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Original article

Biological activities of plant extracts from *Ficus elastica* and *Selaginella vogelli*: An antimalarial, antitrypanosomal and cytotoxity evaluation

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ABSTRACT

The cytotoxic, antiplasmodial, and antitrypanosomal activities of two medicinal plants traditionally used in Cameroon were evaluated. Wood of *Ficus elastica* Roxb. ex Hornem. aerial roots (Moraceae) and *Selaginella vogelii* Spring (Selaginellaceae) leaves were collected from two different sites in Cameroon. *In vitro* cell-growth inhibition activities were assessed on methanol extract of plant materials against *Plasmodium falciparum* strain 3D7 and *Trypanosoma brucei brucei*, as well as against HeLa human cervical carcinoma cells. Criteria for activity were an IC_{50} value < 10 μg/mL. The extract of *S. vogelii* did not significantly reduce the viability of *P. falciparum* at a concentration of 25 μg/mL but dramatically affected the trypanosome growth with an IC_{50} of 2.4 μg/mL. In contrast, at the same concentration, the extract of *F. elastica* exhibited plasmodiacidal activity (IC_{50} value of 9.5 μg/mL) and trypanocidal (IC_{50} value of 0.9 μg/mL) activity. Both extracts presented low cytotoxic effects on HeLa cancer cell line. These results indicate that the selected medicinal plants could be further investigated for identifying compounds that may be responsible for the observed activities and that may represent new leads in parasitical drug discovery.

1. Introduction

Natural products have been used since millennia for the treatment of human diseases and as a result, a large proportion of current drugs in modern medicine have been developed from natural molecules. The search for new biologically active natural products continues to be an intense field of research (Newman et al., 2015). Indeed, the high natural biodiversity represents a broad range of diverse chemical structures with potentially new molecules having promising biological activities. Such new natural molecules can often serve as chemical templates for the design and the synthesis of novel drugs.

Plants have historically proven their value as a rich source of molecules with therapeutic potential and many major current drugs are natural products-derived compounds (Newman and Cragg, 2016). The natural products firstly commercialized for therapeutic use are morphine, isolated from *Papaver somniferum* (Rosenblum et al., 2008) and aspirin, based on the natural product salicin from *Salix alba* (Dias et al., 2012). Since these pioneering drugs, many other plant-derived molecules have been added to the current therapeutic arsenal of medicine, such as artemisinin from *Artemisia annua* used against malaria, capsaicin from

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Capsicum annuum used as pain relievers, the two cannabinoids, i.e. dronabinol and cannabidiol from *Cannabis sativa* used *inter alia* to treat nausea and vomiting caused by chemotherapy, paclitaxel from *Taxus brevifolia* for treating lung, ovarian and breast cancers, silymarin from the seeds of *Silybum marianum* for the treatment of liver diseases, and tiotropium, a derivative of atropine from *Atropa belladonna* used as a bronchodilator in the management of chronic obstructive pulmonary disease (Veeresham, 2012).

Healing with medicinal plants is the basis of traditional medicine (Neuwinger, 2000). Although having a long tradition in alternative medicine, Cameroon has been largely underexplored for new biologically active natural products. The biological effects of extracts from two Cameroonian plant materials were here investigated. The Moraceae plant family includes *Ficus* as one of the main genus with biological activities already described such as antiplasmodial (Muregi et al., 2003), antioxidant (Phan et al., 2012), anticancer (Mbosso et al., 2012, 2015, 2016a, 2016b), antimicrobial (Mbosso et al., 2012, 2015, 2016b), antiulcer (Galati et al., 2001), antidiarrhoeal (Mandal and Kumar, 2002), anti-pyretic (Rao et al., 2002) and gastroprotective (Rao et al., 2008). Note that the latex of some species of *Ficus* is exploited in traditional folk medicine for its antihelmintic activity in South and Central America (de-Amorin et al., 1999). The parasiticidal property of this genus has been ascribed to the presence of ficin (Pistelli et al., 2000) and it was also demonstrated that the latex of *Ficus elastica* Roxb. ex Hornem. (Moraceae) showed a significant antischistosomal activity (Seif el-Din et al., 2014). Leaf extract of *F. elastica* is employed as a diuretic agent besides treating skin infections and allergies (Phan et al., 2012).

