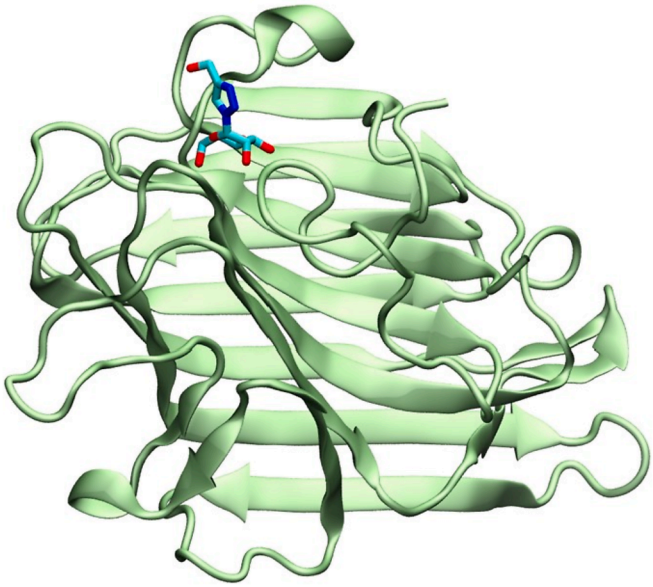

Fig. 3. Structural representation of the (cartoon) complex Concanavalin-A (ConA) from *Canavalia ensiformis* with the 4-(hydroxymethyl)-1-(alpha-D-mannopyranosyl)-1H-1,2,3-triazole (a synthetic derivative of high-mannose – represented in stick). PDB ID: 4PF5 [44].

A. hydrophila, *V. parahaemolyticus*, *S. aureus*, and *E. faecalis*. A lectin extracted from the marine sponge *Aplysina fulva* (AFL) was effective in inhibiting the emission of the biofilm by *S. aureus*, *Staphylococcus epidermidis*, and *E. coli*, but without affecting its plankton forms [42]. Research conducted by Marques et al. [43] showed that lectin isolated from the marine sponge *Chondrilla caribensis* reduced the total biomass of biofilms by the same strains without affecting the viability of these bacteria attached to the biofilm. In addition, this activity was completely inhibited in the presence of alpha-lactose, suggesting that the carbohydrate recognition domain (CRD) is involved in the antibiofilm activity.

The search for substances capable of affecting biofilm formation has attracted the interest of researchers worldwide, as evidence indicates that antibiofilm therapy could minimize the emergence of microbial resistance. In this context, CasuL, a lectin extracted from the leaves of *Calliandra surinamensis* showed variable inhibitory effects on the growth of non-resistant *S. aureus*, MRSA, *E. coli*, and *Staphylococcus saprophyticus*. While *Escherichia coli* growth was not affected by lectin treatment, significant inhibition ($p < 0.05$) was observed for *S. saprophyticcus* and MRSA isolate, although the magnitude of inhibition was below 30%. However, the lectin significantly inhibited biofilm production by all tested bacteria, with an inhibition profile comparable to those obtained with the control drug tetracycline [45].

Still in this context, a lectin extracted *Aplysia dactylomela* eggs (ADEL), binding specifically to galacturonic acid, was able to agglutinate in the presence of *S. aureus* and reduce biofilm biomass by almost 40% without affecting cell viability. The formation of bacterial aggregates can cause a decrease in the number of adherent cells, which may explain why ADEL does not inhibit bacterial growth, but is, instead, effective in inhibiting biofilm production [10]. Studies with *Moringa oleifera* lectin (WSMoL) suggested that the effects of lectins on biofilm formation and bacterial growth can be influenced by the concentration. Thus, while the lectin extracted from the seeds of this plant inhibited biofilm production by *Serratia marcescens* at low concentrations (less than 1.3 $\mu g/mL^{-1}$) without interfering with bacterial growth, it was found to significantly inhibit bacterial growth at a concentration of 2.6 $\mu g/mL^{-1}$, which is significantly better than the inhibitory concentrations demonstrated by the control drug gentamicin (10.4 and 20.8 $\mu g/mL^{-1}$) [26].

3.1.4. Plant lectins with antibacterial activity

Studies have shown that plants produce lectins as part of their defense mechanism. According to Hasan et al. [46], plants are more prone to microbial infections compared to animals, due to the lack of a well-developed immune system, as well as due to mobility incapacity. So, to ensure the perpetuation of the species, reproductive organs, such as fruit bodies and tubers, are developed to store a series of self-protective molecules against invading microbes. In their research, Hasan and colleagues showed that a lectin extracted from *Solanum tuberosum* (StL-20) had remarkable antibacterial activity against *E. coli*, *L. monocytogenes*, *S. enteritidis* and *S. boydii*. In addition, StL-20 was able to inhibit the formation of biofilm by *Pseudomonas aeruginosa* from 5 to 20%, the only bacterium used in this test, as lectin concentration increased from 2.5 to 15 μg/mL, becoming almost constant at 20 μg/mL.

A lectin extracted from the fruiting body *of Sparassis latifolia* showed higher activity against Gram-negative bacteria than against Gram-positive bacteria. The MICs for *resistant E. coli*, *S. aureus* resistant and *P. aeruginosa* were 100, 200 and 50 μg/mL, respectively, which were higher than those of the corresponding normal strains. In addition, it was observed inhibition of the transition from a random spiral to α-helix conformation after interaction with bacterial LPS, indicating that the lectin inhibited the activity in these microorganisms [47].

