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Amazonian plant crude extract screening for activity against multidrug-resistant bacteria

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Abstract. – Antimicrobial resistance is a subject of great concern in public health and also in the designing of strategies for current therapeutic protocols all over the world. New drugs, including those necessary for a reserve armamentarium and exhibiting less side effects deserve special attention. In rural areas, particularly in Brazil, a huge number of natural products, in different artisanal preparations, mainly from plants, have been used by traditional populations to cure diseases. Despite some of these plants have been studied, many of them are awaiting to have their compounds chemically characterized and investigated their pharmacodynamics properties. Further, as well known, the environment plays a crucial role in the metabolism of these plants, yielding different and varied molecular complexes depending on the period of collection, climate conditions, kind of soil and also the plant speciation.

In this report, ethanol crude extract of 10 different botanical specimens from the Amazon region of Brazil, in the Amapa State, were screened for antibacterial activity of 7 clinical resistant microorganisms utilizing as control ATCC bacterial species by the Kirby-Bauer method. Plant extracts of *Geissospermum argenteum*, *Uncaria guianensis*, *Brosimum acutifolium*, *Copaifera reticulate*, *Licania macrophylla*, *Ptycopetalum olacoides* and *Dalbergia subcymosa* yielded activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both multidrug resistant, and *Staphylococcus aureus* ATCC strain.

Key Words:

Plant crude extract, Biological activity, Antimicrobial, Amapa State, Amazon rain forest.

Introduction

The species *Calophyllum brasiliense* (*Clusiaceae/Guttiferae*) also known in the tupi language as "jacareúba", is popularly employed in the treatment of different clinical conditions. The micromolecular composition analysis of extracts from different parts of this plant revealed the presence of fatty acids, xanthones, cumarins, flavonoids and triterpens[1-7] exhibiting activity against fungus and gram positive bacteria[8], including *Bacillus cereus, Bacillus subtilis, Staphylococcus epidermidis* and *Staphylococcus aureus*[7-10]. Isolated compounds, mainly cumarins, exerted antiviral[3,11] and significative molluscicide activity against *Biomphalaria glabrata*[5]. Three xanthones, jacareubin, 6-deoxyjacareubin, and 1,3,5,6-tetrahydroxy-2-(3-methyl-2-butenyl) xanthone showed trypanocidal activity[12]. The coumarin-type mammea purified from a dichloromethane crude extract of leaves of *Calophyllum brasiliense* potently inhibited the growth of *Leishmania amazonensis* and caused important changes in the parasite's ultrastructure[13]. The natural product GUT-70, characterized as a tricyclic coumarin, 5-methoxy-2,2-dimethyl-6-(2-methyl-1-oxo-2-butenyl)-10-propyl-2H,8H-benzo[1,2-b;3,4-b]dipyran-8-one (C23H26O5), isolated from the stem bark of *Calophyllum brasiliense*, significantly inhibited the growth of leukemic cells[14].

There are few studies related to *Geissospermum argenteum* (*Apocynaceae*), also known in northern Brazil as "quinarana da fruta pequena",

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which is mainly used as antimalarial remedy altogether with other Geissospermum genera likewise *Geissospermum sericeum* and *Geissospermum leave* by traditional communities in the Amazon region of Brazil and Andes, being able to impair the intrahepatic cycle of *Plasmodium falciparum*[15]. The indole alkaloid geissoschizoline and two new derivatives, geissoschizoline N-oxide and 1,2-dehydrogeissoschizoline, were obtained from the bark of *Geissospermum sericeum* together with the beta-carboline alkaloid flavopereirine. In spite of antimalarial activity, antitumoral and antioxidant activities have also been reported[16].

The *Uncaria guianensis* (*Rubiaceae-Coptosapelteae*) also known in the amazon region as "unha-de-gato" or cat's claw and "jupindá", is commonly used as a popular anti-inflammatory remedy as already scientifically corroborated[17,18,21,22] and in some assays the plant is more potent than *Uncaria tomentosa*, which is considered the real cat's claw. Herrera et al[19]. observed the gastrointestinal anti-inflammatory effects of plant extracts. The aqueous extracts did not exhibit cytotoxic activity but showed antimutagenic and photomutagenic activity induced by 8-metoxypsoralen and UV radiation in *Salmonella spp*. The indole alkaloids obtained from these plant extracts presented immunostimulant and immunoregulatory activity[20-22]. They also yielded DNA repair action by reducing skin epithelial cell death, which points out to formulating potential sources of solar protectors[23]. In reference to *Uncaria guianensis* chemical composition, a variety of triterpenic glycosides, oxyndolic alkaloids and phenolic components were isolated[20,21,24-29].

