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Antibacterial and antibiofilm lectins from plants – a review

Lectinas antibacterianas e antibiofilmes de plantas - uma revisão

Lectinas antibacterianas y antibiofilms vegetales - una revision

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Abstract
The number of multidrug-resistant bacteria that affect public health has been rising, and there are limited therapy resources to deal with these pathogens. The formation of biofilm by bacteria, makes therapy even harder. In this regard, natural products have been increasingly used as source for new antimicrobial agents and lectins have stood out as a promising option. Thus, this work aims to review on plant lectins with antibacterial and antibiofilm properties against pathogenic microorganisms. Several lectins, extracted from *Punica granatum* (PgTeL), *Portulaca elatior* (PeRol), *Curcuma longa* L. (CLA), *Sterculia foetida* L. (SfL), *Apuleia leiocarpa* (ApulSL), *Schinus terebinthifolius* (SteLL), *Archidendron jiringa Nielsen* (AjL) e *Phthirusa pyrifolia* (PpyLL), demonstrated antibacterial activity. *Canavalia ensiformis* (ConA), *Calliandra surinamensis* (Casul), *Solanum tuberosum* (StL-20), *Canavalia* marítima (ConM) demonstrated antibiofilm activity. Moreover, lectins from *Alpinia purpurata* (ApuL) e *Moringa oleífera* (WSMoL) demonstrated both potentials. Therefore, this review gathered substantial evidence that these lectins might constitute therapeutic alternative to treat infections caused by multidrug-resistant and biofilm-producing Gram-positive e Gram-negative bacteria in the future.
Keywords: Bacterial resistance; Biofilm; Infection; Proteins; Plant products.

Resumo
O número de bactérias multirresistentes que afetam a saúde pública tem aumentado e há recursos limitados de terapia para lidar com esses patógenos. A formação de biofilme por bactérias, torna a terapia ainda mais difícil. Nesse sentido, produtos naturais têm sido cada vez mais utilizados como fonte de novos antimicrobianos e as lectinas têm se destacado como uma opção promissora. Assim, este trabalho tem como objetivo fazer uma revisão sobre lectinas vegetais com propriedades antibacterianas e antibiofilme frente microrganismos patogênicos. Várias lectinas, extraídas de *Punica granatum* (PgTeL), *Portulaca elatior* (PeRol), *Curcuma longa* L. (CLA), *Sterculia foetida* L. (SfL), *Apuleia leiocarpa* (ApulSL), *Schinus terebinthifolius* (SteLL), *Archidendron jiringa Nielsen* (AjL) e *Phthirusa pyrifolia* (PpyLL), demonstraram atividade antibacteriana. *Canavalia ensiformis* (ConA), *Calliandra surinamensis* (Casul), *Solanum tuberosum* (StL-20), Canavalia marítima (ConM) demonstraram atividade antibiofilme. Além disso, lectinas de *Alpinia purpurata* (ApuL) e *Moringa oleífera* (WSMoL) demonstraram ambos os potenciais. Portanto, esta revisão reuniu evidências substanciais de que essas lectinas podem constituir alternativa terapêutica para o tratamento de infecções causadas por bactérias Gram-positivas e Gram-negativas multirresistentes e produtoras de biofilme no futuro.
Palavras-chave: Resistência bacteriana; Biofilme; Infecção; Proteínas; Produtos vegetais.

Resumen
Ha aumentado el número de bacterias multirresistentes que afectan a la salud pública y los recursos terapéuticos para hacer frente a estos patógenos son limitados. La formación de biopelículas por bacterias dificulta aún más la terapia. En este sentido, los productos naturales se han utilizado cada vez más como fuente de nuevos antimicrobianos y las lectinas se han destacado como una opción prometedora. Así, este trabajo tiene como objetivo revisar las lectinas vegetales con propiedades antibacterianas y antibiofilm frente a microorganismos patógenos. Varias lectinas, extraídas de *Punica granatum* (PgTeL), *Portulaca elatio*r (PeRol), *Curcuma longa* L. (CLA), *Sterculia foetida* L. (SfL), *Apuleia leiocarpa* (ApulSL), *Schinus terebinthifolius* (SteLL), *Archidendron jiringa* Nielsen (AjLL) y *Phthirusa pyrifolia* (PpyLL) demostraron actividad antibacteriana. *Canavalia ensiformis* (ConA), *Calliandra surinamensis* (Casul), *Solanum tuberosum* (StL-20), Canavalia maritime (ConM) demostraron actividad antibiofilm. Además, las lectinas de *Alpinia purpurata* (ApuL) y *Moringa oleifera* (WSMoL) demostraron ambos potenciales. Por lo tanto, esta revisión ha reunido evidencia sustancial de que estas lectinas pueden ser una alternativa terapéutica para el tratamiento de infecciones causadas por bacterias Gram positivas y Gram negativas resistentes a múltiples fármacos y productoras de biopelículas en el futuro.
Palabras clave: Resistencia bacteriana; Biopelícula; Infección; Proteínas; Productos vegetales.

