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Phytochemical analysis and modulation in aminoglycosides antibiotics activity by *Lantana camara* L.

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ABSTRACT. Several plants have been evaluated not only for alone antimicrobial activity, but as resistance-modifying agent. This work is the first on the modulation of antibiotic activity by *Lantana camara* L. extracts against multiresistant strains of *Escherichia coli* and *Staphylococcus aureus*. The antibacterial activities of leaf and root ethanol extracts alone or in association with aminoglycosides were determined against bacterial strains by a microdilution test. The minimum inhibitory concentration (MIC) of the extracts was compared with of the aminoglycosides. Phytochemical prospection revealed the presence of quinones, steroids, flavonoids, saponins, tannins, triterpenoids and alkaloids. The results showed antibacterial activities of the extracts and synergistic effects combined with aminoglycosides. The most expressive effects were obtained with root extract but gentamicin or but neomycin against *E. coli* with MICs decreased (312 to 5 μg mL^{-1}). The data from this study are indicative of the antibacterial activity of *L. camara*'s extracts and its potential in modifying the resistance of aminoglycosides analyzed.

Keywords: *Lantana camara* L., antibacterial activity, aminoglycosides, synergism.

Análise fitoquímica e modulação sobre a atividade antibiótica de aminoglicosídeos por *Lantana camara* L.

RESUMO. Este trabalho relata a modulação da atividade antibiótica por extratos de *Lantana camara* L. frente a linhagens multirresistentes de *Escherichia coli* e *Staphylococcus aureus.* Diversas plantas têm sido avaliadas não somente para a atividade antimicrobiana, mas também para a capacidade de modificar a resistência antibiotica. Atividades antibacterianas dos extratos etanólicos das folhas e raízes isoladamente ou em associação com aminoglicosídeos foram determinadas contra linhagens bacterianas por teste de microdiluição. As concentrações inibitórias mínimas (CIM) dos extratos foram comparadas com a dos aminoglicosídeos. A prospecção fitoquímica revelou a presença de quinonas, esteroides, flavonoides, saponinas, taninos, triterpenoides e alcaloides. Os resultados mostraram atividade antibacteriana dos extratos e efeitos sinérgicos combinados com aminoglicosídeos. Os efeitos mais expressivos foram obtidos pelo extrato das raízes em associação com a gentamicina ou neomicina, contra *E. coli* Ec27 com diminuições das CIMs (312-5 μg mL^{-1}). Os dados deste estudo são indicativos da atividade antibacteriana dos extratos de *L. camara* e seu potencial para modificar a resistência aos aminoglicosídeos analisados.

Palavras-chave: *Lantana camara* L., atividade antibacteriana, aminoglicosídeos, sinergismo.

Introduction

The search for new antibacterial agents is important due to the progressive increasing resistance of clinically important pathogens to known classes of antibiotics (COSTA et al., 2009). Bacterial resistance is due to random genetic mutations in the bacterial cell that alter its sensitivity to a single drug or to chemically similar drugs through a variety of mechanisms. These mechanisms can chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify the target site so that it is not recognized by the antibiotic (TENOVER, 2006).

Several bacteria are able to develop changes in their sensitivity, but *Staphylococcus aureus* and *Escherichia coli* have been recognized by their increasing resistance to conventional antibiotics. *Staphylococcus aureus* is one of the most common and devastating human pathogen. In addition of causing different kinds of intoxications, *S. aureus* has been the most common agent of festering infections that attack different tissues and/or organs (e.g. furuncle, carbuncle, abscess, myocarditis, endocarditis, pneumonia, meningitis, bacterial arthritis) (VERHOEFF et al., 1999; MATIAS et al., 2012).

Escherichia coli is one of the microorganisms that have been associated to intestinal and urinary tract infections. These bacteria are known to produce enterotoxins whose properties and role in diarrheal disease have been widely investigated. *E. coli* is not only a very common intestinal pathogen but very often is involved in extra-intestinal diseases in the intensive care unit and in surgical wound infections (MATIAS et al., 2011).

Natural products from plants have been evaluated not only for direct antimicrobial activity, but as a resistance-modifying agent of antibiotics, which can be a synergistic or antagonistic effect. Synergism has been defined as a phenomenon in which two different compounds are combined to enhance their individual activity. If the combination results in worsening effect, it is called antagonism (CHUNG et al., 2011). Compounds with synergistic activity can represent a progress to resistance mechanisms of aminoglycosides (COUTINHO et al., 2008). The main mechanisms which may affect all aminoglycosides are a decreased uptake and/or accumulation of the drug in bacteria and the bacterial expression of enzymes which modify the antibiotic and thereby inactivate it (SHAW et al., 1993).

