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Research article

In vitro antiplasmodial activity of leaves and stem bark fractions of *Spathodea campanulata* P. Beauv (Bignogniaceae)

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Abstract: Malaria is a potentially fatal disease caused by *Plasmodium* parasites transmitted by infected *Anopheles* mosquitoes, and its management is increasingly hampered by growing drug resistance. This study aims to evaluate the antiplasmodial activity of different fractions obtained from the leaves and stem bark of *Spathodea campanulata*. Dried plant materials were extracted to produce dichloromethane, ethyl acetate, and hexane fractions. Phytochemical screening and absorption spectrophotometry were used to identify and quantify secondary metabolites. Antiplasmodial activity was assessed against *Plasmodiun falciparum* 3D7 and Dd2 strains, and IC_{50} values were determined. Leaves showed high alkaloid levels, especially in the hexane, ethyl acetate, and dichloromethane fractions (1028.36 ± 21.36, 950.03 ± 25.44, and 641.8 ± 8.16 µg QiE/mg DM). In stem bark, alkaloids were also abundant in the hexane fraction (793.2 ± 25.32 µg QiE/mg DM). Polyphenols were most concentrated in the ethyl acetate fractions (209.64 ± 3.91 and 212.51 ± 1.29 µg GaE/mg

DM for leaves and stem bark), and flavonoid levels were highest in the ethyl acetate and hexane fractions of both plant parts. Dichloromethane fractions of leaves and stem bark, as well as the ethyl acetate stem bark fraction, showed good activity against *Pf* 3D7 (IC_{50}: 16.69–19.84 µg/mL). The ethyl acetate fractions of leaves and hexane fractions of both plant parts demonstrated moderate activity (IC_{50}: 30.85–38.69 µg/mL). Against *Pf* Dd2, only the dichloromethane fractions and the stem bark ethyl acetate fraction showed moderate activity (IC_{50}: 25.91–39.17 µg/mL). These activities are likely linked to alkaloid, polyphenol, and flavonoid content. The most active fraction was the dichloromethane fraction of the stem bark, which was effective on both strains and may represent potential therapeutic alternatives.

Keywords: *Spathodea campanulata*; *Pf* 3D7 and *Pf* Dd2 strains; antiplasmodial activity; quantitative phytochemical screening; Cameroon

1. Introduction

Malaria is a parasitic disease endemic to sub-Saharan Africa and remains the region's most widespread parasitic infection. According to the World Health Organization (WHO), malaria cases reached 247 million in 2021, up 2 million from the 245 million recorded in 2020, with 602,000 deaths—80% of which occurred in sub-Saharan Africa [1,2]. In Cameroon, malaria is still a major cause of morbidity and mortality. Between 2018 and 2021, deaths declined, however cases increased. In 2021, malaria incidence in health facilities reached 24%, with hospitalization rates of 50% and outpatient consultation rates of 30% [3,4]. Despite preventive measures such as intermittent preventive treatment in pregnant women and young children, distribution of insecticide-treated nets, and treatment with artemisinin-based combination therapies (ACTs), malaria cases have not significantly decreased in resource-limited settings [1,3]. The emergence of partial artemisinin resistance further threatens progress [5–9].

Beyond resistance, populations face challenges, such as low income, limited access to healthcare, and insufficient medical infrastructure [10]. These barriers encourage reliance on traditional medicine (TM), which remains a primary or complementary healthcare option worldwide and contributes to the goal of universal health coverage [11]. The biodiversity of medicinal plants, combined with traditional knowledge, offers promising avenues for new antimalarial treatments [12], as exemplified by quinine and artemisinin, both derived from plants historically used for fever and malaria treatment [13,14].

In this context, *Spathodea campanulata* P. Beauv, traditionally used to treat malaria [15] and other ailments, such as dysentery, ulcers, edema, and skin rashes [16–22], has attracted vast interest. Earlier studies in 1988 reported in vivo schizonticidal activity of the hexane and chloroform extracts of its stem bark extracts against *Plasmodium berghei berghei* in mice [23] and strong antiplasmodial activity of its leaf ethanolic extracts against both chloroquine-sensitive and -resistant *P. falciparum* isolates [24]. In 2023, our work showed that fractions of the flower methanolic extract displayed higher in vitro activity against the *Pf* 3D7 strain than the total extract [25]. A comparative study in 2024 on flowers, roots, leaves, and stem bark revealed that the total extracts of leaves and stem bark were the most active plant parts [26]. To support the development of safe and effective improved traditional medicines against malaria, the present study sought to identify which fractions of *S.*

campanulata leaves and stem bark are most active against *Pf* 3D7 and *Pf* Dd2 strains.

2. Materials and methods

2.1. Sample collection

The plant material consisted of fresh leaves and stem bark of *S. campanulata*. They were collected in Dschang, West Region of Cameroon, specifically in Bafou (latitude 5° North and longitude 10° East), and identified at the Cameroon National Herbarium by comparison with specimen number 50085/HNC.

2.2. Extraction and fractionation

The leaves and stem bark of *S. campanulata* were dried at room temperature away from sunlight for two weeks and then ground into a fine powder using an electric grinder. The powders obtained were subjected to double maceration with 70% ethanol. For extraction, 1 kg of stem bark powder was macerated in 10 L of 70 % ethanol (solvent-to-sample ratio: 10 mL/g), while 800 g of leaf powder was macerated in 8 L of 70 % ethanol (solvent-to-sample ratio: 10 mL/g). The mixtures were filtered, and the filtrates were concentrated under reduced pressure using a rotary evaporator to obtain the crude ethanolic extracts. Extraction yield was calculated as the percentage ratio of the mass of crude extract to the initial dry plant material. The ethanolic extract of the plant was prepared using a method based on the solubility of the compounds in a given solvent [27].