ApulSL is a lectin extracted from *Apuleia leiocarpa* seeds that specifically binds to *N*-acetylglycosamine, a chitin monomer. This lectin showed bacteriostatic activity against Gram-positive bacteria such as *B. subtilis*, *B. cereus*, *E. faecalis*, *M. luteus*, *S. pyogenes*, and *S. aureus*, as well as against Gram-negative bacteria such as *Xanthomonas campestris* pv. *campestris*, *Xanthomonas campestris* pv. *viticola*, *Xanthomonas campestris* pv. *malvacearum*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, and *S. enteritidis*. Since *N*-acetylglucosamine is present in both Gram-positive and Gram-negative bacteria, its interaction with the lectin may explain its antibacterial activity observed [48].

Lectins extracted from seeds of legumes *Vicia faba*, *Lens culinaris* (Fig. 4) and *Pisum sativum*, which specifically interacts with mannose and glucose, showed antibacterial activity against *S. aureus*, *S. mutans*, *P. aeruginosa*, and *K. pneumoniae*, whose mechanisms possibly involves agglutination [49]. Agglutinating capacity was also reported for KRL, a lectin extracted from the rhizome *of Kaempferia rotunda*, which was effective against *B. subtilis*, *B. cereus*, *B. megaterium*, *Sarcina lutea*, *Klebsiella*, *E. coli*, *Shigella sonnei*, and *Salmonela typhi*. The agglutinating activity of KRL was inhibited in the presence of mannose. Additionally, this lectin also inhibited the growth of most of these bacteria, suggesting that it can recognize molecules on the surface of both Gram-positive and Gram-negative bacteria [50]. These findings were corroborated by the study of Rashel Kabir et al. [50], demonstrating that this lectin was able to agglutinate in the presence of *S. aureus* and *E. coli*. However, no agglutinating activity was reported for *Salmonella enteretidis*.

The *Moringa oleífera* seeds lectin (WSMoL), which has a specific affinity for D (+) – fructose, inhibited the growth of pathogenic bacteria, exhibiting significant activity against *Bacillus* sp., *Bacillus pumillus*, *Pseudomonas Stutzeri*, and *Serratia marcescens*. However, bactericidal effects were observed only against *Bacillus* sp., *B. pumillus*, *Bacillus megaterium*, *P. fluorescens*, and *S. marcescens*. In addition, WSMoL altered the membrane permeability of all bacteria tested, including those in which no bactericidal effect was observed [26].

In a study by Ferreira et al. [51], WSMoL showed high activity against *S. aureus*, probably due to the high level of peptide glycan in the cell wall of this bacteria, while *E. coli* was not sensitive to the treatment. On the other hand, a lectin extracted from seeds of *Sterculia foetida* L. showed bacteriostatic activity against Gram-positive and Gram-negative bacteria, including *B. subtilis* and *P. aeruginosa*, which were more sensitive to treatment with lectin [52]. A study by Oliveira et al. [53] demonstrated that the lectin of *Eugenia uniflora* L. (EuniSL) seeds has more significant antibacterial activity than the crude extract of the same

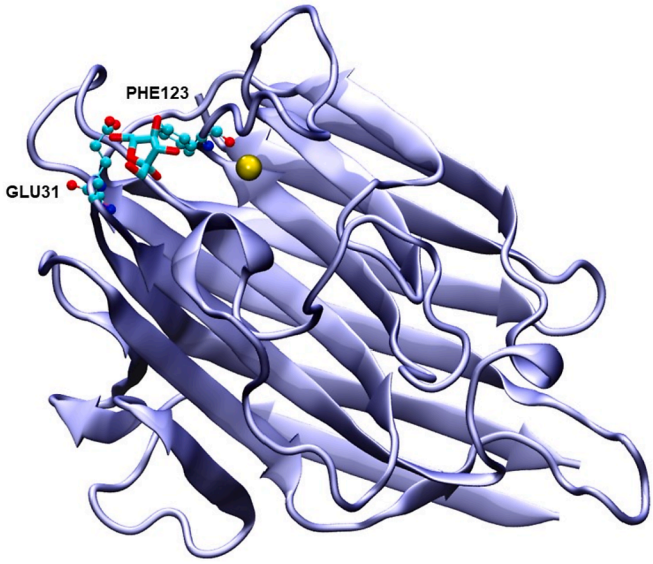

Fig. 4. Representation of the lentil lectin (*Lens culinaris*) complexed with sucrose (in stick). The amino acids within 3 Å are represented in ball-and-sticks. The Ca^{2+} (yellow sphere) is a cofactor required for the activity of most vegetable lectins. Oxygens are colored in red, carbons in cyan, and nitrogen atoms in blue. PDB ID: 1LES [54].

