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Antimalarial and anticancer activities of selected South African *Salvia* species and isolated compounds from *S. radula*

G.P.P. Kamatou [a], R.L. Van Zyl [a], H. Davids [a], F.R. Van Heerden [b], A.C.U. Lourens [b], A.M. Viljoen [c,*]

[a] *Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown, 2193, South Africa*
[b] *School of Chemistry, University of KwaZulu-Natal, Private Bag X01, Scottsville, 3209, South Africa*
[c] *Department of Pharmaceutical Sciences, Tshwane University of Technology, Private Bag X680, Pretoria, 0001, South Africa*

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Abstract

Extracts of seventeen *Salvia* species used in traditional medicine in South Africa were subjected to biological testing. The potential ability to inhibit the *in vitro* growth/proliferation of *Plasmodium falciparum* (FCR-3 strain) and the cytotoxic effects on three human cancer cells [breast adenocarcinoma (MCF-7), colon adenocarcinoma (HT-29) and glioblastoma (SF-268)] and a human kidney epithelial cell line were investigated. The extracts displayed antimalarial activity with IC_{50} values ranging from 3.91 to 26.01 μg/ml and *S. radula* displaying the most favorable activity. Two compounds were subsequently isolated from the active fraction of *S. radula* and identified as betulafolientriol oxide and salvigenin. The two compounds displayed similar or lower antimalarial activity (IC_{50} values: 4.95 and 24.60 μg/ml, respectively) compared to the crude solvent extract. The concentration required to inhibit 50% of cancer cells ranged between 9.69 μg/ml and 43.65 μg/ml, and between 8.72 μg/ml and 59.12 μg/ml against the MCF-7 and SF-268 cell lines, respectively. The IC_{50} values determined for the HT-29 cell line ranged from 17.05 to 57.00 μg/ml, with *S. lanceolata* being the most active. The samples also displayed some degree of toxicity when tested against the human kidney epithelial cells, with IC_{50} values ranging from 12.12 to 53.34 μg/ml. The *in vitro* antimalarial and anticancer activities support the historic and present use of *Salvia* species in traditional medicine.

Keywords: *Salvia*; Antimalarial activity; Anticancer activity; Toxicity; Betulafolientriol oxide; Salvigenin

1. Introduction

Many studies have been carried out on the antimalarial and anticancer activities of various plant species with some encouraging results (e.g. Schwikkard and Van Heerden, 2002; Boik, 2001). Two of the most potent antimalarial drugs originated from plants; quinine from *Cinchona* and artemisinin from *Artemisia annua* (Gessler et al., 1994). Plants have a reputable history of use in the treatment of cancer. In a review by Hartwell (1982), more than 3000 plant species are listed that have reportedly been used in the treatment of cancer, but in many instances, the "cancer" is undefined (Cragg and Newman, 2005). Over 60% of currently used anticancer agents are derived in one way or another from natural sources including plants, marine organisms and micro-organisms (e.g. paclitaxel, topotecan and irinotecan) (Cragg et al., 1997; Cragg and Newman, 2005).

In South Africa, reports on plants used for the treatment of cancer are rare, and can be ascribed to a complex set of signs and symptoms associated with the disease (Steenkamp and Gouws, 2006). With this in mind, it is recommended that when selecting plants for potential anticancer activity, ethnopharmacological properties such as immune, inflammatory and skin disorders should be considered (Cordell et al., 1991; Popoca et al., 1998).

Salvia species have been used in traditional medicines in China, South Africa and many other countries against various infectious and inflammatory diseases and to treat malaria, hard swellings, abscesses, calluses, warts or cancer (Watt and Breyer-Brandwijk, 1962; Ulubelen et al., 1999; Shoemaker et al., 2005). In our previous investigation, we demonstrated that the essential oils of indigenous *Salvia* species exhibited various

* Corresponding author. Tel.: +27 12 382 6360; fax: +27 12 382 6243.
E-mail address: viljoenam@tut.ac.za (A.M. Viljoen).

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biological properties such as anti-inflammatory, antimalarial and antibacterial activities (Kamatou et al., 2005, 2006). In a continuation to verify the efficacy of traditional medicines used in South Africa, the antimalarial and anticancer activities of the solvent extracts of seventeen *Salvia* species were investigated.

2. Materials and methods

2.1. Plant material

The aerial parts of 17 *Salvia* species were collected from various localities in South Africa between December 2003 and December 2004, predominantly from the Cape region (Table 1). The identity of each species was confirmed by the South African National Biodiversity Institute (Pretoria) and voucher specimens were deposited in the Department of Pharmaceutical Sciences, Tshwane University of Technology, Pretoria, South Africa. The air-dried plant material was ground to a fine powder, extracted with a mixture of methanol and chloroform (1:1, v/v) and the solvent evaporated under vacuum at 70 °C.