Fractionation was subsequently performed by liquid-liquid extraction, a technique based on the differential distribution of compounds between two immiscible phases [28]. An aqueous phase was used in combination with organic solvents of increasing polarity (hexane, dichloromethane, ethyl acetate). Crude extracts from the leaves (44.90 g) and stem bark (213.25 g) were subjected to sequential partitioning using a separating funnel. Briefly, 200 mL of each solvent was added to the aqueous phase, followed by vigorous shaking and decantation to recover the corresponding organic fractions. This operation was repeated several times to increase yield.

2.3. Preliminary phytochemical Screening of extracts and fractions

Phytochemical analysis was carried out using characteristic colorimetric tests to identify major chemical groups. Tests were conducted on the crude extracts and fractions of the leaves and stem bark of *S. campanulata*. The main classes of bioactive compounds in the crude hydroethanolic extracts of each part were investigated using standard procedures [29,30].

Test for alkaloids: 0.1 g of extract was resuspended in 6 mL of 60% ethanol, then divided into two test tubes. In the first tube, 2 drops of Dragendorff's reagent were added. The appearance of an orange-red or reddish-brown precipitate indicates a positive test. In the second tube, 2 drops of Bourchadart's reagent were added. The appearance of a brown precipitate indicates a positive test.

Test for terpenes: extract was dissolved in 2 mL of chloroform and evaporated to dryness. To this, 2 mL of concentration H_2SO_4 was added and heated for about 2 minutes. A grayish color indicated the presence of terpenes.

Crude extract was mixed with 2mL of chloroform and concentrated H_2SO_4 was added sidewise. A

red color produced in the lower chloroform layer indicated the presence of steroids. Another test was performed by mixing crude extract with 2mL of chloroform. Then, 2mL each of concentrated H2SO4 and acetic acid were poured into the mixture. The development of a greenish coloration indicated the presence of steroids

Test for sterols: extract was mixed with 2 mL of chloroform and concentrated H_2SO_4 was added sidewise. A red color produced in the lower chloroform layer indicated the presence of sterols.

Test for polyphenols: extract was mixed with 2 mL of 2% solution of $FeCl_3$. A blue-green or black coloration indicated the presence of phenols.

Test for flavonoids: extract was mixed with few fragments of magnesium ribbon and concentrated HCl was added drop wise. A pink scarlet color appeared after a few minutes which indicated the presence of flavonoids.

Test for tannins: After evaporating 5 mL of the extract to dryness, 15 mL of Stiasny's reagent (30% formalin, concentrated HCl: 1/0.5) was added to the residue and maintained at 80°C in a water bath for 30 minutes. The observation of a precipitate in large flakes is characteristic of catecholic tannins. After filtering the previous solution, the filtrate was collected and saturated with sodium acetate, and then 3 drops of 2% $FeCl_3$ were added. The addition of ferric chloride causes the appearance of an intense blue-black coloration, indicating the presence of gallic tannins.

Test for anthraquinones: 1 mL of 2.5% ammonia was added to 1 mL extract. A pink or purple coloration indicates the presence of anthraquinones.

Test for saponins: extract was mixed with 5 mL of distilled water in a test tube and was shaken vigorously. The formation of stable foam was taken as an indication for the presence of saponins

2.4. Quantitative phytochemical screening of the crude extract and fractions of leaves and stem bark

Bioactive compounds were quantified by estimating total polyphenols, flavonoids, tannins, saponins, and alkaloids using spectrophotometric methods.

Total polyphenols were determined using the Folin–Ciocalteu method [31]. An aliquot of 0.1 mL, 4 mg/mL of extract was added to 0.75 mL of Folin-Ciocalteu reagent (1:10 dilution). After 5 minutes, 0.75 mL of Na_2CO_3 (6%) was added, and the mixture was incubated at 25 ± 1°C for 90 minutes in the dark. The absorbance was measured at 725 nm (UVmini-1240, Shimadzu, Japan). Gallic acid in the range 0–1000 µg/mL was used as standard. The results were expressed in µg GaE/mg DM (micrograms gallic acid equivalent per mg dry matter).

Total flavonoids were evaluated using the Aiyegoro & Okoh method [32]. An aliquot of 0.5 mL, 4 mg/mL of extract was mixed with 1.5 mL methanol, 0.1 mL $AlCl_3$ (10%), 0.1 mL CH_3COOK (1 M), and 2.8 mL distilled water. After incubation at 25 ± 1°C for 30 minutes, the absorbance was read at 415 nm. Quercetin (0–1000 µg/mL) served as standard. The results were expressed in µg QE/mg DM (micrograms quercetin equivalent per mg dry matter).

Saponins were quantified following Hiai et al. method [33]. 200 µL of extract was mixed with 200 µl of vanillin in 80% ethanol and 2000 µL of H_2SO_4 (72%). After heating at 60°C for 10 minutes, the absorbance was measured at 535 nm. 0 to 1 mg/mL of saponins were used to establish a calibration curve. The results were expressed in µg SaE/mg DM (micrograms saponin equivalent per mg dry matter).

Alkaloids were determined according to Diouf et al. method with modifications [34]. 200 µL of extract was treated with 200 µL of vanillin in 80% ethanol and 2000 µl of H_2SO_4 (72%). After heating

at 60°C for 10 minutes, the absorbance was read at 535 nm. Quinine (0–1 mg/mL) was used as standard. The results were expressed in µg QiE/mg DM (micrograms quinine equivalent per mg dry matter).

Tannins were measured using Sun et al. method [35]. 0.1 mL of 4 mg/mL extract was mixed with 0.3 mL of HCl (1 N) and 0.6 mL of vanillin (4%) in ethanol. After incubation at 25 ± 1°C for 15 minutes, the absorbance was read at 500 nm. Gallic acid (0–1000 µg/mL) served as standard. The results were expressed in µg GaE/mg DM.