1. Introduction

One of the biggest challenges of global health is the need for new effective antimicrobials, particularly in developing countries, where infectious diseases are responsible for up to half of the deaths (Elisha et al., 2017). Bacterial infections are a leading cause of mortality and morbidity worldwide, accounting for around 700,000 deaths annually (WHO, 2018; CDC, 2019). The main mechanisms of bacterial resistance are the alteration of bacterial permeability, the enzymatic inactivation of antibiotics, the alteration on targets of antibiotics and the production of efflux pump (Hasan, Al-Harmoosh, 2020).

The indiscriminate and disproportionate use of antimicrobials has been responsible for an alarming increase in the rate of antimicrobial resistance (AMR) and selection of resistant strains, being seen as a global public health problem. Infections caused by multidrug-resistant (MDR) microorganisms, such as: extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae, carbapenemase-producing *Klebsiella pneumoniae* (KPC) and methicillin-resistant *Staphylococcus aureus* (MRSA) can be difficult to control, leading to higher costs of treatment, therapeutic failures and death (Silva, Lincopan, 2012; Cantas et al., 2013; Economou, Gousia, 2015; Tacconelli et al., 2018a).

Many low and middle-income countries have already achieved high rates of antimicrobial resistance, which predictions suggest is likely to increase disproportionately. In Brazil, Indonesia, and Russia, 40 to 60% of infection rates are caused by resistant strains and an increase is expected of 4-7 times faster in these countries. In addition, studies predict that 2.4 million people in Europe, North America and Australia will die from infections caused by MDR microorganisms in the next 30 years, which could cost up to US $ 3.5 billion a year (OECD, 2018).

Futhermore, microbial biofilm is another worrying situation. Biofilms are organized groups of microorganisms that live within a self-produced matrix of polymeric substances, composed of several elements, such as proteins, polysaccharides, and extracellular DNA (eDNA), attached on biological and non-biological surfaces, such as glass, porcelain, stainless steel, rubber, and plastic (Greene et al., 2016; Desmond et al., 2018). In addition, biofilm is one of the survival strategies used by bacteria. Under its protection, microbial cells become tolerant and resistant to antibiotics and the host's immune responses, which makes clinical treatment difficult (Hurlow et al., 2015; Wu et al., 2015; Zacchino et al., 2017; Sharma, Vipra, Channabasappa, 2018). Thus, biofilm contributes establishment and maintenance of the infection for longer time, increasing the cost when compared to infections caused by non-biofilm-producing bacteria (Fernández, Bert, Nicolas-Chanoine, 2016; Allisson et al., 2017; Fisher, Gollan, Helaine., 2017). Due to the limited spectrum of antimicrobials available for the treatment of infections caused by these microorganisms, new therapeutic strategies are currently being sought.

On this sense, investigating the properties of natural products has become a promising approach. Natural products have historically been the main sources of medicines for treatment of a wide range of human diseases (Cragg, Newman, 2013; Butler, Robertson, Cooper, 2014). During biosynthesis, these compounds must interact with several enzymes and proteins,

which have characteristics similar to the environment of drug targets (Kellenberger, Hofmann, Quinn, 2011). As a result, natural products have special characteristics in terms of diversity and complexity, and can play a prominent role in the area of drug development (Nicolaou et al., 2012).

Medicinal plants are important sources of phytochemicals or supplements to synthetic chemicals in the prevention and treatment of human diseases, being endowed with great medicinal value and a powerful source of drug discovery/development (Shakya, 2016; Van Wyk, Wink, 2018). Among the various properties that medicinal plants have, the antimicrobial activity of some compounds has been shown to be effective in the treatment of MDR bacteria.

Many plant phytochemicals and secondary metabolites have already demonstrated *in vitro* antimicrobial activities with less toxicity and side effects when compared to synthetic compounds. In addition, many of these compounds are effective against a variety of resistant strains (Ullah et al., 2019). Hence, research on these compounds has become increasingly extensive and, among them, lectins have been shown to be the ones to be investigated. Thus, the present study aimed to collect and analyze *in vitro* experimental studies with lectins extracted from plants with antibacterial and antibiofilm activity with potential use in clinical therapy.

Lectins

Lectins are a heterogeneous group of non-immune proteins that make multivalent and reversible binding to carbohydrates. These proteins specifically recognize through their non-catalytic domain, different sugar structures, such as mono, oligo or polysaccharides present in glycoproteins or glycolipids, without changing carbohydrate structures (Bhutia et al., 2019; Sivaji et al., 2019; Torres et al., 2019).

They can be extracted from many sources, including animals, microorganisms and plants. Lectins found in animals are often associated with cell signaling, whereas plant lectins are known to ward off potential predators or pathogens (Yau et al., 2015; Dos Santos Silva et al., 2019). In plant lectins, the main sources are seeds and mature tubers (Sultana et al., 2019).