The genus *Lantana* (Verbenaceae) is comprised of about 150 species of perennial flowering plants mostly native to subtropical and tropical America, but a few are indigenous to tropical Asia and Africa. Different *Lantana* species are rich in many bioactive molecules with relevant biological and pharmacological activities (HUSSAIN et al., 2011). *Lantana camara* L. is a shrub native from America and Africa cultivated as an ornamental plant in other countries. The leaves extract has been used in treatment of scratching, stomachache, rheumatism, wound healing, biliary fever, toothache, bronchitis, and as an antiseptic. Their roots are used in the treatment of malaria, rheumatism and rash (SOUSA; COSTA, 2012). Previous report shows antiprotozoal properties (JONVILLE et al., 2008), antibacterial (SONIBARE; EFFIONG, 2008), antioxidant (BENITES et al., 2009), nematicidal (BEGUM et al., 2008), antiviral (GARCIA et al., 2010), among others, but this is the first study regarding the modulatory activity of the extracts against multiresistant strains.

Considering the bacterial resistance and antibacterial properties of plants, the aim of the present work was to perform phytochemical analysis of the leaves and roots extracts of *L. camara* L. and to investigate their potentiating of the antibiotic activity of aminoglycosides.

Material and methods

Bacterial material

The bacteria strains tested were *Escherichia coli* Ec27 and *Staphylococcus aureus* Sa358 with antibiotics resistance profiles demonstrated in Table 1. The microorganisms were isolated from clinical samples at Laboratory of the General Hospital of the Federal University of Paraíba, Brazil. The strains were maintained on slants with heart infusion agar (HIA, Difco), and prior to assay, the cells were grown overnight at 37°C in brain heart infusion (BHI, Difco Laboratories Ltd.).

Table 1. Bacterial source and antibiotics resistance profile.

Strains	Source	Antibiotic resistance profile
E. coli Ec27	Sputum	Ast, Ax, Amp, Ami, Amox, Ca, Cfr, Cf, Caz, Cip, Chl, Im, Kan, Szt, Tet, Tob
S. aureus Sa358	Surgical wound	Oxa, Gen, Tob, Ami, Kan, Sis, Neo, Para, But, Net

Ast = aztreonan; Ax = amoxicillin; Amp = ampicillin; Ami = amikacin; Amox = amoxicillin; Ca = cefadroxil; Cfr = cefaclor; Cf = cefalothin; Caz = ceftazidime; Cip = ciprofloxacin; Chl = chloramphenicol; Im = imipenem; Kan = kanamycin; Szt = sulfametrim; Tc = tetracycline; Tob = tobramycin; Oxa = oxacillin; Gen = gentamicin; Sis = sisomicin; Neo = neomycin; Para = paramomycin; But = butirosin; Net = netilmicin.

Standard antibiotics

The antibiotics neomycin, kanamycin, amikacin and gentamicin in powder form were obtained from Sigma Chemical Co. All drugs were dissolved in sterile water.

Plant material

Lantana camara L. were collected in May of 2011, from the Small Aromatic and Medicinal Plants Garden of the Natural Products Research Laboratory (LPPN) at University Regional of Cariri (URCA), in the city of Crato, Ceará state, Brazil. A voucher specimen (#1662) was deposited at the 'Herbarium Caririense Dárdano de Andrade Lima' (HCDAL) of the Department of Biological Sciences, Regional University of Cariri.

Preparation of extracts

A total of 240 g of fresh leaves and 185 g of the roots were kept submersed in 2 L of ethanol and left in this condition for 72h at ambient temperature. After this, the extract was filtered and concentrated using a rotary vacuum evaporator (model Q-344B, Quimis, Brazil) and ultrathermal bath (model Q-214M2, Quimis) was used to remove the ethanol (under reduced pressure, 50°C), obtaining 12.0 g of leaf extract and 1.3 g of root extract with yields of 5.0 and 0.7% (w w^{-1}), respectively.

Phytochemical analysis

Phytochemical tests were conducted to investigate the presence of alkaloids, saponins, tannins, quinones, flavonoids, triterpenes, steroids, heterosides and cumarins. The specific qualitative tests were based on the visual observation of change in color or formation of precipitate after addition of specific reagents (MATOS, 2009).

Antibacterial assay and minimal inhibitory concentration (MIC)

The minimum inhibitory concentrations (MIC) were determined by a microdilution assay (CLSI, 2006). Brain heart infusion broth (BHI) the 3.8% was used for bacterial growth (24h, 35 ± 2ºC). The inoculum was an oven light culture of each bacterial species in BHI broth diluted in the same media to a final concentration of approximately 1 x 10^8 CFU mL^{-1} (0.5 nephelometric turbidity units - McFarland scale). After this, the suspension was diluted to 1 x 10^5 CFU mL^{-1} in BHI 10%. A total of 100 μL of each dilution were distributed in 96-well plates with each extracts, achieving 5 x 10^5 CFU mL^{-1} as final concentration of the inoculums.