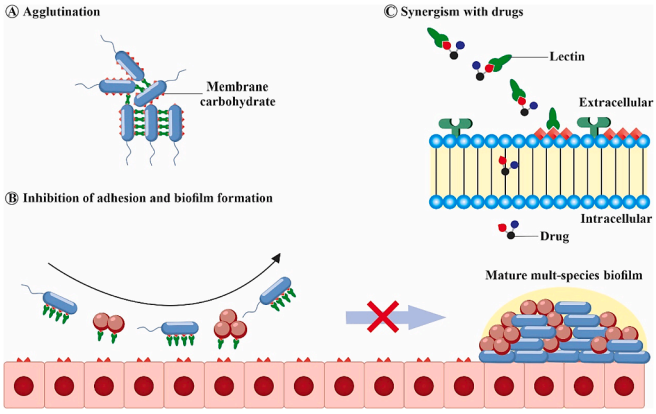

Fig. 5. Suggested mechanism of lectin bioactivity against bacteria. A) Agglutination - Upon finding membrane carbohydrates on the surface of microorganisms, lectins bind to them, agglutinating the cells together, reducing motility and facilitating the activity of antimicrobial drugs. B) Inhibition of adhesion and biofilm formation – Lectins prevent the sites responsible for attaching microorganism to a surface from playing their role, inhibiting adhesion. Adhesion is the first step in the formation of microbial biofilms, and once this adhesion is inhibited, biofilm formation is also affected. C) Synergism with drugs – It is suggested that lectins act by delivering the drug close to the surface of the microorganism, thus facilitating its entry into the cell. The binding performed by the lectins is reversible, allowing them to release the drug upon encountering the microorganism's membrane carbohydrates.

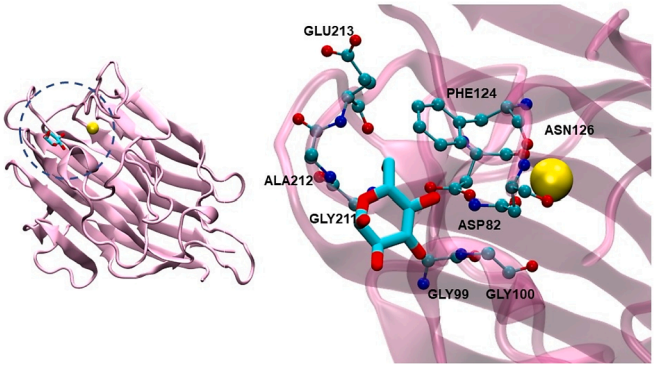

Fig. 6. The structural representation of the chain A of *Vicia faba* lectin protein complexed with a D-glucose is on the left panel. The right panel is a zoomed picture of the active site showing the residues near the glucose (3.5 Å of distance). Ca^{2+} (yellow sphere) is also presented in the near region. PDB ID: 2B7Y [69].

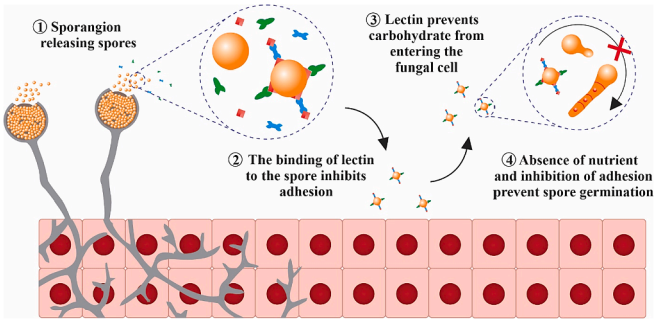

Fig. 7. Suggested mechanism for bioactivity of lectins against fungi. 1 – The release of spores occurs by the sporangios. 2 – Lectins quickly bind to carbohydrates on the surface of spores, inhibiting adhesion to a surface. 3 – Lectins bind to extracellular carbohydrates, reducing the availability of nutrients to the spore. 4 – The absence of nutrients, added to the inhibition of adhesion to a surface, prevent the germination of spores from occurring.

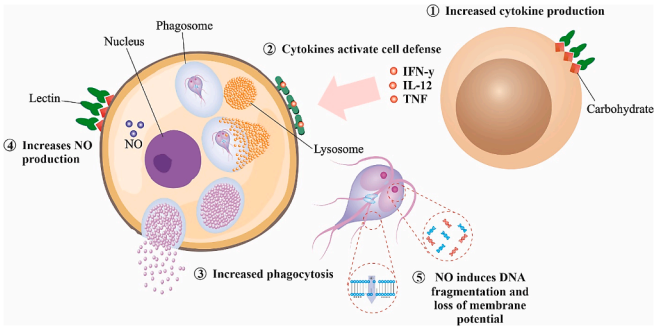

Fig. 8. Suggested mechanism of lectin bioactivity against protozoa. 1 – Lectins stimulate the production of cytokines. 2 – Cytokines activate defense cells, like macrophages. 3 – Macrophages increase their phagocytic activity. 4 – Lectins stimulate macrophages to produce nitric oxide (NO). 5 – NO induces DNA fragmentation and loss of parasite membrane potential, leading to apoptosis.

plant indicating that this lectin may be the main active component of the extract.

Although lectins are mainly found in sexual organs and fruit bodies of plants, they can be expressed by various tissues. Thus, a lectin extracted from the *leaves of Lantana camara*, with specific affinity to chitin, demonstrated antibacterial activity against *P. aeruginosa*, *E. coli* and *K. pneumoniae*, achieving better results when compared to the reference antibiotic Ampicillin [55].

Some activities reported in the literature for crude extracts plants are attributed to the presence of lectins. SteLL, a lectin isolated from the leaves *of Schinus terebinthifolia* showed antibacterial activity against *P. aeruginosa*, *E. coli* and *K. pneumoniae*, as well as against *S. aureus*, *P. mirabilis* and *S. enteritidis*. However, bactericidal activity was detected only against *S. aureus*, *E. coli* and *Proteus mirabilis*. In addition, the antibacterial activity of SteLL was stronger than that of *Schinus terebinthifolia* leaf extract, indicating that the lectin is a major active component with antibacterial activity [7].