Different biological potentials of lectins have been reported, such as their antimicrobial, mutagenic, antitumor, antifungal, insecticide and nematicide (De Medeiros et al., 2017; Bai et al., 2018; Camaroti et al., 2018; Ferreira et al., 2018; Gautam et al., 2018; Torres et al., 2019). Lectins also play important roles in processes associated to cell recognition and interaction, protein synthesis and transport, photosynthesis, regulation of cell division, fertilization, and innate immunity (De Schutter, Van Damme, 2015; Feizi, Haltiwanger, 2015).

Cell surface carbohydrates are potentially lectin-reactive sites and the ability to form lectin complexes with microbial glycoconjugates can be explored as a potential drug mechanism of action (Saha et al., 2014). The interaction between lectins and sugars plays important roles in several biological processes and can be used to measure a wide range of biological activities, including their antibacterial and antibiofilm activity (Klafke et al., 2013; Dias et al., 2015). The ability of lectins to bind to the cell surface carbohydrates of microorganisms has drawn attention to possible drug-application properties of these biomolecules for detection and therapy of bacterial infections (De Juan et al., 2017).

Antibacterial activity

Bacterial cell surfaces are composed of several types of substances, such as teichoic acid, teichuronic acid, lipopolysaccharides and peptidoglycans (Paiva et al., 2010; Lannoo, Van Damme, 2014). Lectins present antibacterial activity due to their interaction with these microbial cell wall components present in Gram-positive and Gram-negative bacteria (Breitenbach Barroso Rabbit et al., 2018). Due to the recognition and interaction, these proteins can cause several actions against microorganisms, including blocking their interaction sites with host cells, preventing invasion and infection;

agglutination, which results in the immobilization microbial cells, contributing to the action of the lectin molecules themselves; or act as adjuvants alongside other antimicrobial agents (Costa et al., 2010; Iordache et al., 2015; Moura et al., 2017a).

The interaction between lectins and bacterial surface glycoconjugates can also lead to inhibition by other mechanisms, such as the change in cell permeability that can lead to reduced nutrient absorption and also interfere with interaction with membrane receptors that trigger intracellular responses (Karnchanatat, 2012). Furthermore, lectins can act against microbial cell adhesion and migration and consequently, alter the virulence of these cells (Iordache et al., 2015; Fang et al., 2016; Silva et al., 2016).

Antibiofilm Activity

Bacteria in the ESKAPE group are associated to higher mortality risks and, consequently, higher health costs. Recently, the WHO added the group to the list of 12 bacteria in which there is a greater need for the development of new antibiotics (Founou, Founou, Essack, 2017; Tacconelli et al., 2018b). In addition to presenting several resistance mechanisms, bacteria belonging to the ESKAPE group are also able to grow in biofilms, which physically impedes the host's cellular immune response and the action of antibiotics against these pathogens (Santajit, Indrawattana, 2016).

Bacterial biofilms are multicellular communities involved in a self-produced polymeric matrix capable of adhering to biotic and abiotic surfaces. Biofilms are present in about 80% of bacterial infections in humans and to control their formation is difficult due to the fact that several antibacterial molecules are unable to penetrate it, being frequently retained in the exopolysaccharide (EPS) matrix. In addition, under the use of antimicrobials, the cells present in the biofilm, can express protective mechanisms, becoming resistant to a considerable number of antibiotics (De la Fuente-Núñez et al., 2013; Dejea, Sears, 2016).

Thus, the use of natural products, including lectins, as a possible strategy to prevent the formation of biofilms, has been the focus of several scientific studies. (Hasan, Ozeki, Kabir, 2014; Slobodníková, 2016). Many studies reported on these proteins as able to affect bacterial growth and start or interrupt intracellular signaling related to biofilm growth, leading to lowest expression of important genes related with virulence and biofilm formation. However, more studies are needed to elucidate and explain these mechanisms (Cavalcante et al., 2013; Saha et al., 2014).

Furthermore, the recognition of glycoconjugates, present in the membranes of microorganisms, allows lectins to inhibit biofilm agents. Lectins with antibiofilm activity can also be adhered to surfaces of medical devices in order to prevent their establishment (Moura et al., 2017b). Thus, lectins can be used to reduce and control problems related to biofilms and antibiotic resistance (Islam, Khan, 2012).

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2. Methodology

The aim of this article was to review the *in vitro* antibacterial and antibiofilm potential of plant lectins. The articles analyzed were obtained through searches on the platforms: Google Scholar, Scielo and Pubmed, and later selected for compatibility assessment with the pre-established inclusion criteria: publication in the interval of the last 10 years (2010 to 2020), in English and full text availability. As exclusion criteria, the following were considered: articles outside the established age range, available in a language other than English, with partially available text, in addition to editorial letters.

3. Results and Discussion

Several studies that evaluated lectins activities against various infections pathogens and have determined their antibacterial potential were gathered in Table 1.

