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Research Article
Phytochemical and Antiplasmodial Comparative Analysis of Leaf and Stem Bark Extracts of *Combretum micranthum* G.Don and *Combretum adenogonium* Steud. ex A.Rich.

[1]Harouna Sore, [2]Moussa Compaore, [2]Mahamadi Sana and [2]Martin Kiendrebeogo

[1]Laboratoy of Pharmacognosy, National Center for Research and Training on Malaria, 01 BP 2208 Ouagadougou, Burkina Faso
[2]Laboratory of Applied Biochemistry and Chemistry, University Joseph KI-ZERBO, 03 BP 7021 Ouagadougou, Burkina Faso

Abstract
Background and Objective: Malaria is the most widespread of insect-borne diseases. It remained a public health concern worldwide and particularly in Sub-Saharan Africa. Every year, malaria causes several thousand deaths and millions of cases, most of them in children under 5 years. This study aimed to highlight the anti-plasmodial properties of *Combretum micranthum* G.Don and *Combretum adenogonium* Steud. ex A.Rich., extracts used as antimalarial traditionally. **Materials and Methods:** A phytochemical study of the organic and aqueous extracts from leaves and stem bark powder was applied using colorimetric and spectrometric analysis. The antiplasmodial activity of extracts was assessed *in vitro* using chloroquine-sensitive 3D7 and chloroquine-resistant Dd2 strains. The dose inducing 50% inhibition of parasite viability was calculated from the sigmoidal dose-response curve. The statistical significance threshold was set at 5%. **Results:** In 100 mg of extract, the phenolic content was decreased from 47.53 to 20.29 mg GAE, the flavonoid content was from 11.49 to 4.55 mg QE and the flavonol content was from 6.14 to 0.55 mg RE. Interestingly, the aqueous extracts of *C. adenogonium* and *C. micranthum*, corresponding to the traditional mode of extraction, were effective against the CQ-sensitive strains 3D7 with IC_{50} <5 µg/mL and ineffective against the CQ-resistant strains Dd2. Their effects were correlated with phenolics, flavonoids and flavonol contents of extracts. **Conclusion:** The use of *C. adenogonium* as a substitute for *C. micranthum* or a combination of the two plants, could reduce the overexploitation of *C. micranthum* and promote the ecological management. These results could justify the traditional use of these plants to treat malarial fevers.

Key words: *Combretum micranthum* G.Don, *Combretum adenogonium* Steud. ex A.Rich., malaria, traditional medicine, phytochemistry, Burkina Faso

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Corresponding Author: Moussa Compaore, Laboratory of Applied Biochemistry and Chemistry, University Joseph KI-ZERBO, 03 BP 7021 Ouagadougou, Burkina Faso Tel: +22670064742

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Investments in malaria control strategies have contributed to an un-significant reduction in malaria cases and deaths worldwide[1]. Malaria remains an uncontrolled disease and one of the main causes of morbidity and mortality. Some 247 million cases of malaria and 619,000 deaths were recorded worldwide in 2021. The burden of malaria was concentrated in Africa and was associated with poverty. Of all malaria deaths, 87% occur in children under 5 years[1]. The advent of COVID-19 has revolutionized the fight against malaria, particularly in low-income countries[2]. Associated with the emergence of strains resistant to current antiplasmodial treatments, the consequences in terms of public health could be enormous in Africa. Consequently, it was necessary to look for new and more effective sources of antimalarial drugs to offset this risk[1]. Among the various approaches available, the exploration and chemical characterization of existing antimalarial plants represented a valid strategy for the discovery of new antimalarial drugs[3]. In these ways, *Combretum micranthum* and *Combretum adenogonium*, frequently used in malaria treatment, were chosen for this study. Additionally, *Combretum micranthum* was widely used for its many therapeutic properties. The aqueous extract of the leaf was one of the most popular drinks in West Africa[4]. The maceration or decoction of leaves, root bark or stems was used to treat digestive disorders, infections and infestations, nutritional disorders and pregnancy and childbirth disorders[5-7]. Also, *Combretum adenogonium* was known and used in traditional West African medicine for the treatment of various types of illnesses, such as coughs, syphilis, leprosy, diarrhea, hypertension, incurable wounds, snakebite, pain, inflammation, the aging process, jaundice, diabetic and incurable wounds, ulcers, black leg, cancers[6-9]. This work involved evaluating the phytochemical profile and anti-plasmodial potential of the leaves and stem bark of *Combretum micranthum* and *Combretum adenogonium*.

MATERIALS AND METHODS

Study area: The main phytochemical and antiplasmodial activities were carried out from January to July, 2022 in the Applied Biochemistry and Chemistry Laboratory (LABIOCA) and Pharmacognosy Laboratory (CNRFP), Ouagadougou, Burkina Faso.