In a study by Moura et al. [56], lectins were extracted from three parts of the *Myracrodruon urundeuva*, corresponding to the leaf (MuLL), bark (MuBL) and heartwood (MuHL), which showed antibacterial activity against resistant *S. aureus* strains (LAC USA300) and non resistant (8325-4). MIC results ranged from 12.5 to 25 $\mu g/mL^{-1}$ for all lectins against the non-resistant strain, a result inferior to the antibiotics cefotaxime, cefoxitin, cefuroxime and ciprofloxacin (1 to 2 $\mu g/mL^{-1}$). However, lectins were better against the resistant strain compared to drugs. Furthermore, at the concentration of 100 $\mu g/mL^{-1}$, the lectins were bactericidal, while only ciprofloxacin presented this result.

3.2. Lectins with antifungal activity

3.2.1. Fungi with medical importance

Regarding antifungal activity, plant-derived lectins as the most reported in the literature, corroborating the evidence that lectins participate in plant defense against insects, bacteria, and fungi [57]. Plant defense mechanisms, such as hypersensitivity response and acquired systemic resistance, are induced after the recognition of specific molecules derived from pathogens (avirulence proteins), restricting the proliferation of aggressor agents [58,59].

The antifungal activity of *Silene latifolia* lectin was demonstrated against yeasts of *Candida albicans*, *Candida catenulate*, *Candida glabrata*, and *Candida rugosa*, as well as against hyphae-generating strains of *Fusarium oxysporum* and *F. solani*, with significant inhibition of mycelium growth in the *Fusarium* strains. Like the antibacterial mechanism reported for some lectins, *S. latifólia* lectin also presented conformational changes in α-helix after binding with manana or laminarin, indicating that these components play an important role in the antifungal activity of lectin [47].

Research conducted by Klafke et al. [60] evaluated the effects of lectins obtained from the leaves of *Abelmoschus esculentus* and the seeds *of Canavalia brasiliensis* (Conbr II), *Mucuna pruriens*, *Clitoria fairchildiana*, *Dioclea virgate*, and *Bauhinia variegata* (BVL) against isolates of *C. albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Cryptococcus gattii*, *Cryptococcus neoformans*, *Malassezia pachydermatis*, *Rhodotorula* sp. and *Trichosporon* sp. The six lectins showed fungicide activity only against *C. parapsilosis*, as the MIC for the other species was higher than 500 μg/mL^{-1}.

Suspensions containing *Candida* blastoconidia were incubated with 500 μg/mL^{-1} of *A. esculentus* lectin (AEL-FITC), which strongly bonded to blastoconidia *of C. parapsilosis*. However, the lectin showed weak interaction with *C. tropicalis* and did not bind to *C. albicans*. The differences observed can be explained by the specificity of lectin to certain surface glycans, as well as to the variable composition of cell walls vary among fungal species, which can influence both physicochemical and biological properties [60].

Pinheiro et al. [11] demonstrated that *Talisia esculenta* lectin (TEL) inhibited the growth of *Microsporum canis* at concentrations above 0.125 mg/mL^{-1}, reaching 100% inhibition at the concentration of 2 mg/mL^{-1}. Affinity tests revealed that D-mannose and *N*-acetyl-D-glycosamine inhibited the antifungal activity of TEL. Experiments were also performed using hair infected with *M. canis* to determine whether the lectin could inhibit the growth of fungi obtained from arthroconidia present in the animal hair. The results obtained showed growth inhibition of 73% in 15 samples of infected hair treated with the lectin at a concentration of 500 mg/mL^{-1}, which is comparable with the effect observed in the control group, where 80% inhibition was obtained. Additionally, the lectin showed affinity to macroconidia and arthroconidia, which may result from its binding to chitin molecules in the conidia wall, preventing its complete development.

The Lectins jackin and frutackin, extracted from the seeds of *Artocarpus integrifolia* and *Artocarpus incisa*, respectively, were reported to inhibit the growth of *F. moniliforme* and *Saccharomyces cerevisiae*, demonstrating agglutinating activities that were inhibited only in the presence of chitin and *N*-acetyl-D-glycamine. Jackin also inhibited the germination of *F. moniliform* at a concentration of 2.25 mg/mL. At the same concentration, this lectin impaired the normal development of hyphae by preventing mycelium from producing spores, which in turn resulted in sterile fungi. Qualitative experiments performed with frutackin found a similar activity to that reported for Jackin. These lectins have high similarity and according to data obtained by fluorescence spectrum, both showed exposed tryptophan residues, indicating that they could freely interact with the chitin column through a hydrophobic interaction between the tryptophan lateral chain and glycosamine rings [61]. Importantly, the affinity of jackin and frutackin to chitin may be responsible for their antifungal activities.