Table 1. Antibacterial activity of plant lectins.

Plant species	Part of the plant	Bacteria	MIC	MBC	Reference
Punica granatum (PgTeL)	Sarcotesta	*Escherichia coli*	12.5 μg.ml^{-1}	25 μg.ml^{-1}	Da Silva et al., 2019c
		B-lactamase producing *E. coli* CTX-M-14	50 μg.ml^{-1}	100 μg.ml^{-1}	
		β-lactamase producing *E. coli* CMY-2	25 μg.ml^{-1}	50 μg.ml^{-1}	
		β -lactamase producing *E. coli* CTX-M-14/CMY-2	25 μg.ml^{-1}	50 μg.ml^{-1}	
		β -lactamase producing *E. coli* CTX-M-1	25 μg.ml^{-1}	50 μg.ml^{-1}	
		MRSA	12.5 μg.ml^{-1}	50 μg.ml^{-1}	
Punica granatum (PgTeL)	Sarcotesta	*Staphylococcus aureus*	6.25 μg.ml^{-1}	25 μg.ml^{-1}	Da Silva et al., 2019a
		MRSA	12.5 μg.ml^{-1}	50 μg.ml^{-1}	
Punica granatum (PgTeL)	Sarcostesta	*Aeromonas* sp.	3 μg.ml^{-1}	Absent	Silva et al., 2016
		Enterococcus faecalis	50 μg.ml^{-1}	Absent	
		Escherichia coli	6.25 μg.ml^{-1}	Absent	
		Klebsiella sp.	3 μg.ml^{-1}	Absent	
		Salmonella enterica serovar. Enteritidis	50 μg.ml^{-1}	Absent	
		Staphylococcus aureus	50 μg.ml^{-1}	Absent	
		Staphylococcus epidermidis	25 μg.ml^{-1}	Absent	
		Staphylococcus saprophyticus	50 μg.ml^{-1}	Absent	
		Micrococcus luteus	50 μg.ml^{-1}	100 μg.ml^{-1}	
		Serratia marcescens	1.25 μg.ml^{-1}	40 μg.ml^{-1}	
		Streptococcus mutans	9 μg.ml^{-1}	18 μg.ml^{-1}	
Portulaca elatior (PeRol)	Root	*Enterococcus feacalis*	8.1 μg.ml^{-1}	Absent	Da Silva et al., 2019b
		Staphylococcus aureus	32.5 μg.ml^{-1}	Absent	
		Pseudomonas aeruginosa	4.06 μg.ml^{-1}	Absent	
Alpinia purpurata (ApuL)	Influorescence	*Staphylococcus aureus*	50 μg.ml^{-1}	200 μg.ml^{-1}	Ferreira et al., 2018
		MRSA	400 μg.ml^{-1}	Absent	
Moringa oleífera (WSMoL)	Seed	*Staphylococcus aureus*	7.8 μg.ml^{-1}	300 μg.ml^{-1}	Ferreira et al., 2011
		Escherichia coli	250 μg.ml^{-1}	Absent	
Curcuma longa L. (CLA)	Rhizome	*Bacillus subtilis*	11 μg.ml^{-1}	Absent	Petnual, Sangvanich, Karnchanatat, 2010
		Staphylococcus aureus	5 μg.ml^{-1}	Absent	
		Escherichia coli	92 μg.ml^{-1}	Absent	
		Pseudomonas aeruginosa	2 μg.ml^{-1}	Absent	
		Bacillus subtilis	128 μg.ml^{-1}	Absent	
		Pseudomonas aeruginosa	128 μg.ml^{-1}	Absent	

