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Artigo

The antibiotic activity of some Brazilian medicinal plants

Maria R. Ferreira de Lima[1], Eulália C.P. Azevedo Ximenes[2], Josiane S. Luna[1], Antônio E. Goulart Sant'Ana[1]*

[1]Instituto de Química e Biotecnologia, Centro de Ciências Exatas e Naturais, Universidade Federal de Alagoas, Cidade Universitária, 57072-970, Maceió, Alagoas, Brasil,
[2]Instituto de Antibióticos, Centro de Ciências da Saúde, Universidade Federal de Pernambuco, Cidade Universitária, 50740-901, Recife, Pernambuco, Brasil

RESUMO: "**Atividade antibiótica de algumas plantas medicinais brasileiras"**. As atividades antibióticas de extratos etanólicos de 16 espécies de plantas usadas em medicina popular no Brasil foram determinadas contra *Staphylococcus aureus, Micrococcus flavus, Bacillus cereus, B. subtilis, Salmonella enteretidis, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Serratia marcescens, Mycobacterium phlei, M. smegmatis* e *M. fortuitum*, contra as leveduras *Candida albicans* e *C. krusei*. Entre os trinta e dois extratos testados, somente aqueles derivados de *Lafoensia pacari* e *Pterodon polygalaeflorus* mostraram atividade contra as cepas bacterianas e nenhum deles apresentou atividade contra as leveduras. O extrato etanólico das folhas de *L. pacari* mostrou valores de concentração inibitória mínima (CIM) na faixa entre 312,5 a 2500 μg/mL, 250 μg/mL, 625 μg/mL, e 1250 μg/mL, respectivamente, contra oito diferentes variedades de *Staphylococcus aureus* Gram-positivas, *Proteus mirabilis* Gram-negativas e os bacilos acido-resistentes *Mycobacterium phlei*, *M. fortuitum* e *M. smegmatis*. O extrato etanólico do caule de *L. pacari* apresentou valores de CIM de 625 μg/mL contra *S. aureus*. Análise química revelou que os extratos brutos continham taninos, esteróides, fenóis, flavonóides, triterpenos e saponinas: as atividades foram altas o suficiente para possibilitar o isolamento guiado pelo bioensaio e a identificação futura dos compostos ativos.

Unitermos: *Lafoensia pacari*, *Pterodon polygalaeflorus,* atividade antibiótica.

ABSTRACT: The antibiotic activities of the ethanol extracts from 16 species of plants used in Brazilian folk medicine have been determined against *Staphylococcus aureus, Micrococcus flavus*, *Bacillus cereus*, *B. subtilis, Salmonella enteretidis, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Serratia marcescens, Mycobacterium phlei, M. smegmatis* and *M. fortuitum*, and the yeasts *Candida albicans* and *C. krusei*. Among 32 extracts assayed, only those from *Lafoensia pacari* and *Pterodon polygalaeflorus* showed activity against the bacterial strains, and none were active against the yeasts. The ethanolic extract from the leaves of *L. pacari* showed minimum inhibitory concentration (MIC) values of 312.5 to 2500, 250, 625 and 1250 μg/mL, respectively, against eight different Gram-positive strains of *Staphylococcus aureus*, the Gram-negative *Proteus mirabilis* and the acid-fast bacilli *Mycobacterium phlei*, *M. fortuitum* and *M. smegmatis*. The ethanolic extract from the stem of *L. pacari* showed an MIC value of 625 μg/mL against *S. aureus*. Chemical analysis revealed that the crude extracts contained tannins, steroids, phenols, flavonoids, triterpenes and saponins: the activities were sufficiently high to present the possibility of future identification of the active components by bioassay-guided fractionation and purification.

Keywords: *Lafoensia pacari*, *Pterodon polygalaeflorus*, antibiotic activity.

INTRODUCTION

Natural resources have, since antiquity, been extensively exploited for medicinal purposes. Numerous plant materials have been employed in folk medicine in attempts to control diseases as diverse as bronchitis, pneumonia, ulcers and diarrhoea. In many countries around the world the use of medicinal plants still contributes significantly in primary health care. In Brazil, large numbers of plants have been used in the form of crude extracts, infusions or plasters in order to treat common infections (Morais et al., 2005; Vendruscolo et al., 2005; Tôrres et al., 2005). Although there is currently little scientific evidence regarding the efficacy of such treatments, traditional medicine is still widely practiced by people living in the interior of the country. Moreover, phytotherapy is becoming an important economic sector in Brazil, and is increasing in popularity as an alternative form of health care (Macedo; Ferreira 2004ab).