The *Simaba cedron* (sinon. *Quassia cedron*), popularly known in northern Brazil as "pau-de-gafanhoto" and "pau-para-tudo" is employed as antimalarial medicine. It is rich in quasinoids[30-36], and some of them present cytotoxic activity[37,38]. Cedronin and cedrin, isolated from *Simaba cedron* seeds, exhibited antimalarial activity *in vivo* and *in vitro* against cloroquine resistant and susceptible strains[37-39]. Cedronin also presented cytotoxic activity in human cervical carcinoma KB cells[37]. In addition, other compounds obtained from the seeds yielded anti-inflammatory activity[40]. The methanolic extracts of *Simaba cedron* seeds exerted ovicidal and larvicide activity in species of the phytoparasite *Tuta absoluta*, which represents a potential natural insecticide[41].

Known by the Amazonian natives as "mururé" or "muirapuranga", the *Brosimum acutifolium* (*Moraceae*), is a timber species indigenously utilized as anti-inflammatory, anti-rheumatic[42] and anti-anemic natural medicine[43]. Its chemical composition is diversified, mainly presenting flavonoids and lignoids[44-50], as well an hallucinogen amine[50]. From the bark of this species some isolated flavones and flavolignanes compounds exhibited cytotoxic effects against a vincristin resistant P388 leukemic cell line[50] and antienzymatic activity for A and C proteinkinase respectively[49]. An identified flavonoid exerted dose-dependent activity on pheochromocytoma PC-12 cell line[50].

As a vernacular term "copaíba", the species *Copaifera reticulata* (*Caesalpinaceae*) is reported since the earliest period of Portuguese colonization of Brazil, as a medicinal oil, used as anti-inflammatory and for its cicatricial activity[52-55]. Maciel et al[53] emphasizes the use of copaiba oil in the popular medicine as stimulant, diuretic, laxative, cicatricial, expectorating, anti-tethanic, antihemorrhagic, antirheumatic, anti-inflammatory, anti-ulcerogenic activities and as antiseptic of woman urinary tract. Also, it is indigenously used in the treatment of bronchitis, syphilitic diseases, skin diseases, leishmaniasis, leukorrhea, psoriasis, diarrhea, urticaria and lung diseases[53]. The copaiba oil was evaluated for its anti-inflammatory and cicatricial effects in oophorectomized rats and yielded superior results when compared to control animals[56,57]. Also, it presented larvicidal activity against *Culex quinquefasciatus* in all larval stages[58]. Aqueous extracts obtained from bark of *Copaifera reticulata* exhibited high antioxidant and free radical neutralization activity, lately attributed to tannins[59-61].

The "anauera", an indigenous Amazonian denomination for *Licania macrophylla* (*Chrysobalanaceae*), besides its medicinal utilization by traditional populations in northern Brazil, it is also employed as timber for construction of houses and boats[62]. There are not reports related to the biological activity and chemical composition of this species, eventhough some other members of the family *Chrysobalanaceae* have been studied concerning their medicinal applications and chemical composition[63-65]. Among some amerindian communities in the Amapa, Brazil, "anauera" is employed to treat diseases commonly caused by protozoans as giardiasis and amebiasis (personal communication).

The *Ptycopetalum olacoides* (*Olacaceae*) named by the amerindians as "muirapuama" has