Sterculia foetida L. (SfL)	Seed	*Escherichia coli*	256 μg.ml^{-1}	Absent	Braga et al., 2015
		Staphylococcus aureus	256 μg.ml^{-1}	Absent	
Apuleia leiocarpa (ApulSL)	Seed	*Bacillus subtilis*	45.12 μg.ml^{-1}	Absent	De Souza Carvalho et al., 2015
		Bacillus cereus	45.12 μg.ml^{-1}	Absent	
		Enterococcus faecalis	90.25 μg.ml^{-1}	Absent	
		Micrococcus luteus	90.25 μg.ml^{-1}	Absent	
		Streptococcus pyogenes	180.5 μg.ml^{-1}	Absent	
		Staphylococcus aureus	180.5 μg.ml^{-1}	Absent	
		Klebsiella pneumoniae	45.12 μg.ml^{-1}	Absent	
		Escherichia coli	180.5 μg.ml^{-1}	Absent	
		Pseudomonas aeruginosa	180.5 μg.ml^{-1}	Absent	
		Salmonella enteritidis	180.5 μg.ml^{-1}	Absent	
		Xanthomonas campestris pv. campestris	11.2 μg.ml^{-1}	22.5 μg.ml^{-1}	
		Xanthomonas campestris pv. viticola	22.5 μg.ml^{-1}	22.5 μg.ml^{-1}	
		Xanthomonas campestres pv. malvacearum	22.5 μg.ml^{-1}	22.5 μg.ml^{-1}	
Schinus terebinthifolius (SteLL)	Leaf	*Escherichia coli*	28.75 μg.ml^{-1}	115 μg.ml^{-1}	Gomes et al., 2013
		Klebsiella pneumoniae	3.59 μg.ml^{-1}	115 μg.ml^{-1}	
		Pseudomonas aeruginosa	1.79 μg.ml^{-1}	14,37 μg.ml^{-1}	
		Staphylococcus aureus	1.79 μg.ml^{-1}	7,18 μg.ml^{-1}	
		Salmonella enteritidis	0.45 μg.ml^{-1}	115 μg.ml^{-1}	
Archidendron jiringa Nielsen (AjL)	Seed	*Staphylococcus aureus*	56.7 μg.ml^{-1}	Absent	Charungchitrak et al., 2011
		Bacillus subtilis	227 μg.ml^{-1}	Absent	
Phthirusa pyrifolia (PpyLL)	Leaf	*Staphylococcus epidermidis*	250 μg.ml^{-1}	Absent	Costa et al., 2010
		Enterococcus feacalis	500 μg.ml^{-1}	Absent	
		Bacillus subtilis	125 μg.ml^{-1}	500 μg.ml^{-1}	

MIC: Minimum Inhibitory Concentration; MBC: Minimum Bactericidal Concentration; MRSA: Methicillin-resistant *Staphylococcus aureus*. Source: Authors.

In recent decades, hospital and community-acquired infections caused by ESBL have increased worldwide. β-lactam ring hydrolysis is the most common resistance mechanism of Gram-negative bacteria against third-generation cephalosporins and this scenario has led to the use of last-resort antibiotics, with the inherent risk of selecting even more resistant bacteria, such as Carbapenemase-producing Gram-negatives (Rotondo, Wright, 2017; Espinosa et al., 2018). With this, there is a growing need for new antimicrobial agents, and lectins isolated from plants have been identified as an alternative (Breitenbach Barroso Rabbit et al., 2018).

Da Silva et al. (2019a) evaluated the antibacterial activity of lectin isolated from the sarcotesta of *Punica granatum* (PgTeL) by the determination of the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). PgTel demonstrated bacteriostatic and bactericidal effect against *E. coli* ATCC 25922 (MIC: 12,5 μg.ml^{-1} and MBC: 25 μg.ml^{-1}) and ESBL-positive *E. coli* CTX-M-14, CMY-2, CTX-M-14/CMY-2, CTX-M-1 clinical isolates (MIC: 25-50 μg.ml^{-1} and MBC: 50-100 μg.ml^{-1}). The lectin was more active against *E. coli* ATCC 25922 and less active against the CTX-M-14 isolate. In a previous study, Silva et al. (2016) reported the bacteriostatic activity of PgTel against ATCCs strains of *Aeromonas* sp., *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella* sp., *Salmonella enterica* serovar. Enteritidis, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* (MIC: 3-50 μg.ml^{-1}). In addition to bactericidal and bacteriostatic activities against *Micrococcus luteus*, *Serratia marcescens* and *Streptococcus mutans* clinical isolates (MIC:1,25-50 μg.ml^{-1} and MBC: 18-100 μg.ml^{-1}).

Complications due to infections caused by *S. aureus* are the major reason for nosocomial and community-based morbidity and mortality worldwide (Harkins et al., 2017). Its ability to trigger infections is due to its virulence factors and resistance to antibiotics used in the treatment of these infections, exemplified by the MRSA outbreak. Most MRSA strains have the *mecA* gene, which encodes a protein that binds to the modified penicillin (PBP2a) which reduces the bacterial affinity for some antimicrobial agents (Montanaro et al., 2016).

Da Silva et al. (2019a) investigated the activity of PgTel lectin and observed the bacteriostatic and bactericidal activities of this lectin against clinical isolates of *S. aureus* (MIC: 6,25 μg.ml^{-1}; MBC: 25 μg.ml^{-1}) and MRSA (MIC: 12,5 μg.ml^{-1}; MBC: 50 μg.ml^{-1}). In another study, conducted by Ferreira et al. (2018), lectin from the bracts of *Alpinia purpurata* (ApuL) demonstrated bacteriostatic activity against *S. aureus* ATCC 6538 (MIC: 50 μg.ml^{-1}) and MRSA (MIC: 400 μg.ml^{-1}). Bactericidal activity was evidenced only against *S. aureus* ATCC 6538 (MBC: 200 μg.ml^{-1}).

ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* sp.) are a group comprising Gram-positive and Gram-negative bacteria. According to WHO reports, death rates related to ESKAPE pathogens have increased in recent years. Furthermore, analyzes of bacterial genomes have led to the conclusion that there is a shortage of potent antibiotics due to the approximately 20,000 potential resistance genes already reported (Aslam et al., 2018). Therefore, the discovery and development of new antimicrobial agents against these pathogens is of great importance.

