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Antileishmanial activity of selected South African plant species

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ABSTRACT

In vitro screening of forty extracts prepared from selected South African plant species was conducted against *Leishmania donovani* (MHOM-ET-67/L82). Crude plant extracts were also subjected to an antiproliferative bioassay in an attempt to determine their potential lethality or safe therapeutic application against rat skeletal myoblast L6 cells. Of all the tested plant species, only 10% exhibited significant leishmanicidal activity with acceptable SI values (SI ≥ 10). The current study is the first scientific account on the significant antileishmanial activity (IC_{50} ≤ 5 μg/ml) of *Bridelia mollis* (Phyllanthaceae), *Vangueria infausta* subsp. *infausta* (Rubiaceae), *Syzygium cordatum* (Myrtaceae) and *Xylopia parviflora* (Annonaceae). Further phytochemical investigations are currently underway in an attempt to isolate and identify the chemical constituents that may be attributable to the leishmanicidal efficacy observed in the study.

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1. Introduction

Leishmaniasis is a major neglected tropical disease that causes a wide spectrum of chronic to deadly infectious parasitic illnesses in humans. The etiological agents responsible for its manifestation are protozoan species of the genus *Leishmania*, which are transmitted by female sandflies belonging to the genera *Phlebotomus* and *Lutzomyia* (Desjeux, 2004). Depending on the causative species and the immune response of the host, the infection can clinically manifest as cutaneous, mucocutaneous, diffuse and visceral leishmaniasis (Alvar et al., 2008). Visceral leishmaniasis which is caused by *L. donovani* is the most fatal form of the disease and intermittent epidemics of the disease have been linked to high morbidity as well as mortality in some East African countries (Antinori et al., 2012). Additionally, co-infection of leishmaniasis with HIV is further exacerbating the situation and the disease is currently expanding into the sub-Saharan Africa. Globally, there is an estimated 1.3 million new cases annually and over 20,000 deaths occur as a direct result of the disease (Desjeux, 2004).

The chemotherapy of leishmaniasis is strongly reliant on pentavalent antimonials, miltefosine, amphothericin B and paromomycin. However, increasing treatment failure rates, high cost and significant side effects are the major drawbacks compromising their effectiveness (Alvar et al., 2012). Novel antileishmanial drugs that could possibly lessen the burden of the disease in endemic countries are highly needed. Secondary plant metabolism has played a significant role in the discovery of novel chemotherapeutic agents against protozoal infections and could therefore yield novel and selective antileishmanial compounds (Singh et al., 2014). South African plant biodiversity has not been extensively explored for antileishmanial plant leads (Mokoka et al., 2014). Previously, we demonstrated that most of the non-polar extracts from indigenous plants used in the treatment of malaria present relatively significant antiplasmodial activity (Bapela et al., 2014). Given that malaria and leishmaniasis are both protozoal infections and share some unique metabolic pathways, the main objective of the current study was to screen nineteen antimalarial South African plant species against *L. donovani* parasitic strain.

2. Materials and methods

2.1. Plant material

Nineteen indigenous plant species were collected at various locations in Mutale Municipality, Limpopo Province, South Africa (Table 1). Voucher specimens of the harvested plant species were identified and deposited at the H.G.W.J. Schweickerdt Herbarium of the University of Pretoria.

2.2. Extraction of plant samples

For each collected plant sample, 20 g of ground plant material was extracted in DCM:50% methanol (1:1). The mixture was homogenized for 10 min using a blender, sonicated for 10 min in an ultrasonic waterbath (Labotec) and then filtered. The filtrate was transferred to a separating funnel and yielded two layers of different polarities, which were then separated. Residual plant material was collected and the extraction procedure was repeated. Methanol in the polar fractions was vaporized with a rotary evaporator at 40 °C and the resulting

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Table 1
Antileishmanial activity, cytotoxicity and selectivity indices of selected South African plant species.