In fact, chitin-binding lectins are more likely to have antifungal activity. Accordingly, the specific chitin-binding lectin extracted from the seed of *M. oleifera* WSMoL, showed significant fungicide effects against *C. albicans*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*. It was observed a decrease in the viability of fungal cells, with more pronounced effects against *C. glabrata* and weaker activity against *C. albicans* and *C. parapsilosis* in comparison with the isopropyl alcohol control. The lectin was found to induce necrosis and apoptosis in all isolates, as evidenced by the presence of double-colored cells (indicative of strong cell damage) in colorimetric tests. The induction of apoptosis by the lectin may be linked to mitochondrial dysfunction, involving depolarization of transmembrane potential, the release of apoptogenic factors, and impaired oxidative phosphorylation. In fact, the results showed membrane potential depolarization in all isolates, with *C. krusei* being the most sensitive species with regard to the antifungal effects of WSMoL [62].

CasuL, a lectin extracted *from Calliandra surinamensis*, showed antifungal activity against *C. krusei*, with MIC and Minimum Fungicide Concentrations (CFM) of 125 and 250 μg/mL respectively, and drastic morphological changes, with retraction of cytoplasmic content and cell rupture. Since Calcofluor is a fluorochrome capable of binding to chitin, it can be used to reveal changes in the cell wall integrity of yeasts and hyphae. Additionally, *C. krusei* cultures treated with CasuL showed a decrease in the fluorescence signal, associated with discontinuous staining in the wall and cytoplasm, evidencing loss of cell wall integrity [45].

Research by Gomes et al. [63] tested the antifungal activity of four chitin-binding lectins extracted from *Dioclea violacea* (Dviol), *Dioclea rostrata* (DRL), *Canavalia brasiliensis* (ConBr), and *Lonchocarpus sericeus* (LSL), against isolates obtained from the vaginal secretion of pregnant and non-pregnant women with or without symptoms of vulvovaginal infection, totaling 30 samples belonging to the genera *Candida*, *Rhodotorula*, *Thicrosporon*, and *Kloeckera*. As shown in Table 2, the lectins presented antifungal concentrations ranging from 2 to 256 μg/mL.

Consistent evidence has indicated that targeting the inflammatory process has a significant impact when considering the management of fungal infections. In this context, two major immunological properties should be considered: resistance (the ability to limit fungal load) and tolerance (the ability to limit host damage caused by the immune response) [64]. Rodriguez-De la Noval et al. [65] conducted *in vitro* experiments to investigate the protective effect of Lectin-Fc fusion proteins (IgG) with affinity to β-1,3-glucan or chitin polysaccharides, including Dectin-1-Fc (IgG2a), Dectin-1-Fc (IgG2b), and WGA-Fc (IgG2a). The results demonstrated that lectins linked to *Aspergillus fumigatus* conidia in germination presenting intense WGA-Fc (IgG2a) activity but had weak effect on hyphae development. Additionally, biofilm production was inhibited by up to 14% with Dectin-1-Fc (IgG2b) and 20% with WGA-Fc after 48 h of treatment. Importantly, the opsonization of conidia in germination with both lectin-Fc fusion proteins increased the deposition of C3 proteins (complement system component with important roles in innate immunity) on the conidia, resulting in increased phagocytosis of conidia by macrophages after opsonization. These findings were further confirmed by *in vivo* tests using infected C57BL/6 mice were treated with 10 μg of lectin-Fc (IgG), which protected the mortality by about 20%. In general, the three lectin-Fc (IgG) proteins exhibited significant antifungal activity against *A. fumigatus*, demonstrating their potential to be used as biopharmaceutical molecules in antifungal therapies [65].

Previous work by Chikalovets et al. [66] found that a mussel lectin, identified as *Crenomytilus grayanus* (CGL), had its expression elevated in the mantle of animals infected with *Pichia pastoris*, reaching peak concentration after12 hours, and returning to the original pattern within 24 h. The higher level of expression of CGL in the mantle implies that this lectin could have a significant contribution to the prevention of microbial reproduction since the mantle is constantly being washed with seawater containing pathogens and pollutants. Additionally, *in vitro* tests with fungi of the genera *Aspergillus* (3), *Penicillium* (4), *Trichoderma* (2) and *Mycelia* (1) cultured in the presence of CGL demonstrated that the agglutinating activity of this lectin was inhibited in the presence of galactose, evidencing its specificity. Furthermore, antifungal assays indicated inhibition of germination in three of the ten evaluated strains.

While many lectins have their antifungal activities attributed to their ability to interact with, studies have demonstrated that these molecules can interact with other components on the cell surface of fungi, inducing morphological alterations (such as the transition from yeast to filamentous forms), increasing the production of reactive oxygen species (ROS) and inhibiting biofilm production. In this context, a lectin extracted from *Helianthus annuus* (Helja) seeds (0.1 μg/μL) inhibited the growth of *C. albicans*, reducing cell viability by 82% after 48 h. In addition, this lectin inhibited morphological transition and biofilm production in *C. albicans*, indicating that the treatment with this lectin can inhibit the pathogenicity of this microorganism [67].

The activity of different lectins against *Candida* strains has been consistently demonstrated. Lectins extracted from *Vicia faba* (Fig. 6), *Lens culinaris*, and *Pisum sativum* with different degrees of purity showed

promising antifungal activity against *C. albicans* [49]. MaL, a lectin extracted from the seeds of *Machaerium acutifolium* showed antifungal activity against *C. albicans*, *C. parapsilosis*, and *C. tropicalis*. In addition, *C. parapsilosis* cultures treated with this lectin (at 18 μM) failed to form visible colonies in Sabouraud agar medium. The lectin significantly altered the membrane permeability and induced the production of ROS. Additionally, scanning electron microscopy (SEM) analyses revealed that the same cultures treated with the lectin at a concentration of 9 μM were characterized by the presence of significantly elongated cells presenting pores in the cell wall and fragmented DNA, indicating that the mechanisms underlying the toxic effects of MaL against *C. parapsilosis* involve cell death by apoptosis [68].