its root medicinally indicated for stimulant, energetic and aphrodisiac activity. Their roots have been exported for more than 100 years to Europe leading to the partial extinction of this plant[66-68]. Their prices usually reach twice of other medicinal plants[69]. It is the component of a commercial medicinal beverage, "catuama", which mixed to other herbs induce the relaxation of cavernosal smooth muscle of rabbits in a dose-dependent manner[70]. The vasorelaxation activity was also observed in isolated organs of other species, confirming the usefulness of the ethanolic preparation in cardiovascular diseases[71]. In clinical trials of healthy volunteers aiming to evaluate the effects of *Ptycopetalum olacoides*, the hematological and biochemical profile were not significantly altered as also there were not adverse actions on the subjects[72]. Also, the ethanolic extract exerted many effects on the central nervous system[73,74], including acethylcholinesterase inhibition, cognitive improvement and ansiolythic activity in rats compared to that observed with pentylenetetrazol and also, diminished mobility similarly to the effect of clonidine. The neuroprotector activity was assessed in the cells of rats' hypocampus deprived of oxygen and glucose, which showed more viability than in the controls. Besides these actions, antioxidant, antifree radicals activity and fungicide properties were observed in *Colletotrichum acutatum* and *Fusarium oxysporum*[75-82]. Triterpenic and steroidal compounds, flavonoids, methylxanthin and alkaloids were isolated from the plant. The α-pinene represents the principal component of the essential oil[83-89].

The *Dalbergia subcymosa* (*Fabaceae-Papilionoideae*), named by the amazonian indigenous population as "verônica da terra-firme", is popularly indicated for the treatment of anemia[90]. Its activity in the treatment of anemia was corroborated by Silva et al[91] detecting significant levels of soluble iron in a concentration of 4.15 p.p.m. In order to evaluate the safety use of *Dalbergia subcymosa* in pregnant women, Peters and Guerra[92] demonstrated in rats, the absence of embryofetotoxicity and no disturbance of postnatal development of the pups indicating that the beverage may be safe for human use as an anti-inflammatory medicine. There are not reports referring to the chemical composition of *Dalbergia subcymosa*.

The *Hymenaea coubaril* (*Fabaceae*), named by the amazonian indigenous people as "jatobá" and "jutai", is utilized by the timber industry besides its popular use as balsamic, fluidificant and expectorant, astringent, anti-diarrheial, anti mycotic, and anti-inflammatory. The essential oil is predominantly composed of α-pinene and limonene[93]. One of the most important compound of this species is the xyloglucan, isolated from many organs[94-106]. Also, diterpenoids[107-111], sesquiterpenoids[112], fatty acids and phenolic compounds[113,114], with special emphasis to proanthocyanidins[115] were detected in this plant.

The "jatobá" resin presented toxic effect and inhibitted appetite in *Spodoptera exígua*[116]. The hydroalcoholic extract prepared from the bark's plant exerted activity against *Staphylococcus aureus*[117] and *Bacillus cereus*[118]. Some diterpenes isolated from "jatobá" leaves exhibited marked fungicide activity[119]. The plant extracts also presented in vitro anti-plasmodium[120] and molluscicidal activity[121]. The plant pericarp presented anti-inflammatory activity, 5-lipooxigenase and tirokinase inhibitory action[122] and skin inhibitory pigmentation induced by UV radiation[123].

Materials and Methods

Botanical Material

From Amapa State, Brazil, barks and resin of 10 different plants, were collected. Voucher specimens were deposited at the herbarium of the Institute of Scientific and Technological Research of the Amapa State (IEPA), Brazil, under the protocols numbers 016603 for *Uncaria guianensis*, 016595 for *Copaifera reticulate*, 016602 for *Simaba cedron*, 016594 for *Licania macrophylla* and 016600 for *Dalbergia subcymosa*. The species *Calophyllum brasiliense*, *Geissospermum argenteum*, *Brosimum acutifolium*, *Ptycopetalum olacoides* and *Hymenaea coubaril* are provisionally kept under registration numbers BRM1, BRM2, BRM5, BRM8 and BRM10 respectively, at the Brazilian Agricultural Research Corporation, Amapá, Brazil (EMBRAPA).

Bacteria Strains

Standard American Type Culture Collection strains (ATCC) of *Proteus mirabilis* (ATCC 7022), *Klebsiella pneumoniae* (ATCC 27853), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Streptococcus pneumoniae* (ATCC 46619), and also the same species ob-

tained from hospital collection of multidrug resistant strains in Brasilia, Brazil, were utilized in the Kirby-Bauer assay[124].

Extraction Procedures

The dried ground barks of each plant and resin of *Copaifera reticulata* were weighed and soaked in ethanol and left for 7 days in maceration at room temperature and repeated 3 times after filtration. Solvent evaporation was performed in a rotary evaporator under reduced pressure and the resulting solute was completely dried in a water bath at 40ºC. The ethanol crude extracts were kept frozen until their use.