In the study performed by Da Silva et al. (2019b), the lectin extracted from the root of *Portulaca elatior* (PeRol) showed bacteriostatic activity against *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (MIC: 8.1, 32.5 and 4.06 μg.ml^{-1}, respectively). However, bactericidal effect was not detected. In another study conducted by Ferreira et al. (2011), the lectin extracted from *Moringa oleifera* seeds (WSMol) showed bacteriostatic activity against the strains of *Staphylococcus aureus* WDCM 00034 (MIC: 7.8 μg.ml^{-1}) and *Escherichia coli* WDCM 00013 (MIC: 250 μg.ml^{-1}). Bactericidal activity was only reported only against *S. aureus* strains (MBC: 300 μg.ml^{-1}). WSMoL was more active against Gram-positive bacteria (*S. aureus*), probably due to the greater amount of peptidoglycan present in its cell wall when compared to Gram-negative bacteria. This peptidoglycan contains N-acetylglucosamine, which is a potential target for lectins with chitin affinity, such as WSMoL (Dos Santos Nunes et al., 2011).

In the study of Petnual, Sangvanich and Karnchanatat (2010), the evaluation of antibacterial properties of lectin extracted from *Curcuma longa* rhizome (CLA) presented inhibitory activity against *Bacilus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 (MIC: 11. 5. 92, 2 μg.ml^{-1}, respectively). Another study performed by Braga et al. (2015) showed the activity of SfL, lectin extracted from the seed of *Sterculia foetida*. This lectin demonstrated bacteriostatic activity against *Bacillus subtilis* CCT 0516, *Pseudomonas aeruginosa* ATCC 23243 and ATCC 8027, *Escherichia coli* ATCC 2536 and *Staphylococcus aureus* ATCC 25619 and ATCC 25925. *Pseudomonas aeruginosa* and *Bacillus subtilis* strains were the most sensitive (MIC: 128 μg.ml^{-1}), followed by *Escherichia coli* and both strains of *Staphylococcus aureus* (MIC: 256 μg.ml^{-1}).

De Souza Carvalho et al. (2015) evaluated the antibacterial activity of lectin extracted from *Apuleia leiocarpa* seeds (ApulSL). ApulSL demonstrated bacteriostatic action against Gram-positive bacteria, as *B. subtilis* ATCC 6633 and *B. cereus* ATCC 11778 (MIC: 45.12 μg.ml^{-1}), *E. faecalis* ATCC 6057 and *M. luteus* ATCC 2225 (MIC: 90, 25 μg.ml^{-1}), and *S. pyogenes* UFPEDA 07 and *S. aureus* ATCC 6538 (MIC: 180.5 μg.ml^{-1}). For these bacteria, the bactericidal activity of ApulSL was not detected. Regarding Gram-negative bacteria, ApulSL demonstrated a bacteriostatic effect against *Klebsiella pneumoniae* ATCC 29665, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. enteritidis* UFPEDA 415 (MIC: 45.12-180.5 μg.ml^{-1}). When evaluating ApulSL against different *Xanthomonas campestre* strains, the lectin demonstrated both bacteriostatic and bactericidal activity. For *X. campestris* pv. campestris Xcc 53, the MIC was 11.2 μg.ml^{-1}, whereas for *X. campestris* pv. viticola

Xcv 137, *X. campestres* pv. malvacearum Xcm 11.2.1 was 22.5 μg.ml^{-1} and for all 3 strains, the MBC value was 22.5 μg.ml^{-1}. This promissing antibacterial activity of ApulSL can be explained by its binding to N-acetylglucosamine residues present in the cell wall of most bacteria.

Another lectin, SteLL, was extracted from leaves of *Schinus terebinthifolius*. The antibacterial potential of this lectin was assessed in the study of Gomes et al. (2013). SteLL demonstrated bacteriostatic and bactericidal activity against *E. coli* WDCM 00013, *P. mirabilis* WDCM 00023, *S. aureus* WDCM 00032, *K. pneumoniae* ATCC 29665, *P. aeruginosa* WDCM 00025 and *S. enteritidis* MM 6247 (MIC: 0.45-28.75 μg.ml^{-1} and MBC: 7.18-115 μg.ml^{-1}). However, it was more efficient in controlling Gram-positive bacteria compared to Gram-negative bacteria. The difference in the susceptibility of these bacteria can be linked to the higher difficulty to overcome the cell wall of Gram-negative bacteria, by that lectin, and reach the periplasmic space (Dos Santos Nunes et al., 2011).

In the work published by Charungchitrak et al. (2011), antibacterial potential of lectin extracted from *Archidendron jiringa* Nielsen seeds (AjL) was evaluated. This lectin showed inhibitory activity against *Staphylococcus aureus* ATCC 25923 and *Bacillus Subtilis* ATCC 6633 (MIC: 56.7 and 227 μg.ml^{-1}).