Recently, medicinal plants have become the focus of intense study regarding their conservation and potential pharmacological effects. Indeed, the search for new

* *E-mail: aegs@qui.ufal.br, antonio.euzebio@pesquisador.cnpq.br, Tel.: + 55-82-3214-1138, Fax: + 55-82-32141700*

pharmacologically active agents, through the screening of natural sources such as microbial fermentations and plant extracts, has led to the discovery of many clinically useful drugs that now play major roles in the treatment of human diseases (Yue-Zong, 1998; Leitão et al., 2006; Funke; Melzig 2006). However, whilst Brazilian folk medicine is substantial, our knowledge of the pharmacological activities and chemical compositions of plant extracts used therein is lacking and demands enhanced levels of scientific attention from local natural product chemists (Falcão et al., 2005; Barbosa-Filho et al., 2005; Barbosa-Filho et al., 2006a; Barbosa-Filho et al., 2006b)

The present paper deals with the screening of plants from Brazilian folk medicine for antimicrobial activity. Only plants with documented uses related to their antimicrobial activities were selected (Table 1). Some of the assayed species are already grown as commercial fruit crops, whilst others are well-known ornamental plants. Many of them have been identified with a number of medicinal uses (Braga, 1953; Corrêa; Penna, 1984), and all can be purchased from healers in local markets.

In our initial screening programme, examples of both Gram-positive and Gram-negative bacteria were chosen for inclusion based on their clinical, pharmaceutical and bromatological importance in infectious diseases (Sant'Ana et al., 2006). However, according to Farnsworth (1966), acid-fast bacilli, yeasts and filamentous fungi should be incorporated into the first screening and, in order partially to fulfill this aim strains of *Mycobacterium* and of *Candida* were also included in our assays.

MATERIAL AND METHODS

Plant materials

Thirty-two extracts from 16 plant species, representing 16 genera within 12 families, were selected for assay based on available ethnobotanical and chemosystematic information (Table 1). The selected plant species were collected and authenticated by Prof. José Elias de Paula [Universidade de Brasilia (UnB-DF), Brasília-DF, Brasil] and Rosangela P. de Lira Lemos [Instituto do Meio Ambiente do Estado de Alagoas (IMA-AL), Maceió-AL, Brasil]. Voucher specimens of all plant species have been deposited in the herbaria at UnB-DF and IMA-AL.

Preparation of plant extracts

Plant material was separated into its selected parts, air dried, ground to a moderately fine powder, extracted with 95% ethanol at room temperature (26 ± 1 °C) for 2 days and filtered. The residue was extracted twice more in a similar manner. Each extract was evaporated to dryness under reduced pressure using a rotary evaporator and stored in labelled, sterile, screw-capped bottles at -20 °C until required for assay. The amount of plant material collected for the preparation of the extracts was dependent on its availability at harvesting, but the minimum quantity in each case was 500 g fresh weight.

Assay of antibiotic activity

The test microorganisms strains were provided by the Departamento de Antibióticos, Universidade Federal de Pernambuco, Recife, Brasil. Clinical isolates of *Staphylococcus aureus* (133, 138, 139, 149, 155, 246, 247, 311, 401 and 403), *Proteus mirabilis* IC 03*, Mycobacterium smegmatis* M11*, M. fortuitum* M5, and stock isolates of *Micrococcus flavus* DAUFPE 323, *Bacillus cereus* DAUFPE 11, *B. subtilis* DAUFPE 10*, Salmonella enteretidis* DAUFPE 415*, Escherichia coli* DAUFPE 84*, Pseudomonas aeruginosa* DAUFPE 39*, Serratia marcescens* DAUFPE 398*,* and *Mycobacterium phlei* ATCC11758, were maintained on Mueller-Hinton agar (Cleeland; Grunberg, 1986), whilst *Candida albicans* DAUFPE 1007 and *C. krusei* DAUFPE 1002 were maintained on Sabourand agar. In order to produce an appropriate inoculum, an overnight culture (grown at 37 ^{o}C) of bacteria in Mueller-Hinton broth, or of yeast in Sabourand broth, was standardised to an opacity equivalent to 0.5 on the McFarland scale (10^8 CFU/mL). The resulting suspension was diluted to yield a cellular concentration of 10^6 UFC/mL, a sterile swab was dipped into the inoculum and streaked across the surface of the appropriate agar-solidified medium**.**

Paper disk diffusion bioassay (Bauer et al., 1966)

Dried ethanolic extracts of the plant parts (500 mg) were dissolved in 5 mL of ethanol: water (1:1), and 20 µl aliquots were applied to individual paper disks (6 mm diameter; Whatman N^{o} 1 for qualitative analysis). After evaporation of the loading solvent, each disk was placed at the centre of a Petri dish containing sterile Mueller-Hinton agar, previously inoculated with the microorganism, and incubated at 37 ^{o}C for 18 h (or 72 h for *Mycobacterium* and *Candida*). At the end of the incubation time, the diameter of the microbial growth inhibition halo was measured (mm) using a ruler with a sliding calliper.