Different species of *Selaginella* genus are exploited in traditional medicine for their anti-nociceptive, anti-inflammatory, anti-mutagenic, anti-spasmodic, cytotoxic, immune and antiretroviral properties (Jiofack et al., 2010). In addition, chemo-taxonomic studies have revealed that the genus *Selaginella* contains a variety of secondary metabolites namely alkaloids, phenolic compounds, terpenoids and many other classes of compounds exhibiting antioxidant, anticancer, antimicrobial, anti-protozoal, antiviral, anti-inflammatory and antiallergic properties (Morat, 1997). Hence, species of *Selaginella* genus have a fairly large spectrum of activity related to medication spanning cancer, cardiovascular diseases, diabetes, gastritis, hepatitis, skin diseases and urinary tract infections (Almeida et al., 2013). To the best of our knowledge, very few biological and phytochemical studies were conducted on the species *Selaginella vogelii* Spring (Selaginellaceae). The aim of the present study is to evaluate two medicinal plant extracts from Cameroon, i.e. the wood of *F. elastica* aerial roots and *S. vogelii* leaves, for their *in vitro* antiplasmodial, antitrypanosomal and cytotoxity potential.

2. Experimental

2.1. Plant materials

The wood of *F. elastica* aerial roots was collected in Yaoundé in August 2015 and *S. vogelii* leaves in Ngwei I in May 2015. The plant's identification was established by a member of the National Herbarium of Cameroon (NHC), where voucher specimens (No. 65646 HNC for *F. elastica* and No. 12000 HNC for *S. vogelii*) were deposited. After Air-drying, the plants materials were crushed into a fine powder by using an electric grinder.

2.2. Extraction

Macerate of the dried aliquot (5.50 kg of *F. elastica* and 7.50 kg of *S. vogelii*) was obtained using methanol (20 and 30 L, respectively) on two accounts for 48 h at room temperature (27 ± 2 °C) (Mohamad et al., 2011). After filtration (Whatman Number One, 320 mm, 4 μm) and evaporation at low pressure using a rotary evaporator (bath at 40 °C), 15 g and 280 g of extracts were obtained for *F. elastica* and *S. vogelii*, respectively.

2.3. Antiplasmodial activity

Malaria parasites (*Plasmodium falciparum* strain 3D7) were maintained in RPMI 1640 medium containing 2 mM L-glutamine and 25 mM Hepes (Lonza). The medium was further supplemented with 5% Albumax II, 20 mM glucose, 0.65 mM hypoxanthine, 60 μg/mL gentamycin and 2–4% hematocrit human red blood cells. The parasites were cultured at 37 °C under an atmosphere of 5% CO_2, 5% O_2, 90% N_2 in sealed T25 or T75 culture flasks. For screening samples against malaria parasites, 25 μg/mL of natural extracts were added to parasite cultures in 96-well plates and incubated for 48 h in a 37 °C CO_2 incubator. After 48 h, the plates were removed from the incubator and 20 μL of culture were removed from each well and mixed with 125 μL of a mixture of Malstat solution and NBT/PES solution in a fresh 96-well plate. The parasite lactate dehydrogenase (pLDH) activity was meseared by absorbance at 620 nm in a 96 well plate reader. The Abs_{620} reading in each well was thus an indication of both the pLDH activity and the number of parasites in that well.

2.4. Antitrypanosomal activity

Trypanosoma brucei (*T. b.*) parasites are the causative agents of African sleeping sickness (human African trypanosomiasis) in humans and Nagana (animal African trypanosomiasis) in cattle. The subspecies responsible for Nagana, *Trypanosoma brucei brucei* (*T.b. brucei*) is not infective to humans and is commonly used for drug screening. To assess antitrypanocidal activity, *in vitro* cultures of *T.b. brucei* in 96-well plates were performed at a fixed concentration of 25 μg/mL for natural extracts (unless otherwise stated). After an incubation period of 48 h, the number of parasites surviving drug exposure was determined by adding a resazurin based reagent. The reagent contains resazurin which was reduced to resorufin by living cells. Resorufin is a fluorophore ($Excitation_{560}$/$Emission_{590}$) and can thus be quantified in a multiwell fluorescence plate reader.

2.5. Cytotoxic activity

To assess the overt cytotoxicity of the extracts, they were incubated at a fixed concentration of 62.5 μg/mL (unless otherwise stated) in 96-well plates containing HeLa (human cervix adenocarcinoma, maintained in a culture medium made of Dulbecco's Modified Eagle's Medium (DMEM) with 5 mM L-glutamine (Lonza), supplemented with 10% fetal bovine serum (FBS) and antibiotics (penicillin/streptomycin/fungizone - PSF) cells for 24 h. The numbers of cells surviving drug exposure were counted using the resazurin based reagent and resorufin fluorescence quantified ($Excitation_{560}$/$Emission_{590}$) in a multiwell plate reader.