The embedded Disc Assay

Sterile filter discs (Hartman paper no. 1) measuring 6 mm in diameter were embedded in each ethanol crude extract in concentrations ranging from 80 µg to 1.25 µg and allowed to dry at room temperature. Frozen stocks of bacterial growth kept in glycerol were grown in semi solid nutrient agar and kept in incubator for 24 hs at 37°C. Typical and homogeneous colonies were transferred to liquid Mueller-Hinton medium to grow until reaching 2×10^8 cfu/mL (0.5 units in the McFarland scale). Inoculum at this density growth was spread out in Petri dishes containing Mueller-Hinton agar. Sequentially, previously embedded and dried discs in ethanol crude extracts were disposed on the agar surface. As controls, dried discs embedded in G sodic penicillin and ethanol were also displaced in the dishes. All essays were carried out in triplicate, including the controls. The dishes were kept in incubator at 37°C for 24 hours. The formation of halo inhibition ray of bacterial colony growth was measured and compared around the discs embedded in crude extracts and control disc containing G sodic penicillin. This essay is based on the Kirby-Bauer method[125].

The experiments were carried out in two steps. The extracts were initially in 80 µg concentration in the discs and those presenting inhibitory activity over bacterial growth were diluted to reach the minimal inhibitory concentration.

Results

Ethanol diluted crude plant extracts of *Geissospermum argenteum*, *Uncaria guianensis*, *Brosimum acutifolium*, *Copaifera reticulate*, *Licania macrophylla*, *Ptycopetalum olacoides* and *Dalbergia subcymosa* yielded activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both multidrug resistant, and *Staphylococcus aureus* ATCC strain (Tables I and II). The minimal inhibitory concentration ranged from 80.0 µg to 1.25 µg of crude extract in the filter disc, exhibiting the *Brosimum acutifolium* extract, the most strong activity against the multidrug resistant *Staphylococcus aureus*. Except for *Dalbergia subcymosa*, all the other plants extracts as in the assay for *Staphylococcus aureus* multidrug resistant, presented activity against *Staphylococcus aureus* ATCC strain, even at less low concentration, ranging from 80.0 µg to 1.25 µg. Against the multidrug resistant *Pseudomonas aeruginosa*, the ethanol crude extract of *Geissospermum argentum* was the solely one to show antibacterial activity, in a 80.0 microg concentration. In all essays, the positive control represented by discs embedded in G sodic penicillin yielded inhibitory halo measuring from 32 to 13 mm, depending on the microorganism being tested. Also, the negative control, immersed in ethanol and dried, did no exhibit any inhibitory effect on the bacterial growth.

Discussion

The initial concentration of 80.0 µg of plant crude extract in the discs is justified by the fact that the complex mixture of molecules should be in different amounts, therefore the highest the initial concentration most probably the detection of any biological activity. Sequentially, serial dilution of the initial concentration allowed us to determine the minimum inhibitory concentration exhibiting antimicrobial activity.

Eventhough standard known antibiotics embedded in the discs were used as control, we could not compare crude extract activity to the one displayed by the utilized antibiotics as it is not known which molecule or molecules exerted antibacterial activity either which mechanism is under way. Therefore, the antibiotic inhibitory activity assess the sensibility of microorganisms to the drugs rather than establishing any chemical and mechanism comparison between known antibiotics used in the assay and unknown crude extracts molecules.

Table I. The minimum inhibitory concentration of bacterial growth of ATCC strains exerted by plant crude extracts by the Kirby-Bauer assay.

Plant crude extract	ATCC bacterial strains						
	Proteus mirabilis	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Staphylococcus aureus*	*Enterococcus faecalis*	*Streptococcus pneumoniae*
Uncaria guianensis	No activity	No activity	No activity	No activity	**10.0 µg**	No activity	No activity
Copaifera reticulata	No activity	No activity	No activity	No activity	**5.0 µg**	No activity	No activity
Simaba cedron	No activity	No activity	No activity	No activity	No activity	No activity	No activity
Licania macrophylla	No activity	No activity	No activity	No activity	**20.0 µg**	No activity	No activity
Dalbergia subcymosa	No activity	No activity	No activity	No activity	No activity	No activity	No activity
Calophyllum. brasiliense	No activity	No activity	No activity	No activity	No activity	No activity	No activity
Geissospermum argenteum	No activity	No activity	**20.0 µg**	No activity	**80.0 µg**	No activity	No activity
Brosimum acutifolium	No activity	No activity	No activity	No activity	**5.0 µg**	No activity	No activity
Ptycopetalum olacoides	No activity	No activity	No activity	No activity	**40.0 µg**	No activity	No activity
Hymenaea coubaril	No activity	No activity	No activity	No activity	No activity	No activity	No activity.