2.5. Evaluation of antiplasmodial activity

In vitro antiplasmodial activity was evaluated on *Pf* 3D7 (chloroquine- and artemisinin-sensitive) and *Pf* Dd2 (chloroquine-resistant, artemisinin-sensitive) strains obtained from MR4 (Malaria Research and Reference Reagent Resource Center). Parasite growth was measured in microtiter plates using SYBR Green I fluorescence assay [36]. Artemisinin and chloroquine served as reference drugs.

The culture medium was complete RPMI 1640 (Roswell Park Memorial Institute), supplemented with hypoxanthine (0.01%), gentamicin (50 mg/mL), Albumax (10%), and L-glutamine (2 mM). Cultures were maintained at +4°C and refreshed daily to replenish nutrients and adjust pH (~7.2).

Healthy O^+ erythrocytes from non-infected donors were used to adjust parasitemia. Cultures were maintained following the Trager and Jensen method [37], at 37°C in an atmosphere of 92% N_2, 7% CO_2, and low O_2. Synchronization was performed with sorbitol, exploiting differential membrane permeability to selectively lyse mature stages [38].

For the microtest, extracts (100 µg/mL) were serially diluted (100–1.56 µg/mL) in 96-well plates containing supplemented RPMI and synchronized infected erythrocytes (1% parasitemia, 1.5% hematocrit). Plates were incubated at 37°C in 5% CO_2 for 72 h. Fluorescence was measured at 485 nm (excitation) and 538 nm (emission) using a Fluoroskan Ascent reader. All experiments were performed in triplicate. IC_{50} values were calculated as the drug concentration inhibiting 50% of parasite growth.

2.6. Data processing methods

Results of phytochemical screening were expressed in terms of color/turbidity changes and metabolite content. Percentage reduction and IC_{50} values were determined from dose–response curves using artemisinin and chloroquine as references. Each sample was tested in triplicate. Data was analyzed using GraphPad Prism 8.0 and Microsoft Excel 2015.

3. Results

A total of 2,200 g of fresh leaves and 10,400 g of fresh stem bark was harvested and dried, with respective weight loss of 67.27% and 75.00%. The pulverized dried leaves (710 g) and stem bark (1,000 g) were macerated in 70% ethanol for 72 h, yielding 49.94 g of crude leaf extract and 232.34 g of crude stem bark extract of *S. campanulata*. Details are presented in Table 1.

Table 1. Extraction diagram for *Spathodea campanulata* leaves and stem bark.

	Leaves	**Stem bark**
Harvested material (g)	2,200	10,400
Dried material (g)	720	2,600
Loss on drying	67.27%	75.00%
Macerated amount (g)	710	1,000
Crude extract (g)	49.94	232.34
Extraction yield	7.03%	23.23%

The crude extracts were fractionated by liquid-liquid extraction using distilled water as the fixed phase and organic solvents of increasing polarity (hexane, dichloromethane, ethyl acetate) as the mobile phases. Four dark-brown fractions were obtained for each plant part: hexane fractions (HF), ethyl acetate fractions (EaF), dichloromethane fractions (DF), and aqueous fractions (WF). From 44.90 g of crude leaf extract, 2.84 g were recovered from the HF, 1.73 g from the EaF, 2.43 g from the DF, and 17.55 g from the WF. Then from 213.25 g of crude stem bark extract, 1.28 g was obtained from the HF, 3.93 g from the EaF, 5.64 g from the DF, and 119.38 g from the WF (Figure 1).

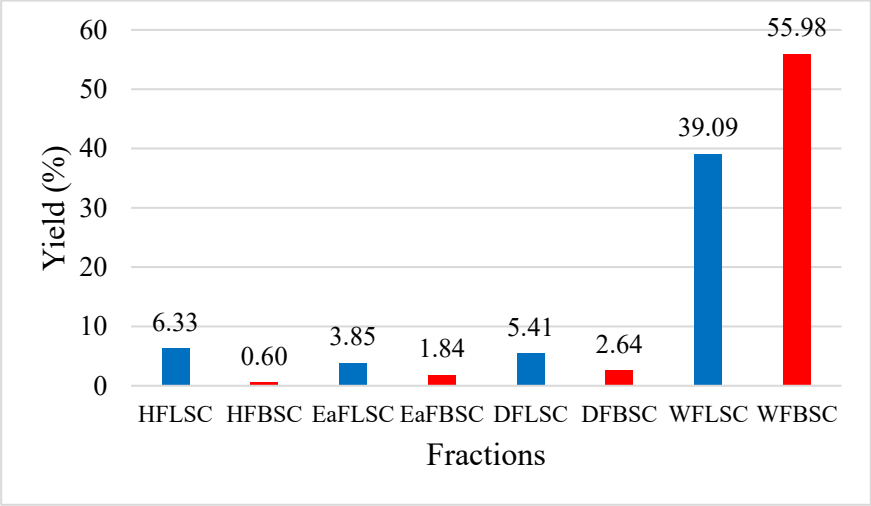

Figure 1. Fractionation of *Spathodea campanulata* aqueous extract. HFLSC = hexane fraction of leaves; HFBSC = hexane fraction of stem bark; EaFLSC = ethyl acetate fraction of leaves; EaFBSC = ethyl acetate fraction of stem bark; DFLSC = dichloromethane fraction of leaves; DFBSC = dichloromethane fraction of stem bark; WFLSC = aqueous fraction of leaves; WFBSC = aqueous fraction of stem bark. Yields are expressed as percentages of crude extract. Fractions from leaves and stem bark are shown in blue and red, respectively.

The results of phytochemical screening of crude extracts and fractions are summarized in Table 2. Both the leaves and stem bark of *S. campanulata* contained all the secondary metabolites investigated. However, sterols were absent from the crude extracts and were only detected in the hexane and dichloromethane fractions. Aqueous fractions of both plant parts were similar to the crude extracts,

containing all metabolites except sterols. Interestingly, terpenes from the bark were extracted in the ethyl acetate fraction but not from the leaves, while tannins from the leaves were extracted in the ethyl acetate fraction but not from the bark. Flavonoids were the most abundant metabolites in the samples.