2.6. Single concentration screening

For each compound concentration, % parasitermia or cell viability was calculated. Extracts were tested in triplicate wells, and a standard deviation (SD) was derived. For comparative purposes, chloroquine (an anti-malarial drug) or emetine (which induced cell apoptosis) or pentamidine (an existing drug used in the treatment of trypanosomiasis) was used as a positive control drug standard at a 0 μM for the first two drugs or at 1 μM in case of pentamidine.

2.7. Dose response

For each sample, percentage viability was obtained against Log (extract concentration) and the IC_{50} (50% inhibitory concentration) determined from the resulting dose-response curve by non-linear regression using Prism 5 for Windows, Version 5.02 (graph Pad Software, Inc) program. For comparative purposes, chloroquine, pentamidine or emetine were employed as drug standards according to the type of test performed. Chloroquine, pentamidine and emetine yielded IC_{50} values in the range of 0.00001–100 μM. Extracts were tested in a range extending from 250 to 0.11 μg/mL (3-fold-dilutions) for antiplasmodial and antitrypanosomal assays, and from 125 to 0.057156 μg/mL (also in a 3-fold dilution series) for cytotoxic assays. In antiplasmodial assay, the R^2 coefficient of determination was calculated to be 0.95, 0.99 and 0.99 for the methanol extract of *Selaginella vogelii* leaves (EBSVF), the wood methanol extract of *Ficus elastica* aerial roots (EBRFE) and chloroquine, respectively. In antitrypanosomal assay, the coefficient was $R^2 = 0.99$ for the three samples, EBSVF, EBRFE and pentamidine. In cytotoxic assay, the R^2 coefficient was computed as 0.93, 0.99 and 0.98 for EBSVF, EBRFE and emetine, respectively.

3. Results and discussion

3.1. Antiplasmodial activity

As observed in Fig. 1, the methanol extract of *S. vogelii* leaves (EBSVF) at a concentration of 25 μg/ml slightly decreased the viability of *Plasmodium falciparum* (58.3 ± 2.1%) with an IC_{50} value of 32.2 μg/mL. In contrast, at the same concentration, the wood methanol extract of *F. elastica* aerial roots (EBRFE) reduced the viability of *Plasmodium falciparum* to approximatively 0% with an IC_{50} value of 9.5 μg/mL, and therefore demonstrated an antiplasmodial activity. The chloroquine used as reference drug showed an IC_{50} value of 7.9 nM. However, this result needs to be re-examined in conjunction with the cytotoxicity results to ensure that the decrease in viability is not caused by a general cytotoxicity of the EBRFE extract.

The remarkable activity of quinine and related drugs and the success of artemisinin have stimulated the search for new plant-derived antimalarials. A large number of plants have been screened for antiplasmodial activity (Krettli, 2009). *S. Vogelii* has not previously been explored as an antimalarial treatment in traditional Cameroonian medicine and was selected owing to the cytotoxic effect of the genus (Jiofack et al., 2010). Multiple efficacy parameters for *in vitro* antimalarial activity have been proposed (Cos et al., 2006). For crude extracts, IC_{50} values should certainly be below 100 mg/mL (Cos et al., 2006) although most promising antimalarial extracts exhibit IC_{50} values under 10 mg/mL (Krettli, 2009; Soh and Benoit-Vical, 2007). Here, the wood methanol extract of *F. elastica* aerial roots (EBRFE) revealed an IC_{50} value lower than 10 μg/mL against *P. falciparum*, arising as a good candidate for further bioassay-guided fractionation. By comparison, hexane extracts of *F. thonningii* were endowed with strong activity against NF54 and K1 strains of *P. Falciparum* with IC_{50} values of 2.7 and 10.4 μg/mL, respectively (Falade et al., 2014). *F. ovata* Vahl bark also demonstrated a high activity with an IC_{50} value of 4.8 μg/ml (Bwalya et al., 2011). In contrast, the methanol extract of *F. platyphylla* had a weak activity against 3D7 and K1 strains of *P. Falciparum* with IC_{50} values of 15.3 and 13.8 μg/mL, respectively (Shuaibu et al., 2008).

