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Charlie Basset, Véronique Eparvier, Laila Espindola

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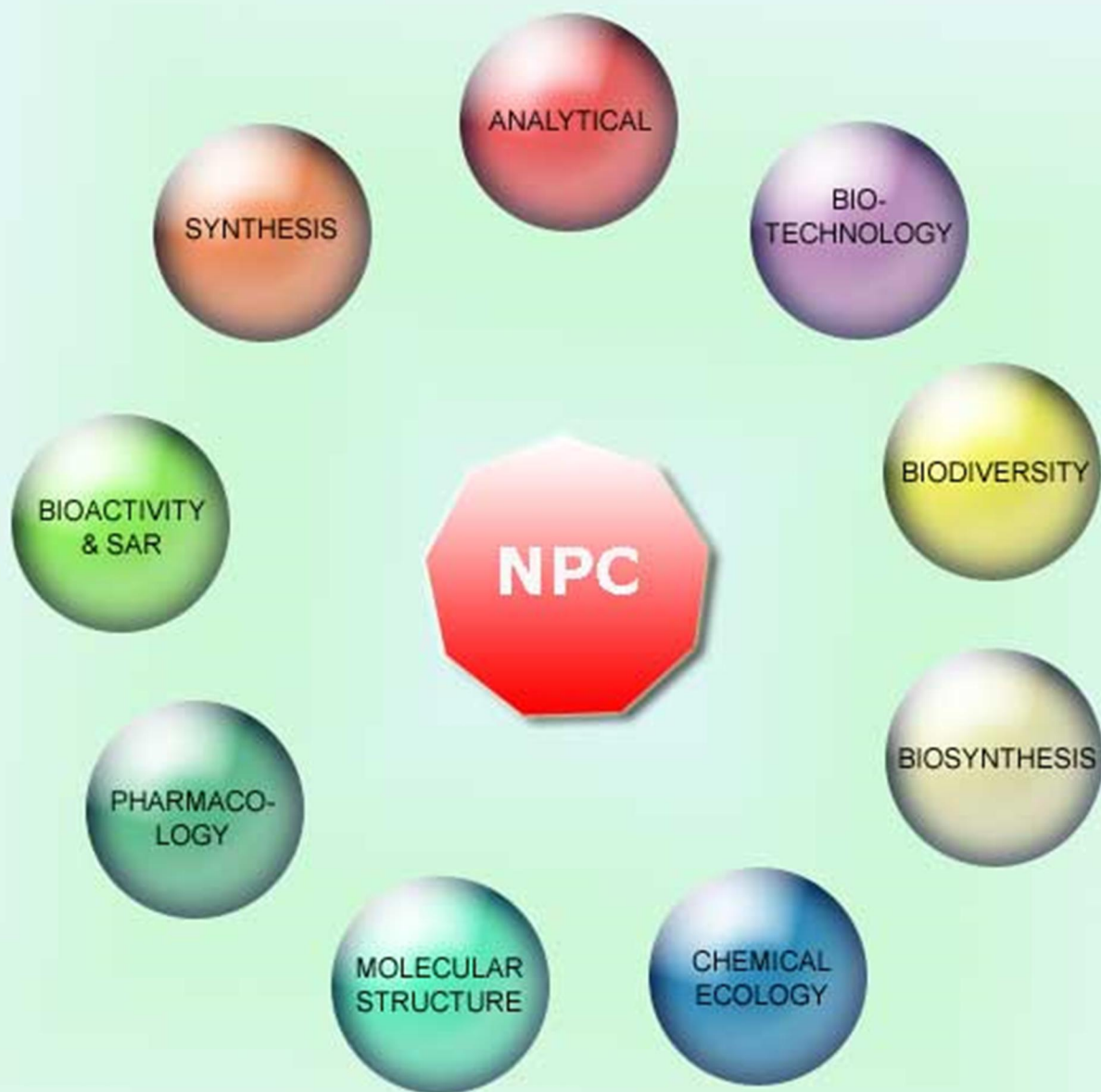
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The Search for Antifungals from Amazonian Trees: A Bio-Inspired Screening

Charlie Basset^{a,b*}, Véronique Eparvier^c and Laila S. Espindola^b

^aCNRS, UMR ECOFOG, Université des Antilles et de la Guyane, 97300 Cayenne, French Guiana, France

^bLaboratório de Farmacognosia, Universidade de Brasília, Brasília, Brazil

^cCNRS – Institut de Chimie des Substances Naturelles, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette cedex, France

basset.charlie@gmail.com

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The anti-fungal activity of 60 extracts from 15 tree species in the French Guiana rainforest against human and wood-rotting fungi was studied. In this way (+)-mopanol (**1**) was isolated from the ethyl acetate extract of *Peltogyne* sp. (Caesalpiniaceae) wood. This work demonstrated that (1) the natural durability of wood can indeed guide the search for antifungal agents, (2) that extracts selected in this bio-inspired process exhibit a broad spectrum of antifungal activity and (3) that the method allows for the isolation of strongly active antifungals.