Minimal inhibitory concentration (MIC) bioassay (Courvalin et al., 1985)

Dried ethanolic extracts of the plant parts (500 mg) were dissolved in 5 ml of ethanol: water (1:1). Ten-fold serial dilutions of each extract with ethanol: water were carried out to prepare a series of eight dilutions (each with a concentration exactly 10-fold larger than that required for the bioassay) for each extract. Petri dishes were prepared by mixing one part of each diluted extract with nine parts of Mueller-Hinton agar medium.

All dishes, including those containing ciprofloxacin (60 μg/mL) used as positive control, were inoculated with the test organism by streaking the medium with a calibrated loop (0.05 mL). After incubation at 37 °C for 18 h (or 72 h for *Mycobacterium*), Petri dishes were examined for the presence or absence of growth. The MIC value was considered to be the lowest concentration of sample able to totally inhibit microbial growth. Each assay was performed in duplicate, on separate days. The results shown in Table 2 are mean values of two independent determinations. Prior to the assays, it was verified that the loading solvent [ethanol: water (1:1)] was completely inactive against the test organisms under the assay conditions.

RESULTS AND DISCUSSION

In a preliminary determination of antimicrobial activity, 32 ethanolic extracts from various plant parts of 17 different species (Table 1) were evaluated. Only extracts from leaves and stems of *Lafoensia pacari* exhibited activity against the Gram-positive *Micrococcus flavus* and *Staphylococcus aureus,* and the Gram-negative *Proteus mirabilis***.** The leaf extract was also active against the acid-fast *Mycobacterium fortuitum*, *M. phlei* and *M. smegmatis* (Table 2). Whilst this latter extract produced large inhibition halos (15 – 17 mm) with *Micrococcus flavus*, *P. mirabilis* and the *Mycobacterium* spp., zones of inhibition were detected with only 8 of the 10 strains of *S. aureus* assayed, and these halos were smaller (10 – 12 mm) and strain dependent. The stem extract produced lower levels of growth inhibition against Gram-positive and Gram-negative bacteria than did the leaf extract.

The largest inhibition of growth of *Micrococcus flavus* (inhibition halo of 20 mm) was produced by the extract from the root bark of *P. polygalaeflorus.* Although the root wood extract from this species was much less active against *M. flavus* (halo: 8 mm), it showed some significant activity against the acid-fast bacilli *Mycobacterium phlei* and *M. smegmatis* (inhibition zones of 15 and 8 mm, respectively). The stem bark extract from *P. polygalaeflorus* was also active against *M. phlei* (Table 2)

None of the tested extracts showed observable activity against *B. cereus*, *B. subtilis, S. enteretidis, E. coli, P. aeruginosa* and *S. marcescens,* nor against the yeasts *C. albicans* and *C. krusei*. In general, the small number of extracts that exhibited antibiotic activity against the clinical isolates might be explained by a possible pre-existent resistant strains.

In the light of the significant activities determined for leaf and stem extracts of *L. pacari,* and for the root extract of *Pterodon polygalaeflorus,* determinations of minimal inhibitory concentrations (MIC) were carried out on these samples (Table 2).

The MIC values for the ethanolic extract from leaves of *L. pacari* were 250 μg/mL for *Proteus mirabilis,* within the range of 312.5 to 2500 μg/mL for various strains of *Staphylococcus aureus*, and within the range of 625 to 1250 μg/mL for the acid-fast bacilli. The ethanolic extract from the stem of *L. pacari* showed MIC values of 625 μg/mL for all strains of *S. aureus.* These values (Table 2) are comparable with those determined for many other ethanolic extracts of medicinal plants as *Entada abyssinica*, *Terminalia spinosa*, *Harrisonia abyssinica*, *Ximenia caffra*, *Azadirachta indica* and *Spilanthes mauritiana* that showed MIC values between 130 and 8000 μg/mL against bacteria (Fabry et al*.,* 1998), whilst values ranging 64 - 1000 μg/mL against bacteria, and 32 - 128 μg/mL against dermatophytes, were reported for *Alstonia macrophylla* (Chattopadhyay et al., 2001). A small number of plants show significantly lower MIC values, for example, those for *Erythrina senegalensis, Bobgunnia madagascariensis, Walteria lanceolata, Uapaca togoensis, Ximenia americana, Khaya senegalensis, Lannea acida, Cissus populnea* and *Keetia ispida* were in the range 23 - 94 μg/mL (Koné et al., 2004), and extracts of *Quercus infectoria* and *Punica granatum* were highly effective against *Escherichia coli* (O157:H7) with MIC values of 90 and 190 μg/mL, respectively (Voravuthikunchai et al., 2004).