A jackalin-related lectin extracted from the seeds of *Helianthus annuus* L. (Helja), which is known as an efficient mannose ligand, showed important effects against pathogenic yeasts such as *C. tropicalis*, *C. parapsilosis*, *C. albicans*, and *Pichia membranifaciens* at a concentration of 200 μg/mL. inhibiting the growth *Candida* strains in up to 50%, while the growth of *P. membranifaciens* was inhibited in 98%. According to the study, the lectin presents a common antifungal mechanism against all the fungal strains, by inducing alterations in the membrane permeability [70].

Many lectins have been classified as metalloproteins due to the presence of metal cations. In fact, metal ions such as Ca^{2+}, Mg^{2+} and Mn^{2+} are cofactors required for activity (especially hemagglutination) of most vegetable lectins [71]. The hemagglutinating activity of *Sophora alopecuroides* lectin (SAL) was inhibited in the presence of D-galactose. Additionally, the agglutination performed by this lectin was potentiated by the addition of Mn^{2+}, indicating that the ion act as a cofactor for SAL activity. Importantly, the lectin inhibited mycelial growth in *Penicillium digitatum* and *Alternaria alternata* cultures after a 24-hour treatment period [72].

3.2.2. Fungi with agriculture importance

In general, lectins can inhibit fungal growth by affecting spore germination and mycelium growth. Lectins showing this type of activity include those obtained from the seeds of *Dracaena guianensis* (Dgui), *Canavalia ensiformis* (ConA), and *Canavalia maritima* (ConM). These lectins present similar properties, acting as mannose/glucose ligands. ConM and Dgui have 90% and 86% similarities in their protein sequence with ConA, respectively. However, only Dgui was found to effectively delay conidia germination and appressorium formation in *Colletotrichum gloeosporioides*, which has a significant impact on the activation of defense mechanisms against pathogen infection. According to the authors, the ability of Dgui, but not ConA or ConM, to specifically inhibit the germination of *C. gloeosporioides* may be due to the differential specificities of these lectins related to complex carbohydrates and glycoproteins. In addition, there may exist subtle differences present in the region of carbohydrate recognition of molecules in relation to the atomic distances involved in hydrogen bonding and van der Waals interactions between lectins and carbohydrates [58].

Capsicum frutescens lectin exhibited strong inhibitory activity in the growth and germination of spores and hyphae of *Fusarium moniliformee*, and *Aspergillus flavus*, while no effect against *Fusarium graminearum*, *Fusarium solani*, *Physalospora piricola*, and *Botrytis cinerea* was observed (Table 2). The sugar-binding specificity of this lectin is similar to that of ConA, both being glucose and mannose ligands in addition to presenting similar molecular mass. However, the lectin of the pepper seed also binds to galactose and fucose, although with less avidity [73].

Ang et al. [74] analyzed the antifungal effects of a lectin extracted from *Phaseolus vulgaris* seed (CPBL) against six species of fungi, including *Phyllosticta citriasiana*, *Magnaporthe grisea*, *Bipolaris maydis*, *Valsa mali*, *Mycosphaerella arachidicola* and *Setosphaeria turcica*. The authors demonstrated that the lectin, at a concentration of 30 μM, inhibited mycelial growth in *V. mali* (by 30.6%) but failed to inhibit this phenomenon in the other strains. Additionally, it was reported that the agglutinating activity of this lectin was inhibited in the presence of glucosamine, besides being an Mg^{2+}-dependent effect.

The binding affinity of MTL to fungal components was examined by an enzyme-linked lectin (ELLA) assay. Fungi of the genera *Fusarium* (2), *Trichoderma* (2), *Haematonectria* (2), *Aspergillus* (1), and *Alternaria* (1), numbered from M1 to M8, were cultured in the presence of MTL demonstrated strong affinity, except for strain number 7. MTL was also able to decrease conidia germination, as well as to strongly inhibit the growth of strains M3, M5, M6, and M8 [17].

A lectin extracted from the red bean *Phaseolus vulgaris* showed antifungal activity against *Coprinus comatus*, *F. oxysporum*, and *Rhizoctonia solani*, which was evidenced by the formation of inhibition zones at the concentrations of 60 and 300 μg/mL. While the agglutinating activity of this lectin activity could not be inhibited by simple sugars, it was inhibited by glycoproteins such as lactoferrin, ovalbumin, and thyroglobulin. According to the author, the fact that this lectin shows a certain degree of structural similarity with chitinases could be, at least partially, responsible for its antifungal activity, since chitinases are known to adversely affect hyphae growth, leading to cell wall rupture through the release of chitin oligosaccharides from the cell wall and cytoplasm leakage [61].

Chitin is a biopolymer composed of repeated GlcNAc abundantly found in nature, especially in the composition of insect exoskeletons, fungal cell walls, nematode eggs, marine diatomaceous and shells of crustaceans and zooplankton. A chitin-binding lectin extracted from *Solanum integrifolium* inhibited the development of fungi such as *Rhizoctonia solani* and *Colletotrichum gloeosporioides*, with inhibition zones of 8 and 12 mm, respectively [63].