Table 2. Qualitative phytochemical screening of extracts and fractions from the leaves and stem bark of *S. campanulate*.

Results	Secondary metabolites							
	Alkaloids	Terpenes	Sterols	Polyphenols	Flavonoids	Tannins	Anthraquinones	Saponins
HFLSC	-	-	+	-	+	-	-	-
DFLSC	-	-	+	-	-	-	-	-
EaFLSC	-	-	-	+	+	+	-	-
WFLSC	+	+	-	+	+	+	+	+
CELSC	+	+	-	+	+	+	+	+
HFBSC	-	-	+	-	+	-	-	-
DFBSC	-	-	+	-	-	-	-	-
EaFBSC	-	+	-	+	+	-	-	-
WFBSC	+	+	-	+	+	+	+	+
CEBSC	+	+	-	+	+	+	+	+

Note: HFLSC = hexane fractions from the leaves of *S. campanulata*; DFLSC = dichloromethane fractions from the leaves of *S. campanulata*; EaFLSC = ethyl acetate fractions from the leaves of *S. campanulata*; WFLSC = aqueous fractions from the leaves of *S. campanulata;* CELSC = crude extract of *S. campanulata* leaves; HFBSC = hexane fractions from the stem bark of *S. campanulata*; DFBSC = dichloromethane fractions from the stem bark of *S. campanulata*; EaFBSC = ethyl acetate fractions from the stem bark of *S. campanulata*; WFBSC = aqueous fractions from the stem bark of *S. campanulata* and CEBSC = crude extract of *S. campanulata* stem bark; (+) = present; (-) = absent.

Quantitative analysis of the leaf fractions and crude extract (Figure 2) showed that alkaloids were present in all samples and were the most abundant metabolites. The HFLSC, EaFLSC, and DFLSC fractions contained the highest alkaloid levels (1028.36 ± 21.36, 950.03 ± 25.44, and 641.8 ± 8.16 µg QiE/mg DM, respectively). Flavonoids were also abundant, with the highest values in EaFLSC, HFLSC, and DFLSC (189.28 ± 9.17, 170.51 ± 12.39, and 136.62 ± 10.77 µg QE/mg DM, respectively). Polyphenols were particularly abundant in EaFLSC (209.64 ± 3.91 µg GaE/mg DM), and present at lower levels in DFLSC (70.44 ± 4.40 µg GaE/mg DM) and HFLSC (44.62 ± 3.15 µg GaE/mg DM). Other samples contained polyphenols at only low levels (8.57–19.53 µg GaE/mg DM). Tannin contents ranged from 0.09 to 0.16 µg GaE/mg DM, while saponins were either absent or very low (0–136.06 µg SaE/mg DM).

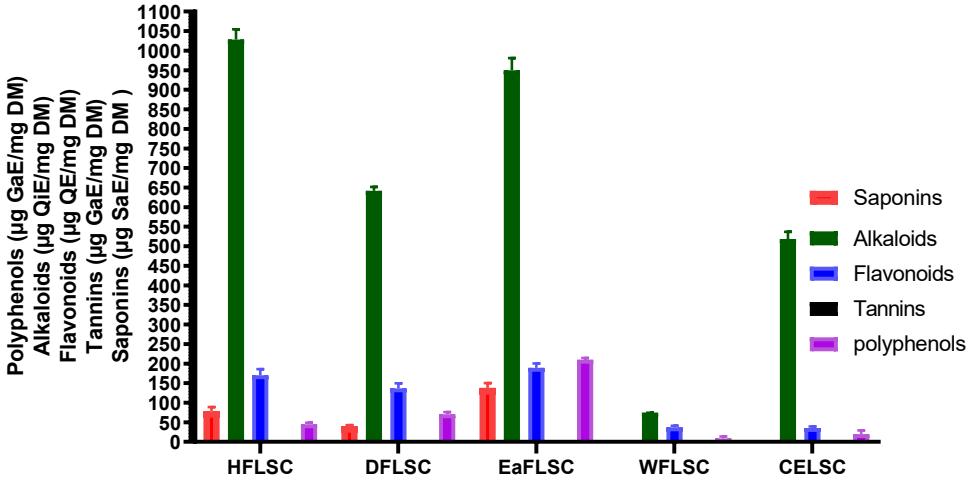

Figure 2. Secondary metabolite content of the crude extract and fractions of *S. campanulata* leaves. HFLSC = hexane fraction; DFLSC = dichloromethane fraction; EaFLSC = ethyl acetate fraction; WFLSC = aqueous fraction; CELSC = crude leaf extract. GaE = gallic acid equivalent; QE = quercetin equivalent; SaE = saponin equivalent; EQi = quinine equivalent; DM = dry matter.

For the stem bark fractions (Figure 3), flavonoids were also the most abundant metabolites, with EaFBSC, HFBSC, and DFBSC containing 141.32 ± 2.44, 138.01 ± 10.74, and 95.85 ± 2.94 µg QE/mg DM, respectively. Alkaloids were present in all stem bark fractions, with highest values in HFBSC (158.64 ± 5.06 µg EQi/mg DM), DFBSC (75.10 ± 5.07 µg EQi/mg DM), and EaFBSC (89.04 ± 8.78 µg EQi/mg DM). Polyphenol content was highest in EaFBSC (212.51 ± 1.29 µg GaE/mg DM), moderate in DFBSC (53.18 ± 2.44 µg GaE/mg DM), and low in HFBSC (15.19 ± 3.88 µg GaE/mg DM). Tannin levels ranged from 0.05 to 0.15 µg GaE/mg DM, while saponins ranged from 0 to 23.72 µg SaE/mg DM.