Table II. The minimum inhibitory concentration of bacterial growth of multi-drug resistant strains exerted by plant crude extracts by the Kirby-Bauer assay.

Plant crude extract	Multi-Drug resistant bacterial strains						
	Proteus mirabilis	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Staphylococcus aureus*	*Enterococcus faecalis*	*Streptococcus pneumoniae*
Uncaria guianensis	No activity	No activity	No activity	No activity	**2.5 µg**	No activity	No activity
Copaifera reticulata	No activity	No activity	No activity	No activity	**2.5 µg**	No activity	No activity
Simaba cedron	No activity	No activity	No activity	No activity	No activity	No activity	No activity
Licania macrophylla	No activity	No activity	No activity	No activity	**40.0 µg**	No activity	No activity
Dalbergia subcymosa	No activity	No activity	No activity	No activity	**20.0 µg**	No activity	No activity
Calophyllum. brasiliense	No activity	No activity	No activity	No activity	No activity	No activity	No activity
Geissospermum argenteum	No activity	No activity	No activity	No activity	**5 µg**	No activity	No activity
Brosimum acutifolium	No activity	No activity	No activity	No activity	**≥ 1.25 µg**	No activity	No activity
Ptycopetalum olacoides	No activity	No activity	No activity	No activity	**40 µg**	No activity	No activity
Hymenaea coubaril	No activity	No activity	No activity	No activity	No activity	No activity	No activity

Preliminary screening for biological activity of plant crude extract is the first step in order to decide the priorities to carry out chemical and biological assays with promising botanical species. Development of new drugs, particularly microbicides are mandatory. The uncontrolled use of antimicrobials, mainly in poor and developing countries, spread out multidrug resistant microorganisms all over the world, mainly carried by human subjects and possibly by animal food products.

Despite estimating the existence of 125,000 plants in the Amazon rain forest, a minimum number of them, about 1,250 species have been in most of the cases, partially investigated[125]. In our research work, all of these plants are currently been utilized to cure a variety of illness by Amazonian communities and, all of them have been scientifically investigated, but variation in the chemical composition determined by geographical location, climate conditions and kind of soil besides other factors, justify the continued studies of these species. Also, corroboration studies are necessary to validate each other results, mainly considering the difficulty to obtain the plants in the forest, having samples in different periods of the year and in different geographical locations which determines soil and climate conditions, besides the fact that some of these plants have products under patent process or already patented in other countries than Brazil. Therefore, continuous research work on these plants are necessary to preserve the local natural resources and preventing the deposition of patents in other countries of their compounds, which do not help natives, and do not stimulate them to preserve and cultivate the useful plants in the Amazon rain forest[126-128]. Actually, new legislations in Brazil, impose restrictions to collect and study samples from the biota, in order to protect the native species in the country, therefore, all the samples and results we have been obtaining are precious and considering the accelerating devastation of the Amazon rain forest, in a few decades a lot of these botanical specimes will be lost[129].

There are some reports concerning antibacterial activity of *Copaifera reticulate*, likewise the recently published work by Santos et al[130], confirming our results. Our work is the first one to report antibacterial activiy of crude extracts of *Geissospermum argenteum, Uncaria guianensis, Brosimum acutifolium, Licania macrophylla, Ptycopetalum olacoides and Dalbergia subcymosa.*

The promising results presented here push us to initiate studies of chemical characterization of extracts exhibiting antibacterial activity and to understand the mechanisms involved in their biological activity. Also, we are presently carrying out in vitro screenings to assess antineoplastic and antiviral activity, mainly against retroviruses, involved in both neoplasia and immunodeficiency pathologies respectively. Our initial studies utilizing ethanol extracts will be extended to other solvents, presenting different polarity, allowing us to extract compounds in a wide spectrum of molecular composition.

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