Keywords: Bio-inspired screening, Antifungals, Natural wood durability, *Peltogyne* sp., (+)-Mopanol.

Fungal diseases are one of the most serious public health problems in the world, especially for immunocompromised patients, but the therapeutic arsenal for treating these infections appears to be limited [1]. However, natural products provide a wide variety of bioactive molecules [2] and many antifungal compounds have been isolated from plants [3, 4].

Previously [5] we proposed that the non-commercial waste from durable woods in French Guiana could provide an important source of extracts containing secondary metabolites which may be useful against human pathogenic fungi. Trees have acquired chemical defences against attackers such as lignivorous fungi [6], and those compounds may be similarly active towards plants or human pathogens [7, 8]. The present work evaluated the selection of Amazonian trees species based on natural wood durability data to facilitate the discovery of antifungal agents.

Sixty samples, 30 obtained from extraction with ethyl acetate and 30 with methanol, were produced from 15 Amazonian species. Natural durability of each species' wood was established on the basis of studies in the literature as (1) very durable, (2) durable, (3) moderately durable, and (4) weakly durable [9]. All extracts were tested against *T. rubrum* LMGO 4218 and *C. albicans* ATCC 10231. Extracts with MIC \leq 256 $\mu\text{g}/\text{mL}$ were considered active.

Of the 28 extracts (46.7%) that showed antifungal activity against at least one of the strains tested, extracts from the woody parts (wood, roots and adventitious roots) presented a greater percentage of activity (56.3%; 18 out of 32) compared with those from the bark (35.7%; 10 out of 28). Figure 1 presents the relative proportion of extracts for each MIC value according to wood class durability. In this selection, the natural durability of the wood affects the probabilities of obtaining more active compounds in plant extracts. Hence, 56% of the extracts produced from class 1 species are active (MIC \leq 256 $\mu\text{g}/\text{mL}$); 40%, from class 2; 38%, from class 3; and 0%, from class 4. A Pearson's chi-square test at the risk threshold $\alpha = 0.01$ confirmed the chance of obtaining an active extract is influenced by the durability classes of the species.

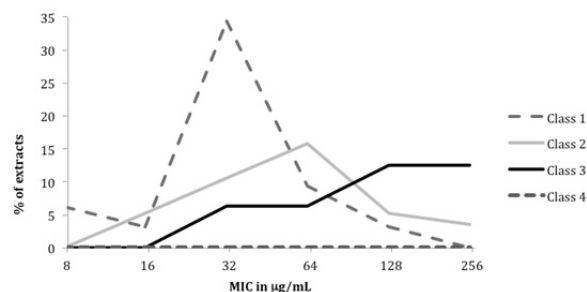


Figure 1: Distribution of antifungal activities according to the wood class durability.

Ten extracts with MIC value \leq 64 $\mu\text{g}/\text{mL}$ against *T. rubrum* LMGO 4218 and/or *C. albicans* ATCC 10231 were then evaluated against three clinical isolates of dermatophytes (*Microsporum gypseum* LMGO 533, *Microsporum canis* LMGO 02, and *Trichophyton mentagrophytes* LMGO 09), four yeasts (*Candida parapsilosis* ATCC 22019, *Candida glabrata* LMGO 44, *Candida krusei* LMGO 174, and *Cryptococcus neoformans* LMGO 02) and two wood-rotting fungi (*Pycnoporus sanguineus* L. (Murrill) 270 (CTFT) and *Coriolus versicolor* (L.ex Fr) Quélet CTB 863). The MIC ($\mu\text{g}/\text{mL}$) values obtained are reported in table 1.

We conducted a non-parametric Kruskal-Wallis test with a risk threshold $\alpha = 0.01$ to compare the MIC median values of the extracts against all dermatophytes, yeasts and wood-rotting fungi used in the assay. The results showed no significant difference between the three categories of fungi ($p > 0.05$). This analysis demonstrated the tested fungi exhibited equivalent sensitivity to the extracts. As a conclusion, our plant extracts have a broad spectrum of antifungal activity.