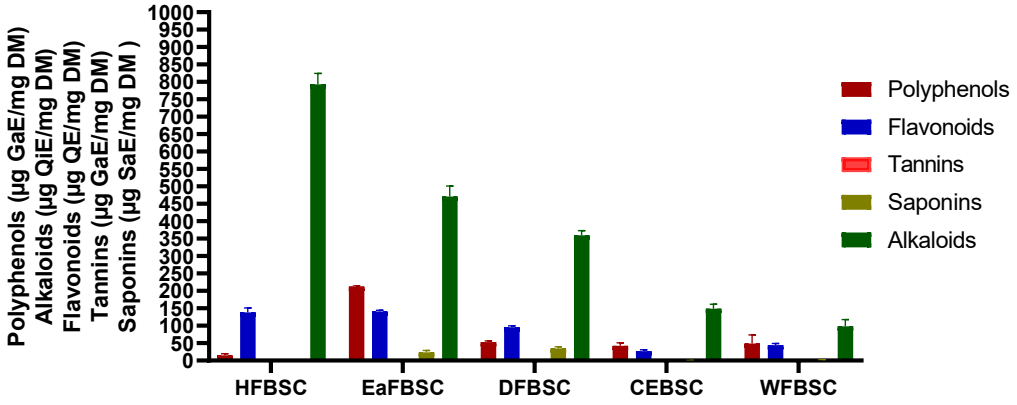

Figure 3. Secondary metabolite content of crude extract and fractions of *S. campanulata* stem bark. HFBSC = hexane fraction; EaFBSC = ethyl acetate fraction; DFBSC = dichloromethane fraction; CEBSC = crude stem bark extract; WFBSC = aqueous fraction; GaE: Gallic acid equivalent; QE: Quercetin Equivalent; SaE: Saponin Equivalent; QiE: Quinine Equivalent; DM: Dry matter.

For the *Pf* 3D7 strain (Figure 4) and *Pf* Dd2 strain (Figure 5), all tests were performed in triplicate (Table 3). Reference drugs (artemisinin and chloroquine) confirmed their expected activity: efficacy against *Pf* 3D7 (sensitive) and resistance of *Pf* Dd2 to chloroquine, validating the chemosensitivity assays.

Of the 10 fractions tested, none displayed high activity ($IC_{50} \leq 5$ µg/mL) or promising activity (5.1–10 µg/mL) against either strain. The crude extracts showed no activity against either *Pf* 3D7 or *Pf* Dd2. The DFLSC, DFBSC, and EaFBSC fractions showed good activity against *Pf* 3D7 (IC_{50} = 16.69–19.84 µg/mL), while EaFLSC, HFLSC, and HFBSC showed moderate activity (IC_{50} = 30.85–38.69 µg/mL). Marginal activity was observed in the aqueous leaf fraction, while no activity was detected in the aqueous stem bark fraction.

Against *Pf* Dd2, only DFLSC, DFBSC, and EaFBSC showed moderate activity (IC_{50} = 25.91–39.17 µg/mL). Marginal activity was observed in four fractions (ethyl acetate leaf, aqueous leaf, aqueous stem bark, and hexane leaf).

Table 3. IC_{50} values obtained against *Pf* 3D7 and *Pf* Dd2.

IC_{50} (μg/mL)										
Dd2						3D7				
Extracts	Test 1	Test 2	Test 3	Average	SD	Test 1	Test 2	Test 3	Average	SD
eae	32.5	43.15	41.86	39.17	5.82000	21.79	13.96	23.77	19.84	5.187571686
eaf	42.32	46.6	47.43	45.45	2.74000	32.47	27.92	32.88	31.09	2.752943879
eee	>100	>100	>100	>100	ND	>100	>100	>100	>100	ND
eef	53.31	60.76	38.32	48.47	8.80348	57.09	54.63	55.86	55.86	1.230000000
ehe	53.68	44.31	53.66	50.55	5.41000	39.9	37.83	38.34	38.69	1.078471140
ehf	43.8	41.57	41.95	42.44	1.19000	30.27	28.73	33.55	30.85	2.461787968
ece	>100	>100	>100	>100	ND	>100	>100	>100	>100	ND
ecf	>100	>100	>100	>100	ND	>100	>100	>100	>100	ND
ede	30.86	26.23	27.69	28.26	2.37000	15.68	17.04	17.35	16.69	0.888313008
edf	30.04	20.95	26.74	25.91	4.58000	19.07	20.01	20.05	19.71	0.554616985
CQ	0.3200	0.3500	0.3200	0.3300	0.0173	0.009	0.012	0.009	0.01	0.0017
ART	0.00415	0.00415	0.00415	0.00415	0.0000	0.0052	0.0040	0.0046	0.0046	0.0006

Note: IC_{50}: half-maximal inhibitory concentration; Dd2: chloroquine-resistant and artemisinin-sensitive *Plasmodium falciparum* strain; 3D7: chloroquine- and artemisinin sensitive *Plasmodium falciparum* strain; eae: ethyl acetate fraction of *S. campanulata* stem bark; eaf: ethyl acetate fraction of *S. campanulata* leaves; eee: aqueous fraction of *S. campanulata* stem bark; eef: aqueous fraction of *S. campanulata* leaves; ehe: hexane fraction of *S. campanulate* stem bark; ehf: hexane fraction of *S. campanulate* leaves; ece: crude extract of *S. campanulata* stem bark; ecf: crude extract of *S. campanulata* leaves; ede: dichloromethane fraction of *S. campanulata* stem bark; edf: dichloromethane fraction of *S. campanulata* leaves; CQ: chloroquine; ART: artemisinin; SD: standard deviation; ND: not determined.