The initial solution of each extracts was performed using 10 mg of extract dissolved in 1 mL of dimethyl sulfoxide - DMSO to obtain an initial concentration of 10 mg mL^{-1}. From this concentration, several dilutions were made in distilled water in order to obtain a stock solution of 1024 µg mL^{-1}. Further serial dilutions were performed by addition of BHI broth to reach a final concentration in the range of 8-512 µg mL^{-1}.

The experiments were performed in triplicate and the microdilution trays were incubated at 35 ± 2ºC for 24h. Antibacterial activity of the extracts were detected using a colorimetric method by adding 25 μL of resauzurin staining (0.01%) aqueous solution in each well at the end of the incubation period. The MIC was defined as the lowest extracts concentration able to inhibit the bacteria growth, as indicated by resauzurin staining (dead bacterial cells are not able to change the staining color by visual observation – blue to red).

Modulation of antibiotic activity

For the evaluation of the extracts as modulators in the resistance of aminoglycosides antibiotics, MIC of the antibiotics were determined in the presence or absence of the extracts at sub-inhibitory concentrations (MIC of the extracts/8). The experiments were performed by microdilution assay (CLSI, 2006), utilizing suspensions of 10^5 CFU mL^{-1} in BHI and antibiotics concentration range of 0.0012-2.5 mg mL^{-1} (2-fold serial dilutions). The plates were incubated for 24h at 37ºC and controlled using DMSO in MIC determination and antibiotic modulation activity tests were performed.

Results

The Table 2 shows that phytochemical prospection revealed the presence of compounds such as quinones, tannins phlobaphenes, tannins pyrogallates, steroids, flavones, flavonols, flavononols, flavonones, chalcones, catechins, proanthocyanidins, triterpenoids, alkaloids and saponins.

Table 2. Phytochemical screening of *L. camara* L. leaves and roots extracts.

Extracts	Metabolites identified																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Leaves	+	+	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+
Roots	-	+	+	-	-	+	+	+	+	-	-	+	+	+	-	+	-	+

1 = Phenols; 2 = tannins condensed; 3 = tannins pyrogallates; 4 = anthocyanins; 5 = anthocyanidins; 6 = flavones; 7 = flavonols; 8 = flavononols; 9 = flavonones; 10 = xanthones; 11 = chalcones; 12 = aurones; 13 = proanthocyanidins; 14 = catechins; 15 = alkaloids; 16 = triterpenoids; 17 = saponinas, 18 = steroids + = presence; - = absence

Table 3 shows the MICs of the extracts and synergic effect combined with antibiotics. The antibacterial properties of the extracts were observed for the inhibitory activity against *E. coli* and *S. aureus* multiresistant strains. The data showed that both bacteria strains presented greater sensitivity to leaves extract with MIC (256 μg mL^{-1} against *E. coli*) and (512 μg mL^{-1} against *S. aureus*), while MICs of the antibiotics were in the range of 40 to 625 µg mL^{-1}.

The MICs for all antibiotics used here decreased in presence of the extracts. The most expressive effect was obtained for the activity of gentamicin but root extract or amikacin on *E. coli* with MIC reduction (312 to 5 µg mL^{-1}). The root extract showed weak antibacterial activity, but presented synergetic effect for all antibiotics in association (Table 3). In general, the extracts interference (synergism) on antibiotic action was correlated to the antibiotic type and bacteria strain. The controlled DMSO showed a MIC ≥ 1024 µg mL^{-1} and no modifying antibiotic activity.

Table 3. MIC values (μg mL^{-1}) of aminoglycosides with and without the leaves and roots extracts of *L. camara* L.

Samples	*E. coli* Ec27			*S. aureus* Sa358		
	MIC alone	MIC combined		MIC Alone	MIC combined	
		LE 32 μg mL^{-1}	RE 128 μg mL^{-1}		LE 64 μg mL^{-1}	RE 128 μg mL^{-1}
Neomycin	156 (R)	78 (R)	5 (S)	78 (R)	20 (R)	40 (R)
Amikacin	312 (R)	40 (R)	5 (S)	156 (R)	78 (R)	40 (R)
Kanamycin	312 (R)	40 (R)	20 (R)	625 (R)	156 (R)	156 (R)
Gentamicin	312 (R)	20 (R)	5 (R)	40 (R)	20 (R)	20 (R)
LE	256	-	-	512	-	-
RE	> 512	-	-	> 512	-	-

Leaves (LE) and roots (RE) extracts; R = Phenotypic profile of resistance according with CLSI (2006); S = Phenotypic profile of sensitivity according with CLSI (2006).