Several extracts showed antifungal activities, such as the *Humiria balsamifera* wood methanolic extract and the *Spirotropis longifolia* adventitious roots ethyl acetate extract. Further fractionation of the former is under study while results of the latter are published [4]. This paper focusses on the *Peltogyne* sp. wood ethyl acetate extract.

Table 1: Antifungal activities of plant extracts against human and plant pathogen fungi (MIC, in µg/mL).

Scientific Name	Plant part	Extraction solvent	Dermatophytes			Yeasts				Lignivorous	
			<i>M. g.</i> LMGO 533 ^a	<i>M. c.</i> LMGO 02	<i>T. m.</i> LMGO 09	<i>C. p.</i> ATCC 22019	<i>C. g.</i> LMGO 44	<i>C. k.</i> LMGO 174	<i>C. n.</i> LMGO 02	<i>Pycnoporus sanguineus</i>	<i>Trametes versicolor</i>
<i>Humiria balsamifera</i>	wood	MeOH	32	128	256	4	32	8	32	32	16
	wood	AcOEt	32	> 256	128	8	64	16	32	32	64
<i>Licaria guianensis</i>	wood	MeOH	32	16	32	8	64	8	64	64	8
<i>Manilkara huberi</i>	wood	MeOH	128	> 256	> 256	> 256	> 256	256	> 256	128	32
<i>Peltogyne</i> sp.	wood	AcOEt	> 256	64	128	128	8	64	64	128	64
<i>Spirotropis longifolia</i>	wood	MeOH	64	64	256	> 256	> 256	8	> 256	32	64
	roots	AcOEt	128	256	> 256	256	> 256	8	> 256	256	32
	adventitious roots	MeOH	256	> 256	> 256	> 256	> 256	64	> 256	> 256	32
	adventitious roots	AcOEt	32	64	64	64	128	8	64	8	32
<i>Zygia racemosa</i>	wood	MeOH	64	> 256	64	> 256	64	64	64	64	32
Itraconazole			0.5	4	0.	0.25	1	2	1	1	0.5

^a *M. g.*: *Microsporum gypseum*, *M. c.*: *Microsporum canis*, *T. m.*: *Trichophyton mentagrophytes*, *C. p.*: *Candida parapsilosis*, *C. g.*: *Candida glabrata*, *C. k.*: *Candida krusei*, *C. n.*: *Cryptococcus neoformans*.

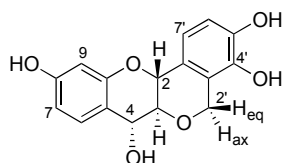
Bioguided fractionation of the *Peltogyne* sp. wood ethyl acetate extract gave (+)-mopanol (**1**, figure 2), which was tested against 14 strains of human pathogenic fungi (six dermatophytes and eight yeasts) and a human MRC5 cell line. Antifungal positive controls and mopanol exhibited IC₅₀ values greater than 128 µg/mL, while Docetaxel showed an IC₅₀ less than 0.25 µg/mL on MRC5 cells. Except for one strain, mopanol showed strong activity against *Candida* species with MIC values ranging from 0.5 to 4 µg/mL, and excellent antifungal selectivity compared with cytotoxicity on MRC5 cells (Selectivity index ranging from > 32 to > 256) (Table 2).

Table 2: Antifungal and cytotoxic activities of mopanol (MIC and IC₅₀, in µg/mL).

Strain	(1)	Fluconazole	Itraconazole	Selectivity index ^b
<i>M. c.</i> LMGO 25 ^a	32	2	0.5	> 4
<i>M. c.</i> LMGO 22	64	> 64	> 16	> 2
<i>M. g.</i> LMGO 10	64	16	0.25	> 2
<i>T. r.</i> LMGO 08	> 64	> 64	> 16	> 2
<i>T. r.</i> LMGO 06	16	2	0.25	> 8
<i>T. m.</i> LMGO 09	64	> 64	32	> 2
<i>C. a.</i> LMGO 102	0.5	> 64	> 16	> 256
<i>C. a.</i> ATCC 10231	2	4	0.5	> 64
<i>C. p.</i> ATCC 22019	1	4	0.5	> 128
<i>C. p.</i> LMGO 05	1	4	0.5	> 128
<i>C. g.</i> LMGO 44	32	8	0.5	> 4
<i>C. t.</i> LMGO 35	4	1	0.25	> 32
<i>C. k.</i> LMGO 174	1	> 64	16	> 128
<i>C. gattii</i> LMGO L1	> 64	2	0.25	> 2