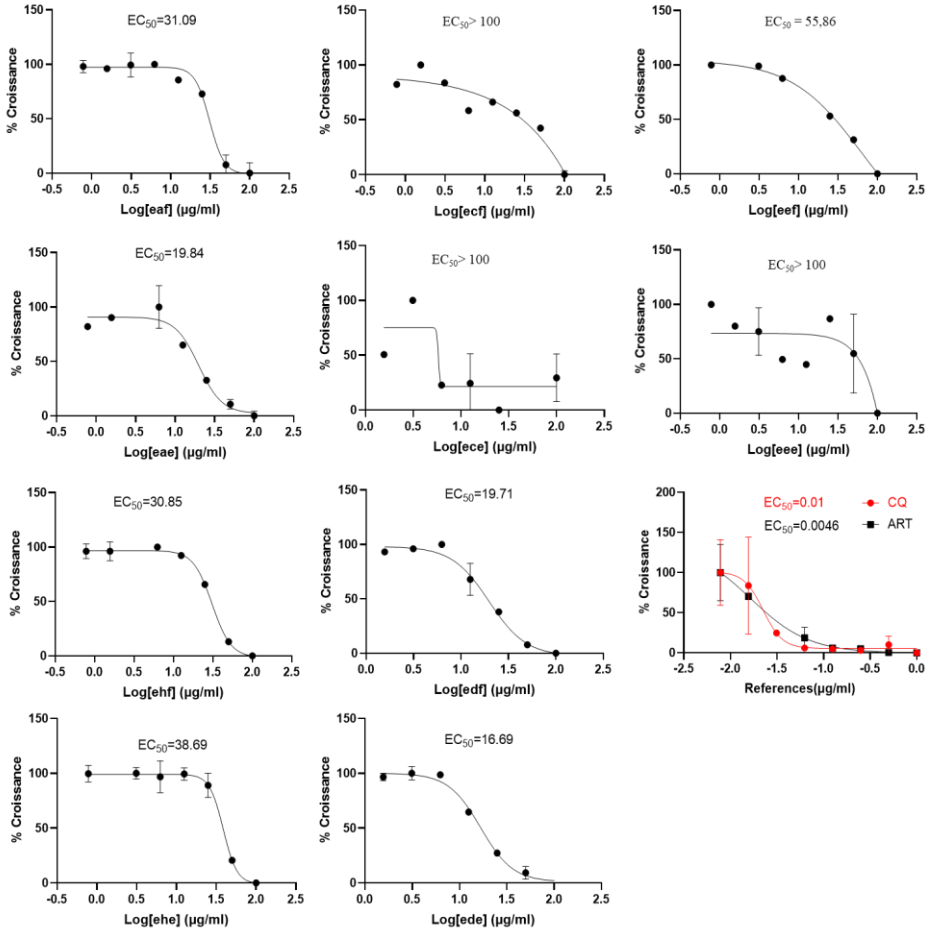

Figure 4. IC$_{50}$ values of crude extracts and fractions of *S. campanulata* leaves and stem bark against *Pf* 3D7. eaf: ethyl acetate fraction of *S. campanulata* leaves; ecf: crude extract of *S. campanulata* leaves; eef: aqueous fraction of *S. campanulata* leaves; eae: ethyl acetate fraction of *S. campanulata* stem bark; ece: crude extract of *S. campanulata* stem bark; eee: aqueous fraction of *S. campanulata* stem bark; ehf: hexane fraction of *S. campanulata* leaves; edf: dichloromethane fraction of *S. campanulata* leaves; ehe: hexane fraction of *S. campanulata* stem bark; ede: dichloromethane fraction of *S. campanulata* stem bark; CQ: chloroquine; ART: artemisinin.