2.2. Preparation of samples

Stock solutions of the solvent extracts and reference compounds [5′-fluorouracil (Merck), chloroquine diphosphate (Sigma), quinine sulfate (Fluka)] were prepared in dimethyl sulfoxide (Saarchem) at a concentration of 10 mg/ml and stored at −20 °C. The dilutions were prepared with appropriate experimental medium on the day of the experiment.

2.3. In vitro maintenance of Plasmodium falciparum and the antimalarial assay

The chloroquine-resistant *P. falciparum* FCR-3 strain was continuously cultured according to the procedure described by Trager and Jensen (1976) with modifications as described by Van Zyl and Viljoen (2002). The antiplasmodial activity was assessed using the [^{3}H]-hypoxanthine method (Desjardins et al., 1979; Van Zyl and Viljoen, 2002) against a single cycle (48 h) of growth. Dilutions of the test samples were plated out in triplicate in a 96-well plate before parasitized red blood cells (0.5% parasitaemia and 1% haematocrit) were added and incubated for 24 h at 37 °C in a candle jar. The [^{3}H]-hypoxanthine (Amersham) was then added to the plate and incubated for a further 24 h. The amount of the [^{3}H]-hypoxanthine incorporated into the parasite DNA was determined with beta scintillation counting (Wallac®). The inhibitory concentration which killed 50% of parasites as indicated by the *in vitro* uptake of [^{3}H]-hypoxanthine (IC_{50} value) was calculated. Chloroquine diphosphate and quinine sulphate were used as reference antimalarial drugs.

2.4. In vitro cancer cell line maintenance and sulforhodamine B assay

Cells lines representing the most common human cancers (WHO, 2006) were obtained from the National Cancer Institute (NCI). These included the breast adenocarcinoma (MCF-7), the glioblastoma (SF-268) and the colon adenocarcinoma (HT-29).

Table 1
The IC_{50} values (mean±S.D., μg/ml) of antimalarial activity and cytotoxic effects of solvent extracts of indigenous *Salvia* species

Species	Location	Antimalarial activity (n=3)	Cytotoxic effects on various human cell lines (n=3)			
			HT-29	MCF-7	SF-268	Kidney cells
S. africana-caerulea	SWC[a]	22.68±2.80	27.10±1.08	23.36±4.20	8.72±1.52	14.38±3.39
S. africana-lutea	SWC[a]	15.86±5.04	20.00±3.41	43.65±8.38	nc	25.01±1.94
S. albicaulis	KBG[b]	15.83±1.94	25.33±1.11	35.25±5.66	27.50±0.89	37.29±0.58
S. aurita	KBG[b]	8.92±2.63	24.58±6.41	17.28±1.71	44.87±2.48	28.31±4.94
S. chamelaeagnea	KBG[b]	8.71±1.96	29.53±5.14	18.12±1.67	34.98±4.07	24.76±7.60
S. disermas	KBG[b]	24.17±4.10	26.87±0.57	38.56±1.28	59.12±2.75	53.34±3.90
S. dolomitica	Ex Manning	7.62±1.44	nc	37.05±2.10	nc	40.26±9.07
S. garipensis	KBG[b]	13.95±3.76	nc	39.44±3.90	nc	42.44±3.03
S. lanceolata	SWC[a]	26.01±2.95	17.05±3.50	26.15±2.15	nc	26.71±6.41
S. muirii	KBG[b]	11.87±2.13	55.63±1.30	39.07±2.86	nc	37.00±5.41
S. namaensis	Swartberg	25.38±2.11	24.39±3.42	36.36±3.07	nc	21.91±2.89
S. radula	Road to Derby	3.91±0.52	32.10±2.93	9.69±0.92	27.55±4.52	20.12±4.02
S. repens	KBG[b]	8.25±2.09	43.62±5.17	23.36±2.16	nc	23.24±4.72
S. runcinata	Klerkskraal Dam	16.61±3.33	55.37±2.10	43.42±5.46	nc	22.00±3.75
S. schlechteri	KBG[b]	17.51±2.05	57.00±11.67	18.37±0.47	54.40±4.42	28.16±4.69
S. stenophylla	East of Clarens	6.50±1.37	17.41±2.65	23.74±1.96	43.86±3.43	12.12±2.02
S. verbenaca	De Rust	23.97±1.10	50.04±5.39	31.50±13.70	nc	20.85±2.59
5′-FU		–	7.00±2.02	1.11±0.31	nc	>100
Chloroquine		0.06±0.01	–	–	–	>100
Quinine		0.14±0.03	–	–	–	>100
Betulafolientriol oxide	(1)	4.95±2.00[c]	–	–	–	>100
Salvigenin	(2)	24.60±1.38[c]	–	–	–	>100

nc: IC_{50} values not calculated because the percentage inhibition at 100 μg/ml was less than 80%. –: not determined.
[a] SWC: South Western Cape.
[b] KBG: Kirstenbosch Botanical Garden.
[c] Mean±s.e. (n=1) due to the small quantity of the isolated compound.