The antibiotic activity observed for *L. pacari* could partly explain the popular use of this plant as an anti-inflammatory agent and in the treatment of gastric ulcer. Within the family Lytraceae, two other species have been verified to possess anti-inflammatory properties, namely, *Lawsonia inermis* and *Heimia salicifolia* containing, respectively, the naphthoquinone lawsone and the quinolizidine alkaloid cryogenine as the biologically active components (Kaplan et al., 1967; Watson; Malone, 1977; Ali et al., 1995).

The presence of ellagic acid, gallic acid and catechin in *Lafoensia pacari* has been previously reported (Solon et al., 2000) from the hydro alcoholic stem bark extract. Likewise, the present extract showed to contain tannins as well as steroids, phenols, flavonoids, triterpenes and saponins.

The results presented by *L. pacari* are highly favourable compared, by example, with the MIC values of 50 and 200 μg/mL, respectively, for the purified flavonoids 5,7,4'-trimethoxiflavone and 200 μg/mL to 5,7,3',4'-tetramethoxiflavone derived from *Kaempferia parviflora* (Yenjai et al., 2004).

The observed antibiotic activity against *S. aureus* (32-2000 μg/mL) of the leaf extract of *Alstonia macrophylla* has been attributed to the presence of ursolic acid together with other minor components (Chattopadhyay et al., 2001). The antibiotic activity of the condensed tannins, catechin and epicatechin has been previously demonstrated by Esquinazi et al. (2002). Fogliani at al. (2005) reported the antibiotic activity of the ellagitannins, whilst the activity of the terpenoids compounds is well known (Peres et al., 1997). The antibiotic activity of extracts of *L. pacari* could

Table 1. Plant materials submitted to the antimicrobial activity assay based on their ethnobotanical uses

FAMILY / Species and voucher reference	City-state of collection and date of harvest	Plant part assayed	Ethnobotanical use	Reference
ANACARDIACEAE *Schinus terebinthifolius* Raddi. JEP 3643 (UB)	Murici – AL, 12/2001	Stem bark	Febrifuge; depurative; anti-rheumatic and anti-ulcer	Braga, 1953; Corrêa; Penna, 1984, Balbach, 1963; Balbach, 1966, Pereira et al., 2005
ANNONACEAE *Annona crassiflora* Mart JEP 3369 (UB)	Brasilia – DF 08/1999	Leaves, stem bark and stem	Anti-diarrhoeal	Braga, 1953; Corrêa; Penna, 1984, Martins, 1989; Dos Santos; Sant'Ana, 2001
Annona muricata L. 8530 – IMA – AL	Maceió - AL. 08/2000	Leaves, stem and roots	Anti-parasitic; emetic; anti-rheumatic; astringent; anti-diarrhoeal	Braga, 1953; Corrêa; Penna, 1984; Gemtchújnicov, 1976
ARALIACEAE *Didymopanax morototoni* (Aubl.) Decne & Planchon.JEP 3634 (UB)	Murici – AL, 07/2000	Stem	Used to treat pain	Corrêa; Penna, 1984
ASTERACEAE *Senecio jurgensenii* Hemls. JEP 3564 (UB)	Eldorado do Sul – RS, 9/1999	Leaves and flowers	In the treatment of malaria, fever and wound healing	Milliken, 1997
CELASTRACEAE *Austroplenckia populnea* (Reissek) Lundell. JEP 3747 (UB)	Planaltina - GO, 01/2001	Stem, roots bark and roots	Anti-tumour; anti-microbial	Corrêa; Penna, 1984
CLUSIACEAE *Rheedia brasiliensis* (Mart.)Planch & Triana. JEP 1793 (UB)	March. Deodoro – AL 08/1999	Stem	Tonic; anti-ulcer; used for wound healing and in the preparation of leather	Corrêa; Penna, 1984
FABACEAE *Erythrina mulungu* Mart ex. Benth JEP 3605 (UB)	S. J. da Tapera – AL, 08/2000	Stem	Tranquilizer; in the treatment of bronchitis, inflammations and (locally) lupus	Corrêa; Penna, 1984; Delorme; Miolla, 1979
Pterodon polygalaeflorus Benth. JEP 3410 (UB)	Brasilia – DF, 08/2000	Leaves, stem bark, root bark, root wood and seeds	Anti-rheumatic; in the treatment of throat infections	Corrêa; Penna, 1984; Nunan, 1985
LYTHRACEAE *Lafoensia pacari* A. St. Hil. JEP 3535 (UB)	Brasilia – DF, 01/1999	Leaves, stem bark and stem	Febrifuge; anti-tumour; tonic; in the treatment of gastric ulcer and inflammations	Corrêa; Penna, 1984, Ali et al., 1995; Lima; Martins, 1996; Sartori; Martins 1996; Albuquerque et al., 1996
SAPINDACEAE *Cupania oblongiflora* Mart. JED 3538 (UB)	Matriz de Camaragibe – AL, 11/1999	Leaves and stem	In the treatment of coughs and whooping cough	Corrêa; Penna, 1984
Serjana lethalis A. St. Hil. JEP 3698 (UB)	Brasília - DF, 09/2002	Leaves and stem	Narcotic	Corrêa; Penna, 1984
SIMAROUBACEAE *Simarouba amara* Aubl. JEP 3640 (UB)	Itabaiana – SE, 09/2001	Stem	Febrifuge; anti-diarrhoeal	Corrêa; Penna, 1984
STERCULIACEAE *Guazuma ulmifolia* var. *tomentosa* (Kunth) K. Schum. JEP 3644 (UB)	NS Socorro – SE, 09/2001	Stem bark	Astringent; depurative; in the treatment of syphilis and skin disease	Braga, 1953 Corrêa; Penna, 1984; Balbach,1963; Balbach,1966; Milliken, 1997; Vieira 1992
ZINGIBERACEAE *Costus spiralis* (Jacq.) Roscoe.	Maceió – AL, 03/2003	Leaves	Anti-tumour; diuretic; anti-syphilitic; tranquilizer; in the treatment of renal stones	Corrêa; Penna, 1984, Balbach,1963; Balbach,1966
Renealmia exaltata L. F.	Brasilia – DF, 07/1994	Leaves	Anthelmintic; tonic; in the treatment of stomach ache	Corrêa; Penna, 1984, Balbach,1963; Balbach,1966