Evidence has indicated that, like the interaction with bacterial components, the interaction of lectins with fungal carbohydrates may involve different degrees of affinity [75]. Thus, it was observed that a lectin extracted from the root of *Portulaca elatior* (PeRoL), which has a great affinity to trehalose, but also bind to galactose, glucose, mannose, and *N*-acetylglucosamine, showed fungicide activity against fungi of the genus *Candida* [24]. Lunatin, a lectin extracted from the seeds of *Phaseolus lunatus*, inhibited the growth of *Pythium aphanidermatum*, *Fusarium solani*, *F. oxysporum*, and *Botrytis cinerea*. Curiously, this lectin had its hemagglutinating activity inhibited by D-galactose, D-fructose, D-glucose and mannitol [75].

Chen et al. [76] demonstrated that the *Phaseolus coccineus* lectin (PCL) inhibited the growth of *Gibberalla sanbinetti*, *Sclerotinia sclerotiorum*, *Helminthosporium maydis*, and *Rhizoctonia solani*. However, the hemagglutinating activity of this lectin was inhibited by sialic acid, which resulted in an abrupt increase in the lectin MIC, indicating that binding to sialic acid may be significantly involved in the antifungal activity of PCL. *Amaranthus viridis* Linn lectin (AVL), inhibited the growth of *Botrytis cinerea* and *Fusarium oxysporum* at 100 and 200 μg/disc, respectively but had no significant activity against *Rhizoctonia solani*, *Trichoderma reesei*, *Alternaria solani*, and *F. graminearum*. The lectin had its activity inhibited in the presence of T-antigen, *N*-acetyl-D-galactosamine, and *N*-acetyl-D-lactosamine, in addition glycoproteins asialofetuin and fetuin. Since a mixture of GlcNAc oligomers of chitin hydrolysate did not inhibit agglutination, it was suggested that the antifungal action of this lectin may not involve its binding to chitin molecules [77].

A galactose-specific lectin extracted from the roots of *Astragalus mongholicus* (AMML) was reported to inhibit the mycelium growth in *Botrytis cincerea* cultures with an IC_{50} of 1.2 μM, in addition to presenting significant antifungal activity against *Colletorichum* sp. and *Drechslera turcica* at the concentration of 100 μg/well. Furthermore, AMML showed weak ribonuclease activity against yeast tRNA at 1.25 U/mg. Although this lectin was initially described as a galactose-specific molecule, it was also capable of binding to L-ramnose and celobiosis, indicating that AMML shows plasticity with regard to the binding to carbohydrates [57].

3.3. Lectins with antiprotozoal activity

The role of lectins in the control of protozoa is not yet completely defined and, in this context, targeted research is likely moving more slowly than that addressing the effects of lectin against other microorganisms such as bacteria and fungi. Nevertheless, consistent evidence has demonstrated that lectins present immunomodulatory properties, stimulating the production of cytokines that play important roles in the host defense against certain parasites.

Accordingly, Thomazelli et al. [13] obtained promising results against *Leishmania amazonensis* using the lectin ConA extracted from *Canavalia ensiformis*. This lectin was found to increase the phagocytosis of amastigotes by peripheral blood mononuclear cell (PBMC)-derived macrophages, in addition to potentiating the elimination of promastigotes in a post-infection period of 24, 48 and 72 h. The treatment with ConA increased the production of cytokines such as IFN-γ IL-6, TNF-α, IL-4, IL-2 and IL-10, as well as restored the levels of these mediators following *Leishmania* infection, which significantly contributes to overcoming L. *amazonensis* infection.

Other lectins with significant immunomodulatory effects are ScLL and ArtinM, extracted from *Synadenium carinatum* and *Artocarpus heterophyllus*, respectively. These proteins increased the production of cytokines such as IL-12 (ScLL and ArtinM) and IL-10 (ArtinM) by bone marrow-derived macrophages (BMDM), which was comparable to the LPS. They also stimulated the production of nitric oxide (NO), a mediator with key roles in pathogen killing [12].

The marine sponge lectin from the *Chondrilla caribensis* (CCL) was effective against *Leishmania infantum* promastigote, causing direct damage to the parasite structure (IC50 = 1.2 μM). This lectin interacts with galactose residues, this carbohydrate is a component of the lipophosphoglycan (LPG) and glycoinositol phospholipid (GIP), glycans present on the surface of *Leishmania* promastigotes. *Leishmania's* membrane components change throughout its cell cycle. In the amastigote form, LPG expression is reduced, while glycoinositol phospholipid (GIP) is present in both forms. In molecular docking tests, CCL was able to interact with GIP, revealing that lectin bioactivity is maintained throughout the *L. infantum* cell cycle. Furthermore, CCL was able to induce the production of ROS, which leads to cell death in the parasite [78]. The *Parkia pendula* lectin (PpeL) inhibited the development of L. *infantum* promastigote (IC50 = 10.5 μM). Its activity could be inhibited in the presence of α-methyl-mannoside, indicating that its leishmanicidal activity activity may occur through interaction with mannose residues present in LPG and GIP in *L. infantum* membrane [79].