According to a recent study, two bioflavonoids, hinokiflavone and 2,3-dihydrohinokiflavone, isolated from *Selaginella bryopteris* possessed an *in vitro* anti-protozoal activity against *P. falciparum* K1 (IC_{50} values of 2.3 and 4.5 μM, respectively) (Kunert et al., 2008). Thus, the weak parasiticidal property of crude extract EBSVF might be attributed to the presence of these bioflavonoids at low concentrations. Indeed, it is well-established that the *Selaginella* genus is a rich source of steroids, bioflavonoids and lignans (Almeida et al., 2013). Three fractions (toluene, ethyl acetate and butanol) obtained from an ethanolic extract of *S. Bryopteris*, also showed an antiplasmodial activity against *P. falciparum* K1 strain with IC_{50} values of 4.6, 1.0, and below 5 μg/mL, respectively (Kunert et al., 2008).

3.2. Antitrypanosomal activity

The methanol extract from *S. vogelii* leaves (EBSVF) affected the growth of trypanosomes at 25 μg/mL concentration with a percentage of viable parasites estimated to be 0.3 ± 0.1% (see Fig. 2). The methanol extract of *F. elastica* (EBRFE) also reduced the viability of *T. b. brucei* at the same concentration, giving 2.0 ± 0.1% of viability, thus exhibiting an antitrypanosomal property. Furthermore, EBSVF and EBRFE extracts were both in the lower range of IC_{50} values (2.4 and 0.9 μg/mL, respectively), whereas the reference drug pentamidine exhibited an IC_{50} value of 0.17 nM (Table 1).

The two plants have not previously been used as antitrypanosomial treatment in traditional Cameroonian medicine and were

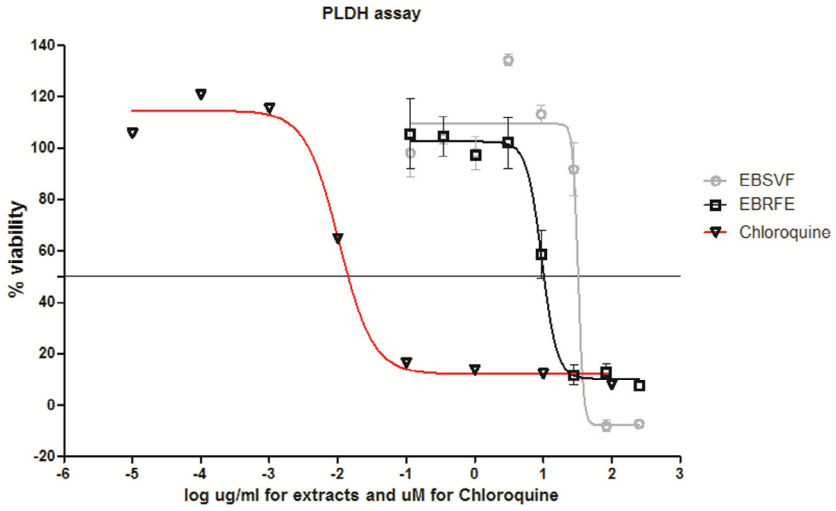

Fig. 1. Dose-response curve for antimalarial assay.

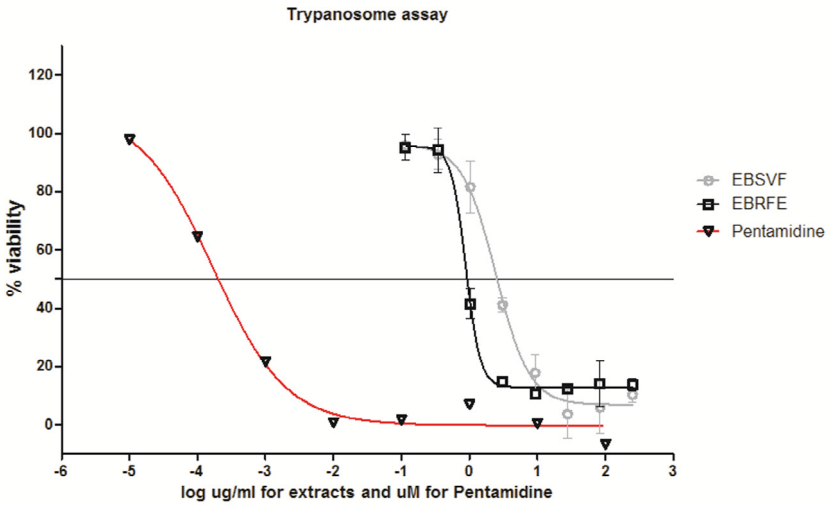

Fig. 2. Dose-response curve for trypanosome assay.

Table 1
In vitro assays of the methanol extracts.