Table 2. Antimicrobial activity and minimum inhibitory concentrations (MIC)[a] of plant extracts against the tested microorganisms

Species	Plant part assayed	Gram-positive microorganisms									Gram-negative Microorganism	Acid fast bacilli (*Mycobacterium*)		
		Micrococcus flavus DAUFPE 323	Strains of *Staphylococcus aureus*								*Proteus mirabilis* CI 03	*M. fortuitum* M5	*M. phlei* ATCC 11758	*M. smegmatis* M11
			CI 133	CI 138	CI 139	CI 149	CI 155	CI 311	CI 401	CI 403				
Lafoensia pacari	Leaves	17 (nd)	10 (625)	12 (625)	11 (625)	10 (312.5)	11 (2500)	11 (312.5)	11 (625)	11 (625)	15 (250)	15 (1250)	17 (625)	16 (1250)
	Stem bark	9 (nd)	na	na	na	na	na	na	na	na	na	na	na	na
	Stem	8 (nd)	7 (625)	10 (625)	11 (625)	9 (625)	12 (nd)	9 (625)	11 (625)	10 (625)	10 (nd)	na	na	na
Pterodon polygalaeflorus	Stem bark	na	na	na	na	na	na	na	na	na	na	na	8 (nd)	na
	Root bark	20 (nd)	na	na	na	na	na	na	na	na	na	na	na	na
	Root wood	8 (nd)	na	na	na	na	na	na	na	na	na	na	15 (nd)	8 (nd)
Ciprofloxacin (reference antibiotic)		30	17 (0.625)	19 (0.625)	18 (0.625)	19 (0.625)	19 (nd)	14 (0.625)	20 (0.625)	24 (0.625)	33 (0.25)	32 (1.25)	34 (0.625)	32 (1.25)

[a] MIC = The values indicate the halos of inhibition (mm) in the paper disk diffusion bioassay and the MIC (μg/mL) (in parenthesis).

be explained by the presence of tannins (Solon et al., 2000), flavonoids and terpenoids as has been found for *P. polygalaeflorus* (Fascio et al., 1976; Dos Santos et al., 1972; Mahajan; Monteiro, 1973; Campos et. al., 1994).

The present work has shown that *L. pacari* is a potential source of antibiotic agents and its activity against various strains of *Staphylococcus aureus* might be considered sufficient to perform further studies for isolation and identification of the active principles

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