The snake *Bothrops leucurus*, produce a lectin (BLL) that also showed affinity to galactose, reaveling activity against *Leishmania amazonensis* and *Leishmania brasiliensis*. In the tests by Aranda et al. [80], BBL showed immunomodulatory activity, by reducing the survival of amastigotes, as well as reducing the amount of infected cells (1.6 μM), a similar result obtained in the treatment with pentamidine. Furthermore, infected and uninfected macrophages treated with BLL had their production of cytokines (IL-10, INF-ϒ, TNF-α, IL-6 and IL-1β) and NO increased. When the lectin was used together with galactose, its action was reduced, indicating that its bioactivity depends on its carbohydrate recognition domain (CRD). In cytotoxicity tests, BLL was more selective to parasites than host cells.

Lectins have also been demonstrating experimentally promising molecules in the control of toxoplasmosis, a disease with high prevalence and mortality rates in Brazil. Studies demonstrated that the *in vivo* treatment of C57BL/6 mice infected with *Toxoplasma gondii* with these lectins stimulated the production of Th1, Th2 and Th17 cytokines. Of note, regulation of the Th1 response is required to control inflammatory tissue damage. Additionally, the control of *T. gondii* infection requires a balance between the production of pro-inflammatory and anti-inflammatory cytokines, including IL-12, IFN-γ, and IL-10 [12]. Immunomodulatory effects were also demonstrated by *Bothrops pauloensis* lectin (BpLec), which increased IL-6 secretion by HeLa cells after infection with *T. gondii* taquizoites. BpLec also reduced the secretion of the migration inhibitory factor (MIF), probably by interacting with proteins on the parasite surface [81].

Earlier reports have indicated that lectins have the potential to be used in the treatment of sexually transmitted infection caused by *Trichomonas vaginalis*, since both surface and secreted proteins of *T. vaginalis* present N-glycan residues that can function as binding sites to lectins [82]. It is postulated that due to its antiviral and antiparasitic properties, lectins could treat simultaneously infections by HIV, HSV, and *T. vaginalis*. This evidence is supported by reports demonstrating that cyanovirin-N and griffithsin, lectins with antiretroviral properties, were capable of binding to N-glycans of *T. vaginalis*, leading to the agglutination of the parasite. In addition, these lectins, as well as galactin-1, reduced the recovery of *Tritrichomonas foetus* in a mice model of vaginal infection, demonstrating a significant potential for the treatment of infection.

In addition to the immunomodulatory effects, lectins were found to cause direct damage to the structure of parasites. Thus, lectin extracted from the seeds of *Phaseolus vulgaris* demonstrated significant toxicity against *T. vaginalis* trophozoites, leading to complete loss of the membrane structures, as well as the destruction of the nucleus and cytoplasm. *T. vaginalis*, the etiological agent of trichomoniasis, is a parasite that colonizes the urogenital tract of both female and male individuals. It was demonstrated *P. vulgaris* lectin presented more significant effects than metronidazole (the standard reference drug for the treatment of this condition in humans), leading to pronounced alterations in the structure of trophozoites, including swelling, and plasma membrane disruption, and redistribution of pinocytotic and phagocytic vacuoles, with large empty areas in the cytoplasm [83].

As demonstrated for bacteria and fungi, lectins can also induce protozoa agglutination. The ability of lectins to select and complex with microbial glycoconjugates made them useful as cell probes capable of detecting a variety of constituents. In this context, an experiment carried out by Moura et al. [84] showed that a lectin isolated from the marine sponge *Cliona varians* (CvL) agglutinated *Leishmania chagasi* promastigotes, revealing that galactose receptors are present at this stage of the parasite life cycle. Further research demonstrated that *Phaseolus vulgaris* lectin showed leishmanicidal activity against *Leishmania donovani*, eliminating 100% of promastigotes after 24 h of treatment, similar to the effect obtained with amphotericin B [85].

4. Perceptions, conclusions, and perspectives

Lectins represent biomolecules with multiple pharmacological potentialities, being particularly effective against microorganisms, such as biofilm-producing bacteria and fungi. In addition, their immunomodulatory properties may represent, with the advancement of research, an alternative to current antibiotic therapy. It is noteworthy to emphasize that there are still many gaps with regard to the properties of lectins and therefore, this literature review gathered data in order to provide a better understanding of how these proteins act in different organisms.

Most studies included in this work indicated that lectins present affinity to specific carbohydrates, which only partially explain the bioactivities reported for lectins. Although most studies suggest that the antiprotozoal activity of lectins occurs due to immunomodulatory mechanisms, this evidence is limited by the low number of articles investigating this subject. Lectins have the ability to induce agglutination in a variety of cells. However, lectin-induced agglutination in erythrocytes may represent a significant toxic effect to humans, which remains to be better investigated.

In general, plant lectins are more effective in inhibiting the growth of microorganisms, as well as in interfering with the production of biofilms and modulating the antimicrobial activity of commercial drugs. On the other hand, lectins extracted from animals (mainly fish and mussel) seems to have important roles in the defense against invading agents as their expression is increased during infection. Nevertheless, *in vivo*

research is urgently required for the elucidation of both the mechanisms of action and toxic effects of lectins, especially when considering the interaction of lectins with carbohydrates in several cell types.

In conclusion, the multiple biological properties of lectins make them interesting molecules in the context of scientific research, especially in antimicrobial drug development. It is expected that the advances in lectin engineering will result in the production of recombinant lectins with the potential to be used as therapeutic agents against current health problems such as antimicrobial microbial resistance.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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