^a *M. g.*: *Microsporum gypseum*, *M. c.*: *Microsporum canis*, *T. r.*: *Trichophyton rubrum*, *T. m.*: *Trichophyton mentagrophytes*, *C. a.*: *Candida albicans*, *C. p.*: *Candida parapsilosis*, *C. g.*: *Candida glabrata*, *C. t.*: *Candida tropicalis*, *C. k.*: *Candida krusei*, *C. gattii.*: *Cryptococcus gattii*.

^b Calculated on MRC5 cells (IC₅₀/MIC)



1

Figure 2: Structure of (+)-mopanol, isolated from *Peltogyne* sp.

Mopanol is a common secondary metabolite of the genus *Peltogyne* [10] but, to the best of our knowledge, no antifungal or cytotoxic properties have been described previously from this genus.

It is clear from this study that among tree species in French Guiana, the probability of detecting antifungal activity is higher when the species is highly durable.

The extracts from this study have a broad spectrum of action, as they are widely active on dermatophytes, yeasts and lignivorous fungi ($p > 0.05$). Therefore, it is efficient to look for new antifungals by (i) selecting species that produce durable wood and (ii) evaluating the antifungal activities of the extracts on a small number of fungal strains. Bio-inspired screening has allowed us to select *Peltogyne* sp. for further investigation, and the wood of this species could be highly durable due to the antifungal agent (+)-mopanol (**1**). This active compound presents very good antifungal selectivity towards *C. albicans* and other *Candida* spp., especially, against *C. krusei* - one of the species responsible for antifungal resistance [11] (MIC fluconazole > 64 µg/mL; MIC itraconazole = 16 µg/mL; MIC mopanol = 1 µg/mL). Mopanol also can be considered a lead compound for antimycotic agents development.

Experimental

General experimental procedures: Filtrations were carried out on polyamide columns (Chromabond® 6 mL). The optical rotations were measured on an Anton Paar MCP 300 polarimeter. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian 400MR spectrometer equipped with a 5 mm Auto X PGF ¹H/¹⁵N-³¹P inverse detection probe. NMR spectra were recorded at 400 MHz for ¹H and at 100.6 MHz for ¹³C. HR-ESI-MS measurements were carried out on a quadrupole-time-of-flight instrument (UltratOF-Q, BrukerDaltonics, Billerica, MA). Analytical HPLC was performed on a Supelco Discovery® C₁₈ column (150 × 4.6 mm, 5 µm) using a Waters system equipped with a W600 pump, a W2996 photodiode array absorbance detector, and a W2420 evaporative light scattering detector. The flow rate was set to 1 mL/min using a linear gradient of water mixed with an increasing proportion of acetonitrile. Separations were performed on a Supelco Discovery® C₁₈ column (150 × 21.2 mm, 5 µm) using a Waters system equipped with a W600 pump and a W2487 dual wavelength UV detector. The samples were injected manually through a Rheodyne injector at a flow rate of 15 mL/min, and the effluents were monitored at 214 and 254 nm.

Microorganisms, cells and culture media: The species of human pathogenic microorganisms used in this study were the dermatophytes *Trichophyton rubrum* (*T. r.* LMGO 06 and *T. r.* LMGO 08), *Microsporum gypseum* (*M. g.* LMGO 10 and *M. g.* LMGO 533), *Microsporum canis* (*M. c.* LMGO 22 and *M. c.* LMGO 25), and *Trichophyton mentagrophytes* (*T. m.* LMGO 09), and the yeasts used were *Candida albicans* (*C. a.* ATCC 10231 and *C. a.* LMGO 102), *Candida parapsilosis* (*C. p.* ATCC 22019 and *C. p.* LMGO 05), *Candida glabrata* (*C. g.* LMGO 44), *Candida tropicalis* (*C. t.* LMGO 35), *Candida krusei* (*C. k.* LMGO 174), *Cryptococcus gattii* (*C. g.* LMGO L1), and *Cryptococcus neoformans* (*C. n.* LMGO

02). LMGO (Laboratório de Micologia de Goiás) strains are clinical isolates from patients at the Federal University of Goiás Hospital, Brazil. Strains were maintained on potato dextrose agar. The lignivorous fungi used were *Pycnoporus sanguineus* L. (Murrill) 270 (CTFT) and *Trametes versicolor* (L.ex Fr) Quélet CTB 863, provided by the UR 40 CIRAD, Tropical Wood team, Montpellier, France. All strains were cultured onto an appropriate new agar plate at 28 °C for 2 days (yeasts) or 5 days (filamentous and lignivorous fungi) prior to any antimicrobial test. The strain used in the cytotoxicity assays was MRC5 normal lung tissue cells, which were provided by the *Cibliothèque Cellulaire* of ICSN, Gif-sur-Yvette, France.