Plant species and family	Voucher number	Plant part	Extraction solvent	*L. donovani*[a] (IC_{50} (μg/ml))	Cytotoxicity[b] (IC_{50} (μg/ml))	Selectivity[c] index
Albizia versicolor Welw. ex Oliv. (Fabaceae)	120,322	Roots	DCM	33.0	72.1	2
			50% MeOH	69.4	52.3	1
		Stem bark	DCM	56.3	55.1	1
			50% MeOH	42.3	42.0	1
Anthocleista grandiflora Gilg. (Loganiaceae)	120,323	Stem bark	DCM	12.1	55.6	5
			50% MeOH	45.7	70.1	2
Bridelia mollis Hutch. (Phyllanthaceae)	120,324	Roots	DCM	1.92	51.4	27
			50% MeOH	>100	49.6	ND
Capparis tomentosa Lam. (Capparidaceae)	120,325	Roots	DCM	12.1	40.8	3
			50% MeOH	67.7	70.4	1
Clematis brachiata Thunb. (Ranunculaceae)	120,326	Roots	DCM	10.5	42.6	4
			50% MeOH	55.3	72.3	1
Clerodendrum glabrum E. Mey. (Verbenaceae)	120,327	Leaves	DCM	13.4	62.2	5
			50% MeOH	55.6	72.7	1
Cussonia spicata Thunb. (Araliaceae)	120,328	Root bark	DCM	8.15	47.8	6
			50% MeOH	>100	69.1	ND
Dichrostachys cinerea Wight et Arn. (Fabaceae)	120,329	Roots	DCM	10.5	51.6	5
			50% MeOH	92.9	65.3	1
Diospyros mespiliformis Hochst. ex A.DC. (Ebenaceae)	120,330	Roots	DCM	7.70	24.3	3
			50% MeOH	54.0	60.4	1
Pappea capensis Eckl. & Zeyh. (Sapindaceae)	120,331	Twigs	DCM	8.36	54.0	6
			50% MeOH	76.8	55.2	1
Parinari curatellifolia Planch. Ex Benth. (Rosaceae)	120,332	Stem bark	DCM	13.6	57.6	4
			50% MeOH	>100	55.4	ND
Pyrenacantha grandiflora Baill. (Icacinaceae)	120,333	Roots	DCM	5.60	0.52	0.1
			50% MeOH	76.9	10.5	0.1
Rauvolfia caffra Sond. (Apocynaceae)	120,334	Stem bark	DCM	19.6	26.9	1
			50% MeOH	62.4	57.2	1
Senna petersiana (Bolle) Lock. (Fabaceae)	120,335	Leaves	DCM	15.7	59.3	4
			50% MeOH	72.9	66.8	1
Syzygium cordatum Hochst. (Myrtaceae)	120,336	Leaves	DCM	4.95	65.7	13
			50% MeOH	>100	53.8	ND
Tabernaemontana elegans Stapf. (Apocynaceae)	120,337	Stem bark	DCM	36.3	4.68	0.1
			50% MeOH	>100	38.2	ND
Vangueria infausta Burch. subsp. *infausta* (Rubiaceae)	120,338	Roots	DCM	4.51	45.7	10
			50% MeOH	>100	71.5	ND
Ximenia caffra Sond. (Olacaceae)	120,340	Leaves	DCM	1.79	8.68	5
			50% MeOH	42.6	74.1	2
Xylopia parviflora (A. Rich.) Benth. Oliv. (Annonaceae)	120,341	Roots	DCM	5.01	51.5	10
			50% MeOH	>100	69.1	ND
Miltefosine				0.191		
Podophyllotoxin					0.007	

Data shown represent mean values of two independent experiments run in duplicate.
[a] *Leishmania donovani* strain (MHOM-ET-67/L82).
[b] Rat skeletal myoblast L6 cell line.
[c] Selectivity Index (SI): IC_{50} for L6 cells/ IC_{50} for *L. donovani*.

aqueous extracts were freeze-dried using a bench top manifold freeze dryer (Virtis). Non-polar fractions were concentrated under vacuum at 30 °C and the acquired plant extracts were subjected *to in vitro* screening. Both root and stem extracts were analysed from one of the investigated plant species.

2.3. In vitro antileishmanial assay

The inhibitory effects of the forty crude plant extracts were evaluated against axenically grown amastigote forms of *Leishmania donovani* (MHOM-ET-67/L82) following the resazurin assay protocol (Adams et al., 2009). Each extract was dissolved in 10% DMSO to afford a stock solution with a concentration of 10 mg/ml. All tests were performed in 96-well microtiter plates, conducted in duplicates and repeated twice. Amastigotes were cultivated in Schneider's medium (SM) supplemented with 10% heat-inactivated FBS under an atmosphere of 5% CO_2 in air. Plates were incubated for 48 h and resazurin solution was then added to each well in order to assess the viability of *Leishmania* parasites. The absorbance was read on a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation) with an excitation and emission wavelength of 536 nm and 588 nm, respectively. The IC_{50} values were calculated by linear regression based on dose response curves. Miltefosine was used as positive control.

2.4. Cytotoxicity assay

The inhibition of mammalian cell growth was assessed *in vitro* by cultivating rat skeletal myoblast L6 cells in the presence of different extracts covering a concentration range (from 0.002 to 100 μg/ml) in 96 well culture plates (Ahmed et al., 1994). Podophyllotoxin was used as a positive control. Tests were conducted in duplicates and repeated twice. After 70 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. Alamar Blue (10 μl) was then added to each well and the plates were incubated for another 2 h. The plates were then read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. The IC_{50} values were calculated by linear regression from the sigmoidal dose inhibition curves using

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