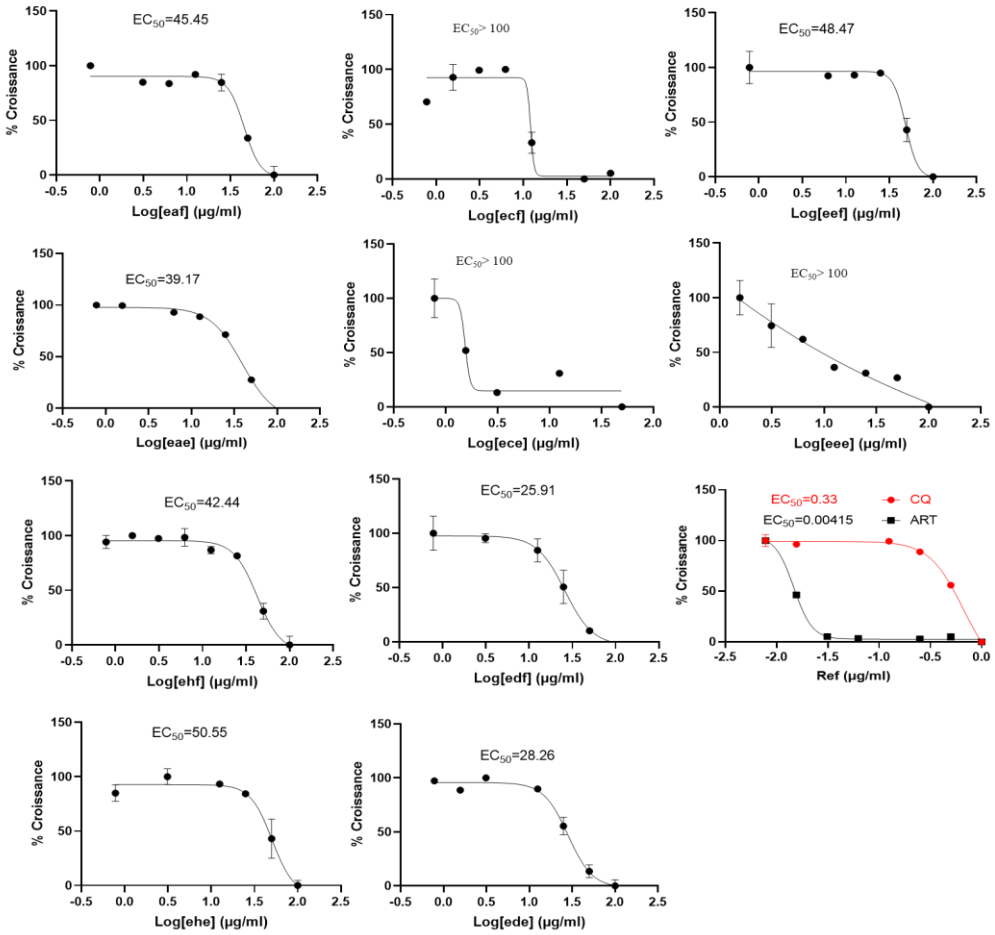

Figure 5. IC_{50} values of crude extracts and fractions of *S. campanulata* leaves and stem bark against *Pf* Dd2. eaf: ethyl acetate fraction of *S. campanulata* leaves; ecf: crude extract of *S. campanulata* leaves; eef: aqueous fraction of *S. campanulata* leaves; eae: ethyl acetate fraction of *S. campanulata* stem bark; ece: crude extract of *S. campanulata* stem bark; eee: aqueous fraction of *S. campanulata* stem bark; ehf: hexane fraction of *S. campanulata* leaves; edf: dichloromethane fraction of *S. campanulata* leaves; ehe: hexane fraction of *S. campanulata* stem bark; ede: dichloromethane fraction of *S. campanulata* stem bark; CQ: chloroquine; ART: artemisinin.

4. Discussion

Reports of the emergence of specific markers of partial resistance to artemisinin in Rwanda and Uganda [5–9] suggest that progress in the fight against malaria may be slowing down in Africa. As with antibiotic resistance, antimalarial drug resistance results from the massive and uncontrolled use of certain compounds, which can lead to the selection of resistant *Plasmodium* strains over time. Diversifying the arsenal of effective antimalarial drugs is therefore essential to limit the spread of resistance and reduce malaria-related mortality. In our context, characterized by the high cost of drugs, limited access to health facilities, and the potential spread or emergence of artemisinin-resistant strains, the search for alternative medicines remains highly relevant. The present study investigated the potential activity of various extracts of *S. campanulata* leaves and stem bark against *P. falciparum*

strains 3D7 (chloroquine- and artemisinin-sensitive) and Dd2 (chloroquine-resistant and artemisinin-sensitive).

Qualitative phytochemical analyses of secondary metabolites were done, while in previous studies, only the qualitative dosage had been done. The quantitative dosage revealed the presence of various secondary metabolites in all samples tested, particularly in the aqueous fractions and crude extracts. The profile of metabolites is heterogeneous and depends on several factors, including the plant part harvested, geographic origin, collection period, and climatic conditions [26,24,39–42]. These factors strongly influence plant growth and metabolism and may affect metabolite quality and quantity over time. The presence of saponins, terpenes, and sterols was also reported in a qualitative analysis of crude extracts and fractions of *S. campanulata* flowers collected in Dschang [25]. Spathodols, caffeic acids, phenolic acids, and flavonoids have already been identified in the leaves of this plant [40]. In 2008, sterols and terpenoids were identified in the hexane fraction of leaves harvested in Kerala, India. While alkaloids, terpenoids, and saponins were present in the ethanol fraction, and flavonoids and steroids in the chloroform and methanol extracts [43]. In 2017, alkaloids, saponins, phenolic compounds, flavonoids, tannins, and reducing sugars also reported in aqueous stem bark extracts collected in Dschang [41]. More recently, alkaloids, coumarins, glycosides, polyphenols, and saponins were detected in 2020 in aqueous and hydroalcoholic extracts of stem bark harvested in Akonolinga, Centre Region, Cameroon [42].

The difficulty in reading the colored reactions of alkaloids, polyphenols, flavonoids, and tannins in certain qualitative tests due to the dark colors of the extracts was systematically detected in the crude extracts and fractions by quantitative spectrophotometry, clearly confirming the sensitivity of this technique. Saponins were absent in some samples. Alkaloids were particularly abundant in all samples, with higher levels observed in hexane, ethyl acetate, and dichloromethane fractions. The higher content of polyphenols, especially in the ethyl acetate fraction compared with flavonoids, had already been reported in flower extracts harvested in India [44].

Chemosensitivity assays on strains 3D7 and Dd2 did not identify any *S. campanulata* extracts as promising candidates, based on the reference IC_{50} values (5.1–10 µg/mL) [45]. However, good activity was observed against strain 3D7 for the dichloromethane fractions of leaves and stem bark, as well as the ethyl acetate fraction of stem bark (IC_{50} = 16.7–19.7 µg/mL). Moderate activity was recorded for the ethyl acetate and hexane fractions of both the leaves and stem bark against 3D7, and for the dichloromethane fractions of leaves and stem bark and the ethyl acetate fraction of stem bark against Dd2 (IC_{50} = 25.9–39.2 µg/mL). Studies by Dhanabalan et al. (2008) showed that the leaf ethanol fraction of *S. campanulata* exhibited very good antiplasmodial activity (IC_{50}: 7.5–90 µg/mL) against both chloroquine-sensitive and resistant *Plasmodium falciparum* compared to the leaf crude extract (IC_{50}: 68.5–100.8 µg/mL) [24]. Our results are consistent with these studies, showing that the fractions are more active (IC_{50}: 16.69–55.86 µg/mL) than the crude extracts of the leaves and stem bark (IC_{50}: > 100 µg/mL). The leaf fractions appear to be more active in this study compared to ours. This could be explained by the fact that in the previous study the extraction was done using heat with a Soxhlet apparatus, while in the present study we performed maceration. Our previous work, studies of Mbosso Teinkela et al. (2024) was a comparative study on leaves, flower, stem bark, and roots and demonstrated that total ethanolic extracts of the leaves and stem bark were the parts exhibiting the best activity against chloroquine-resistant *Plasmodium falciparum* (IC_{50}: 93.68 and 79.68 µg/mL, respectively) [26]. The present results on the activity of the fractions of these two parts obtained by liquid-liquid extraction technique (dichloromethane fractions of leaves and stem bark, as well as the