In the study by Costa et al. (2010), the antimicrobial assays of lectin PpyLL, from leaves of *Phthirusa pyrifolia*, demonstrated bacteriostatic activity against *Staphylococcus epidermidis* UFPEDA 9, *Streptococcus faecalis* ATCC 6057 and *Bacillus subtilis* UFPEDA 16, with MIC of 250, 500 and 125 μg.ml^{-1}, respectively. In addition, bactericidal activity was observed against *B. subtilis* UFPEDA 16 strain (MBC: 500 μg.ml^{-1}). Although PpyLL did not show bactericidal activity for all of the isolates tested, it was able to cause a cluster of cells at the bottom of the test tube that could be observed even without the aid of a microscope after 6 hours. Thus, this lectin, like others, can recognize bacterial carbohydrates on cells surface and agglutinate them, promoting cell immobilization, inhibition growth or even promoting its destruction.

Among the lectins evaluated and which showed antibacterial activity, the lectin extracted from the plant *Punica granatum* (PgTeL) was the best studied and the most potent, being reported in studies by Da Silva et al., 2019a, Da Silva et al., 2019c and Silva et al., 2016. In addition, in these studies, this lectin showed activity against several bacteria of medical interest, including ESBL and MRSA.

In the evaluation of inhibitory activity against Gram-positive bacteria, the lectins from *Punica granatum* (PgTeL), *Curcuma longa* (CLA) and *Schinus terebinthifolius* (SteLL) showed the greatest potential, with activity against *Staphyloccocus aureus*, MRSA, *Bacillus subtilis*, *Streptococcus mutans* and *Enteroccocus faecalis*. In the bactericidal activity evaluation, *Punica granatum* and *Schinus terebinthifolius* lectins were the most potent, presenting bactericidal action against *Staphylococcus aureus*, MRSA, *Micrococcus luteus*, *Serratia marcescens* and *Streptococcus mutans*.

On the other hand, the lectins extracted from *Punica granatum*, *Portulaca elatior*, *Curcuma longa* and *Schinus terebinthifolius* were responsible for the greatest inhibitory activity against Gram-negative bacteria, including isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Aeromonas* sp. and *Serratia marcescens*. Besides that, the lectins extracted from *Punica granatum*, *Portulaca elatior* and *Schinus terebinthifolius* showed the best bactericidal activity against isolates of *Pseudomonas aeruginosa*, *Serratia marcescens* and *Escherichia coli*.

The studies evaluated showed lectins with bacteriostatic and bactericidal action against several pathogenic bacteria, including some bacterial isolates resistant to antibiotics and difficult to suppress. Therefore, these results in plant lectins showed they are promising sources for the development of new antibacterials.

Studies that conducted evaluation of plant lectins activities against biofilm formation by various bacterial pathogens were gathered in Table 2.

Table 2 Antibiofilm activity of plant lectins.

Plant species	Part of the plant	Bacteria	Concentration	Inhibition	Reference
Canavalia ensiformis (ConA)	Full plant	*Escherichia coli*	10 to 2000 μg.ml^{-1}	6 to 63-fold	Jin, Lee, Hong, 2019
		Lysteria monocytogenes	100 μg.ml^{-1}	140-fold	
Alpinia purpurata (ApuL)	Inflorescence	*Staphylococcus aureus*	1.56-50 μg.ml^{-1}	52-60%	Ferreira et al., 2018
Calliandra surinamensis (Casul)	Leaf	MRSA	50-800 μg.ml^{-1}	38-52%	Procópio et al., 2017b
		Staphylococcus saprophyticcus	6.25-800 μg.ml^{-1}	18-72%	
Moringa oleifera (WSMoL)	Seed	*Bacillus* sp.	0.65-41,6 μg.ml^{-1}	8-90%	Moura et al., 2017b
		Serratia marcescens	0.325-20.8 μg.ml^{-1}	40-74%	
Solanum tuberosum (StL-20)	Tuber	*Pseudomonas aeruginosa*	2.5-80 μg.ml^{-1}	7-18%	Hasan, Ozeki, Kabir, 2014
Canavalia marítima (ConM)	Seed	*Streptococcus mutans*	100-200 μg.ml^{-1}	30-33%	Cavalcante et al., 2011; Cavalcante et al., 2013

Source: Authors.

Jin, Lee and Hong (2019) evaluated the antibiofilm potential of a lectin extracted from *Canavalia ensiformis* (ConA). This lectin was able to inhibit the growth of biofilms of enterohemorrhagic *Escherichia coli* EDL933 and *Listeria monocytogenes* ATCC 19115 by adhering to the surface of the bacterial cell wall, thus preventing their initial adheresion to solid surfaces. In addition, the results suggest that concentrations between 100 and 500 μg.ml^{-1} are efficient in inhibiting biofilm formation by both bacteria.