Plant material: Plant material (wood, roots, adventitious roots, stem and bark) of 15 durable species belonging to 10 families was collected at the *Piste de Saint-Elie*, Sinnamary, and in Regina, French Guiana. V. Eparvier and M.F. Prevost (IRD) carried out botanical identifications. The voucher specimens were deposited in the Herbarium of French Guiana (CAY). Dates of collection, voucher numbers, uses and durability class of each species are available in the supporting information (Table 1S, supplementary data).

Extraction: Plant material was dried at room temperature and ground into powder. From each sample, 200 g was extracted three times at room temperature for 48 h with ethyl acetate (3 × 500 mL) and then twice for 48 h with methanol (2 × 500 mL). AcOEt and MeOH solvents were distilled before use. The extracting solution were recovered by filtration, concentrated to dryness under reduced pressure at a temperature below 30 °C and stored at - 20 °C.

Antifungal evaluation: The standard microdilution test as described by the Clinical and Laboratory Standards Institute guidelines (M27-A3 and M38-A2) was used to determine minimal inhibition concentrations (MIC) against dermatophyte fungi and yeast [12]. The protocol for dermatophyte fungi was used for lignivorous ones. Crude extracts and pure compounds were tested at concentrations ranging from 512 to 1 µg/mL and from 256 to 0.5 µg/mL, respectively. Fluconazole and itraconazole were used as positive controls and were tested at concentrations between 64 and 0.125 µg/mL and between 16 and 0.031 µg/mL, respectively. The microplates were incubated at 32 °C, and results were observed after 5 days for filamentous and lignivorous fungi and after 2 days for yeasts. The MIC values (table 2S, supplementary data) refer to

the lowest concentration preventing visible growth in the wells. All assays were conducted in duplicate.

Cytotoxicity evaluation on mammalian cells: The cytotoxicity towards MRC5 cells was monitored at the *Laboratoire de Cultures Cellulaires*, ICSN, Gif-sur-Yvette, France [13]. (+)-Mopanol (1) was tested against MRC5 cells at concentrations between 128 and 0.25 µg/mL, and cell growth was tested after 24 h incubation, allowing us to calculate the IC₅₀ and evaluate the antifungal selectivity (IC₅₀/MIC). Docetaxel (Sigma) was used as a positive control and tested at concentrations between 128 and 0.25 µg/mL against MRC5 cells.

Bioguided isolation of (+)-mopanol (1) from *Peltogyne* sp.: The ethyl acetate of extract *Peltogyne* sp. wood (700 mg) was filtered through a polyamide column and eluted with 2x5 mL of methanol. After evaporation, 376 mg were obtained from the first elution and 100 mg from the second. The 376 mg were fractionated by semi-preparative HPLC (gradient water/acetonitrile), and 15 fractions (F₁-F₁₅) were obtained. F₁₄ showed good antifungal activities and allowed the isolation of compound 1 (10 mg, 0.0005%). NMR and optical data for this compound are in agreement with previously published data [14, 15].

Statistical analyses: The influence of durability class on antifungal activities of extracts was analyzed by the Pearson's chi-square test. The homogeneity of the MIC values obtained for the 3 classes of fungi (dermatophytes, yeasts and lignivorous ones) was analyzed by the Kruskal-Wallis nonparametric test. MIC values were classified according to R₁ = 4 µg/mL, R₂ = 8 µg/mL, R₃ = 16 µg/mL, R₄ = 32 µg/mL, R₅ = 64 µg/mL, R₆ = 128 µg/mL, R₇ = 256 µg/mL and R₈ ≥ 512 µg/mL. For both tests, p < 0.01 was considered significant (Statistical Package for the Social Sciences SPSS-16).

Supplementary data: Information on the 15 plants studied (family, date of collection, voucher number and durability class, table S1) and the antifungal activity of extracts (MIC in µg/mL, table S2) can be obtained in the supplementary data section. Chemical data of compound (1) are also available in the supplementary data section.

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