ethyl acetate stem bark fraction, showed good activity against chloroquine-sensitive *P. falciparum* with IC_{50}: 16.69–19.84 µg/mL) confirm our previous work on the flower fractions (Mbosso Teinkela et al. 2023) also obtained by the same extraction technique, which shows that the dichloromethane, ethyl acetate, and hexane fractions on chloroquine-sensitive *P. falciparum* (IC_{50}: 28.1, 30.2, and 29.7 µg/mL, respectively) were more active than the total extract of the flowers (IC_{50}: > 100 µg/mL) [25]. All of this reinforces the idea that the fractions exhibit the best activities compared to the total extract, whether for the flowers, leaves, stem bark, or roots. Due to the fact that in all these studies fractions were obtained by liquid-liquid extraction technique, we can say that the fractionation technique had no impact on the activities observed.

The fractions exhibiting good antiplasmodial activity were also those with the highest alkaloid, polyphenol, and flavonoid contents. These three classes of metabolites are well known for their antiplasmodial potential. For example, alkaloids demonstrated strong antiplasmodial activity (IC_{50} < 2 µM), such as flinderole B from *Flinderia amboinensis* (Rutaceae) and astiphyllanine B from *Alstonia macrophylla* (Apocynaceae), against both Dd2 and 3D7 strains [46]. Acetylcaranine, an alkaloid isolated from *Atropa belladonna* (Amaryllidaceae), showed activity against Dd2 with an IC_{50} of 1.1 µg/mL [47]. Plant polyphenols also demonstrated strong activity against both 3D7 and Dd2. Methyl gamalate, a polyphenol isolated from *Swintonia foxworthyi* (Burseraceae), inhibited parasite growth with IC_{50} values of 2.01 µM (3D7) and 2.99 µM (Dd2) [48]. Other polyphenols showed comparable results: ellagic acid from *Terminalia mollis* (Combretaceae) (IC_{50} = 0.56 µM) [49], lauryl gallate from *Cyclicodiscus gabunensis* (Leguminosae) (IC_{50} = 2.2 µM) [50], and kaempferol 3-O-rhamnoside from *Schima wallichii* (Theaceae) (IC_{50} = 3.4 µM) [51]. Among flavonoids, Artopeden A from *Artocarpus champeden* (Moraceae) exhibited strong activity against 3D7 with an IC_{50} of 0.11 µM [52], while nymphayol B, isolated from *Macaranga tanarius* leaves, displayed potent activity against 3D7 with an IC_{50} of 0.05 µg/mL [53]. *Spathodea campanulata* contains alkaloids, though specific isolated alkaloids are not frequently cited in the research, we mainly observed that several flavonoids and phenolic compounds have been isolated from the stem bark and many more leaves. These include, for example, Kaempferol isolated from the stem bark [54], 8-methoxy kaempferol-3-*O*-glucoside and Kaempferol-3-*O*-glucoside isolated from the stem bark [55]; verminoside isolated from leaves and stem bark, kaempferol 3-*O*-beta D-(2-*O*- β-D-glucopyranosyl) glucopyranoside from leaves [56]; umbelliferone from leaves [57], kaempferol 3-*O*-(6-*O*-α-L-rhamnopyranosyl)-β-D-galactopyranoside, kaempferol 3-*O*-β-D-(6-*O*-α-L rhamnopyranosyl)-β-D-glucopyranoside, Kaempferol 3-*O*-(2-*O*-β-D-xylopyranosyl)-β-D-galactopyranoside [58]; in accordance with the results of the quantitative screening and could therefore justify the antiplasmodial activity observed. The dichloromethane and ethyl acetate fractions that showed good activity against the 3D7 strain could be the subject of further studies, particularly for cytotoxicity studies and the reproduction of activity with the synthesis of nanoparticles.

5. Conclusions

Liquid-liquid extraction using solvents of increasing polarity (hexane, dichloromethane, ethyl acetate) enabled us to obtain eight fractions, four of which were derived from the crude leaves extract and four others from the stem bark of *S. campanulata*. A variety of classes of secondary metabolites were found at varying levels: alkaloids, polyphenols, and flavonoids were the most important. According to previous work, the leaf and stem bark fractions possess the best antiplasmodial activities.

In this study, the stem bark fractions are evaluated for the first time. The dichloromethane fraction of *S. campanulata* stem bark exhibits the best antiplasmodial activity against chloroquine-sensitive *Plasmodium falciparum*. This observed activity is thought to be linked to the alkaloid and flavonoid content of this fraction. Consequently, it would therefore be interesting to continue studies on this fraction by synthesizing the nanoparticle in order to improve the activity and thus make it an improved traditional medicine, as well as to purify this fraction in order to isolate the active principle and thus make it a phytomedicine.

Author contributions

Synthia Kemda Tassemo: Methodology, Writing-Reviewing and Editing Judith Caroline Ngo Nyobe: Data Curation, Reviewing and Editing Hans Denis Bamal: Writing-Original draft preparation, Reviewing and Editing Eugene Ekoune Kame: Software, Writing-Reviewing and Editing Noella Molisa Efange: Software, Reviewing and Editing Lawrence Ayong: Investigation, Reviewing and Editing Else Carole Eboumbou Moukoko: Supervision, Visualization, Reviewing and Editing Jean Emmanuel Mbosso Teinkela: Conceptualization, Visualization, Reviewing and Editing. All authors have read and approved the final version of the manuscript for publication.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest in this paper.

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