Tested extracts or compounds	Antimalarial	Antitrypanosomal	Cytotoxicity
	IC_{50} (in μg/mL for extracts and μM for the reference drugs)		
EBSVF[a]	32.2	2.4	24.5
EBRFE[b]	9.5	0.9	20.9
Reference drug[c]	0.0079	0.00017	0.04

IC50: 50% inhibitory concentration, i.e. the concentration of extract/compound that reduces by 50% the growth or proliferation of cells.
The number of replicates was 3.
[a] (EBSVF) methanol extract of Selaginella vogelii leaves.
[b] (EBRFE) wood methanol extract of Ficus elastica aerial roots.
[c] Reference drugs, i.e. chloroquine, emetine and pentamidine for antimalarial, cytotoxicity and antitrypanosomal activities, respectively used at a concentration of 10 μM for the first two drugs or at 1 μM in case of pentamidine.

selected because of the cytotoxic effect of *Selaginella* genus and of the parasiticidal property of *F. elastica* (Pistelli et al., 2000; Seif el-Din et al., 2014). Interestingly, *F. elastica* has been traditionally used for treating skin infections and allergies, as well as a diuretic agent (Phan et al., 2012) while the *vogelii* genus has been employed to treat cancer, cardiovascular diseases, diabetes, gastritis, hepatitis, skin disorders, and urinary tract infections (Almeida et al., 2013). However, no antitrypanosomal activities have been reported to date from both plants.

According to Weniger et al., ginkgetin is the second most studied bi-flavonoid of the *Selaginella* genus. This compound has an *in vitro* antiprotozoal property against *T. Cruzi* (Weniger et al., 2006). Hinokiflavone isolated from *S. bryopteris* also possesses an *in vitro* antiprotozoal activity against *Trypanosoma* sp (Weniger et al., 2006; Kunert et al., 2008). The crude extract EBSVF may also contain a high concentration of such bioflavonoids responsible for the antiprotozoal activity in the *S. vogelii* species. On the other hand, three fractions of ethanolic extract from *S. bryopteris* (toluene, ethyl acetate and butanol) did not show antitrypanosomal activities against *T. Brucei rhodesiene*, yielding IC_{50} values of 24.1, 12.4 and 28.5 μg/mL, respectively and against *T. Cruzi* with IC_{50} values higher than 30, 20.5, and above 30 μg/mL, respectively (Kunert et al., 2008).

There is very little information available on the antitrypanosomal effects of the genus *Ficus*. Methanol extract stem bark of *Ficus platyphylla* showed an antitrypanosomal activity with minimum lethal concentrations of 25 μg/ml (Sawadogo et al., 2012). Methanol stem bark extract of *Ficus sycomorus*, ceased *T. b. brucei* motility *in vitro* within the incubation time of less than one hour but with low IC_{50} value (4 mg/mL) (Nwodo et al., 2015).

3.3. Cytotoxic activity

The methanol extract of *S. vogelii* leaves (EBSVF) and the wood methanol extract of *F. elastica* aerial roots (EBRFE) showed IC_{50} values at 20 μg/mL, whereas standard drug emetine exhibited an IC_{50} value of 0.04 μM (Table 1 and Fig. 3). A very low cytotoxic activity against HeLa cells was thereby observed for both extracts. Indeed, none of the two extracts were cytotoxic at 62.5 μg/mL.

These plants have rather a great significance for their traditional use in the treatment of other pathologies than cancer. *Ficus thonningii* and *F. platyhylla* showed very weak cytotoxicity with IC_{50} values $\geq$1500.0 μg/ml on NBMH mammalian cell lines (Shuaibu et al., 2008). The ethanolic extracts from *S. bryopteris* did not display significant cytotoxic activity against the rat skeletal myoblast cell line (L-6 cells) with IC_{50} values >90, 32.6, and >90 μg/mL, for extracting solvents, toluene, ethyl acetate, and butanol, respectively (Kunert et al., 2008).