Ferreira et al. (2018) showed that concentrations between 1.56 and 50 μg.ml^{-1} of ApuL, a lectin extracted from *Alpinia purpurata*, reduced the biofilm of *Staphylococcus aureus* UFPEDA-02 by between 50 and 60% when compared to untreated cells. This is likely due to the fact that the antibiofilm activity of lectins involves the ability of these molecules to alter cell viability, interact with constituents of the exopolymeric biofilm matrix, interrupt polymerization and inhibit signaling pathways (Cavalcante et al., 2013; Moura et al., 2017b).

Procopio et al. (2018) presented the potential antibiofilm of *Calliandra surinamensis* lectin (Casul). Casul was able to significantly reduce the biofilm of MRSA UFPEDA-670 and *Staphylococcus saprophyticcus* UFPEDA-833. For *S. saprophyticcus* strain, an inhibitory effect higher than 50% was observed using concentrations of 100 μg.ml^{-1}, and for MRSA this inhibition was established with 400 μg.ml^{-1}. In addition, a higher inhibitory effect was obtained for *S. saprophyticcus*, with 72% reduction in biofilm using 800 μg.ml^{-1}. So, this research indicates a potential use of CasuL on medical devices surface coverage, which could prevent biofilm formation from these bacteria.

Hasan, Ozeki and Kabir (2014) evaluated the antibiofilm activity of StL-20, a lectin extracted from the *Solanum tuberosum*. It was tested against an isolate of *Pseudomonas aeruginosa* PA01 and could inhibit its biofilm formation by 5 to 20%, with varying concentrations. The inhibitory effect had a considerable increase in concentrations between 2.5 and 15 μg.ml^{-1} and became almost constant above 20 μg.ml^{-1}. *P. aeruginosa* is a well-known biofilm forming bacteria. As lectins are divalent molecules, Stl-20 might present binding sites for saccharides, proteins and other components in the biofilm and thereby affected its polymerization.

WSMoL, the *Moringa oleifera* seed lectin, had its antibiofilm potential reported by Moura et al. (2017a). WSMoL demonstrated antibiofilm activity against *Bacillus* sp. UFPEDA 189 and *Serratia marcescens* ATCC 14756, inhibiting biofilm formation of *S. marcescens* at low concentrations (0.325-1.3 μg.ml^{-1}) and *Bacillus* sp. at all concentrations tested (from 20.8 to

41.6 μg.ml^{-1}). This activity is due the ability of these lectins to interact with glycoconjugates and polysaccharides present in the bacterial cell wall. These interactions can damage the cell wall and membrane and be responsible for compormising biofilm development (Paiva et al., 2010; Klafke et al., 2013; Trentin et al., 2013; Hasan, Ozeki and Kabir, 2014). Thus, interactions between lectins and bacterial cells may also be related to the inhibitory effect on biofilm formation, preventing the attachment of the bacterial polysacaccharides on surfaces, as among other bacterial cells. Other studies reported that the antibiofilm activity of lectins involves their binding to the exopolymer matrix, interrupting its polymerization and signaling molecules, resulting in the prevention of the expression of important genes related to the biofilm development and other virulence factors (Cavalcante et al., 2013; Klafke et al., 2013; Hasan, Ozeki and Kabir, 2014).

The study performed by Cavalcante et al. (2011) reported the antibiofilm activity of a lectin extracted from *Canavalia maritime* (ConM). It was able to inhibit the biofilm of *Streptococcus mutans* UA159 at concentrations from 100 to 200 μg.ml^{-1}. In a second study conducted by Cavalcante et al. (2013), ConM's activity can be attributed not only to its direct action on bacterial cells, but also to its ability to inhibit genes related to the formation of biofilm and virulence. Based on that, the mechanism of action of these lectins needs a better understood, however, the results of the study suggest that lectin can act by initiating or interrupting intracellular signaling pathways that culminate in a suppressed expression of these genes associated with virulence and biofilm formation in *S. mutans*.

4. Conclusion

Due to the scarcity of antimicrobials, research and validation of new compounds with antimicrobial activity is urgent. Regarding the antibacterial activity, lectins are important due to their ability to interact with microbial cell wall components, such as teichoic acid, teichuronic acid, lipopolysaccharides, and peptidoglycans. Due to this interaction, these proteins can promote several actions against the pathogens, such as the blocking the binding sites with hosts cells and agglutination. On the other hand, their antibiofilm activity works by initiating or interrupting intracellular signaling pathways, what induces a lower expression of important genes related to virulence and biofilm formation, and therefore, have been shown to be candidates for new antibacterial and antibiofilm drugs. Thus, this research suggests that plant lectins have a valuable potential for the development of new antimicrobial agents, but further research in needed to understand the mechanisms already known and discover new mechanisms of action of the lectins, as well as their possible toxicities, allowing its possible application in clinical trials.

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