Discussion

In the phytochemical analysis of the extracts was detected the presence of diverse classes of secondary metabolites that show a wide variety of biological activities including antibacterial. The antibacterial activity of flavonoids is due to their ability to complex with extracellular and soluble protein and to complex with bacterial cell wall while that of tannins may be related to their ability to inactivate microbial adhesions, enzymes and cell envelop proteins (KONATÉ et al., 2012). *L. camara* is rich in many bioactive compounds, and a phytochemical review has been told the presence of terpenoids, phenylpropanoids and flavonoids, as the main class components with relevant biological activity (SOUSA; COSTA, 2012). Phytochemical investigations report the presence of flavonoids and proanthocynidines in premature leaves of *L. camara* L. (BHAKTA; GANJEWALA, 2009).

In previous reports the antibacterial activity of *L. camara* and *Lantana* species were verified, but this is the first work regarding to the modulation of antibiotic activity by extracts of *L. camara* L. against multiresistant strains. The acetone extracts of *L. camara* L. and *L. rugosa* Thunb. leaves shows antibacterial activity against two Gram-negative (*E. coli* and *Pseudomonas aeruginosa*) and two Gram-positive (*Enterococcus faecalis* and *S. aureus*) inhibited the growth. MIC values varied from 0.39 to 6.3 mg mL^{-1} (McGAW; ELOFF, 2005). The hexane extract from *L. hispida* Kunth aerial parts inhibited the growth of *Mycobacterium tuberculosis* H37Rv (MIC 200 μg mL^{-1}) (JIMÍENEZ-ARELLANES et al., 2003).

Several triterpenoids isolated from *L. camara* leaves showed antibacterial activity. The lantic acid was found to possess strong antibacterial activity against *E. coli* and *Bacillus cereus*, in which 0.08 and 0.1 μg were the minimum inhibition doses, respectively, compared to 0.05 and 0.005 μg for chloramphenicol, respectively (SALEH et al., 1999). The camarinic acid was active (30 mg $disk^{-1}$) against *S. aureus* and *S. typhi* with an average antibacterial index of 0.95 and 0.55. By comparison, chloramphenicol against *S. aureus*, and tetracycline against *S. typhi* had an index of 1.6 and 0.8 at the same concentration (BARRE et al., 1997). The linaroside and lantanoside were effective against *Mycobacterium tuberculosis* strain (MICs 6.25 μg mL^{-1}) (BEGUM et al., 2000).

The mechanisms to inhibit the bacterial growth are varied, but here can be due in part to the hydrophobic nature of some components of the extracts. Thus, they can interact with the lipid bilayer and affect the cell membrane, interfering with respiratory chain activity and energy production, or even make the cell more permeable to antibiotics, provoking the interruption of vital cellular activity (NICOLSON et al., 1999). Some compounds can permealilize the cell membrane, increasing the penetration of antibiotics, among them, terpenoids (LEON et al., 2005).

The mechanism of action of terpenoids is not fully understood but is speculated to involve membrane disruption by the lipophilic compounds, with permeability enhancement. This property can facilitate the antimicrobial agents to penetrate into the cell, leading to an activity enhancement. The improvement of antibacterial activity against the Gram-negative bacteria *E. coli* demonstrated a significative result due as the gram-positive bacteria are more susceptible to natural products (SILVA et al., 2007).

The root extract was effective in changing the resistant phenotype of the bacterium to the sensitive one, and this capacity was more evidenced in the Gram-negative bacteria. The Gram-negative bacteria present structural particularities that difficult the antibiotics penetration, as the lipopolysaccharide structures containing polysaccharides of different length that largely contribute to cell surface properties, such as membrane permeability and antibiotic susceptibility (YOKOTA; FULLII, 2007).

Previous works have described the potential of vegetal extracts as antibiotics and strong tendency as potentiated of aminoglycosides have been observed. In one study, extracts of *Croton campestris* A. were analyzed in association with aminoglycoside and MIC reduction against *E. coli* was observed (MATIAS et al., 2011). Other study shows synergistic effect of the leaves and roots extracts of *L. montevidensis* Briq. on aminoglycoside activity. The maximum effects were obtained with root extracts on gentamicin activity against *E. coli* with MIC reduction (312 to 2 μg mL^{-1}) (SOUSA et al., 2011).

Conclusion

In conclusion, the data obtained in this study are indicative of the potential antibacterial and modulatory activity of the extracts. It is suggested that it could be used as a source of plant-derived natural products with resistance-modifying antibacterial activity of aminoglycosides for use against multiresistant strains of *E. coli* and *S. aureus* acquired from hospital and from community.

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