However, the very weak cytotoxic activity observed here for EBSVF is contrary to that observed for other species of the *Selaginella* genus. For instance, in previous work, two compounds (a biflavanone, 2,2″,3,3″-tetrahydrorobustaflavone 7,4′,7″-trimethyl ether and the biflavonoid, robustaflavone 7,4′,7″-trimethyl ether) isolated from the methanol extract of *S. doederleinii* (whole plants) exhibited a good cytotoxic activity against the colorectal carcinom cells HCT116 with IC_{50} values of 19.1 and 15.6 μg/mL, respectively, and against the bronchioalveolar carcinoma NCI-H358 with IC_{50} values of 23.5 and 20.1 μg/mL, respectively (Lee et al., 2008). The ethyl acetate extract of *S. moellendorffii* inhibited the growth of ovarian adenocarcinoma cancer cells (Setyawan, 2011). *S. delicatula* behaves like an anticancer agent (Chen et al., 2005) as well as *S. doederleinii* (Li et al., 2014). Water extract of *S. doederleinii* has a moderate antimutagenic activity against the benzo[*a*]pyrene-induced mutation associated with cancer cell progression (Lee and Lin, 1988). *S. labordei* was reported to have anti cancer features (Tan et al., 2009).

S. tamariscina is problably the most powerful medicinal plant from the *Selaginella* genus. This plant is widely employed as an anticancer, antioxidant and as an anti-inflammatory agent (Le et al., 2012). It also possesses the following properties: anti-bacterial, anti-hypertensive, and anti-hyperglycemic effects

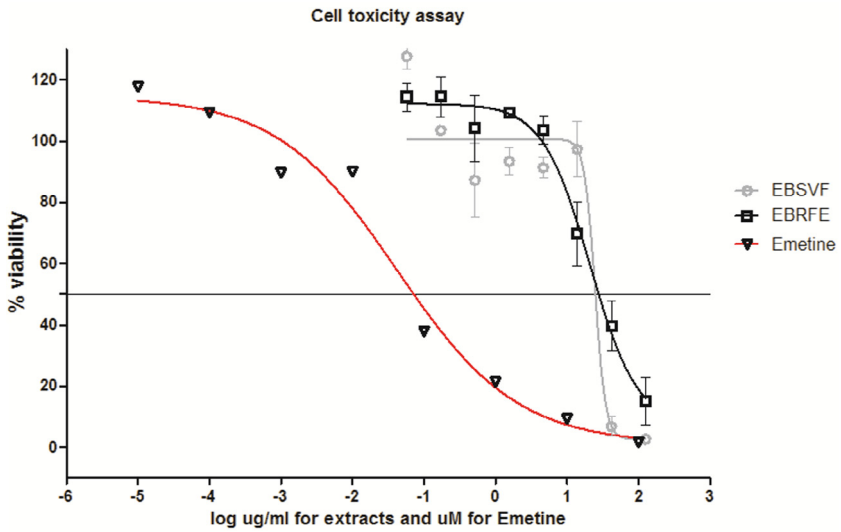

Fig. 3. Dose-response curve for cell toxicity assay.

(Miao et al., 1996; Zheng et al., 1998, 2011). As concerns its anticancer activity, *S. tamariscina* was reported to exhibit several functions: it can inhibit the invasion and metastatic activities of lung cancer cells, as well as the growth of metastasic A549 cell and Lewis lung carcinoma (Yang et al., 2007); shows significant tumoricidal effects against cultured HL-60 human leukemia cells (Lee et al., 1999); induces the expression of tumor suppressor gene of p53 (Lee et al., 1996); degrades U937 leukemia cancer cells (Lee et al., 1996; Yang et al., 2007); reduces the proliferation of nucleus antigen cell from stomach epithelium (Lee et al., 1999); and acts as chemo-preventive for gastric cancer (Lee et al., 1999).

Finally, as EBRFE and EBSVF extracts showed substantial antiprotozoal and antitrypanosomal activities without toxicity on HeLa cells which suggested that the effects on parasite cultures may not arise from a general cytotoxic effect of crude extracts.

4. Conclusions

This study has demonstrated that the crude extracts of the wood of *F. elastica* aeriel roots and *S. vogelii* leaves presented low antiplasmodial and very important antitrypanosomal activities associated with a low cytotoxicity. The comparison between the parasiticidal and cytotoxicity effects suggests that the decreased viability of parasites may not be caused by a general cytotoxicity of the extracts. These results indicate that the selected medicinal plants should be explored more actively in order to isolate the main compounds responsible for the parasiticidal action. It is important to mention that to the best of our knowledge, this study represents the first report on cytotoxic, antimalarial and antitrypanosomal evaluation for the wood of *F. elastica* aerial roots and *S. vogelii* leaves. The obtained results support to some extent the traditional uses of these plants for the treatment of parasitic diseases. Isolation, purification, and structure elucidation of constituents from these plants are warranted to support discovery of novel antiplasmodial and/or antitrypanosomal compounds.

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Competing interest

The authors declare no conflict of interest.

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