Biological materials: Leaves and stem barks of *Combretum micranthum* were collected at Gampéla (Coordinates: 12°20'36.6"N, 1°23'43.8"W) on 18 November, 2021 between 10 am and 12 pm. *Combretum adenogonium* was collected at Kougri (Latitude and Longitude: 12.36263 and -1.05177) on 30 November, 2021 between 9 am and 12 pm. Species identification was carried out at the Ecology and Plant Biology Laboratory. These herbarium numbers were 7027 and 7030, respectively. The chloroquine-sensitive 3D7 and chloroquine-resistant Dd2 strains were provided by BEI Resources, National Institute of Allergy and Infectious Diseases (NIAID), NIH, USA.

Chemicals: The RPMI-1640, PBS, Hypoxanthine, Albumax II, HEPES buffer, L-glutamine, Gentamicin, Sodium hydroxide, 3-acetylpyridine adenine dinucleotide, Nitro Blue Tetrazolium, Phenazine ethosulfate, Lithium L-Lactate, Trizma base, Hemin chloride, Sodium chloride, D-sorbitol, Dimethylsulfoxide and Giemsa were supplied from Sigma (Germany). The organic solvents and culture supplies were from Sigma (Belgium).

Extraction: A maceration was carried out with 20 g of each plant material in 200 mL of extraction solvent (Chloroform methanol or distilled water) for 24 hrs at room temperature with mechanical stirring. As 50 g of each sample was also used for a decoction with distilled water for 20 min. The organic extracts were then condensed on a rotary evaporator until dry (lbx instrument, EVA 180; LabBOx, Germany). The aqueous extracts were freeze-dried (ALPHA 1-2 LD plus; Germany).

Phytochemical analysis

Qualitative analysis: The detection of bioactive constituents was evaluated using colorimetric tests. Singularly, saponosides, polyphenols, flavonoids, alkaloids, anthraquinones, coumarin and terpenoids were screened using Ciulei's methods[10].

Quantitative analysis: The total phenolic and total flavonoids were quantified according to the Lamien-Meda *et al.*[11] method. The total phenolic compound content was determined using the standard calibration curve plotted with gallic acid (0-100 mg/mL) and the results were expressed as mg gallic acid equivalent per 100 mg extract (mg GAE/100 mg). The quantities of flavonoids in the bark and leaf extracts were expressed as mg quercetin equivalent per 100 mg extract (mg QE/100 mg). Total flavonols were determined according to the previous method by Almaraz-Abarca *et al.*[12]. The quantities of flavonols in the bark and leaf extracts were expressed as mg rutin equivalent per 100 mg extract (mg RE/100 mg).

Antiplasmodial activities

Parasite growth inhibition: The antiplasmodial activity of medicinal plant extracts was evaluated on 3D7 and Dd2 strains supplied by BEI Resources, National Institute of Allergy and Infectious Diseases (NIAID, NIH, USA). The anti-plasmodial activity of the extracts was evaluated as the inhibition of parasite growth. It was measured through the production of Lactate Dehydrogenase (pLDH) by *Plasmodium*[13]. Parasite growth was determined by measuring the amount of Lactate Dehydrogenase (pLDH) produced. Cultures were maintained in fresh O Rh^+ human erythrocytes at 2% hematocrit in a complete medium (RPMI 1640 with 25 mM HEPES, 2.05 L-Glutamine). This medium was then enriched with 5% mixed human serum or 10% bovine serum. Samples were incubated in a total assay volume of 200 µL (RPMI, 2% hematocrit and 2% parasitemia) for 72 hrs in a humidified atmosphere (5% CO_2, 14% O_2 and 80% N_2) at 37°C in 96-well flat-bottom plates. Duplicate assays were performed for each concentration of each extract. After culturing, the contents of each plate well were gently mixed and transferred to a new plate as follows: 20 µL of each well was transferred to the new plate in the same order, followed by 100 µL of MALSTAT reagent and 25 µL NTB/PES (2-Nitro-5-thiobenzoate). After 15 min incubation at 37°C, the plates were read at 650 nm. Parasitized and non-parasitized O^+ erythrocytes were used as positive and negative controls, respectively.

Cytotoxicity of extracts: The therapeutic property of a medicinal substance is only of value if it has no toxic effects on the host cell. It was therefore a very important parameter that provides a rapid and effective overview of the toxic potential of extracts. Cellular hemolysis is an indicator of the cytotoxicity of bioactive substances. The cytotoxicity of each extract was assessed on human red blood cells according to the method described by Haddouchi *et al*.[14], with slight modification. The concentration of the extracts was 100 µg/mL on a suspension of human blood erythrocytes in PBS (Phosphate buffered saline) pH 7.4 and 20% Triton X-100 was used as a membrane disruptor. In an Eppendorf tube, 5 mL PBS (pH 7.4) was added to 5 mL blood and centrifuged at 2200 rpm at 4°C for 15 min. The resulting supernatant was removed and the process was repeated twice on the pellet. At the end, the final supernatant was removed and the red blood cells (RBC) were diluted to 10% (v/v) in PBS. For the assay, 40 µL of each concentration was added to 760 µL of previously prepared RBCs. A negative control comprising 10 µL of PBS and 190 µL of 10% RBC and a positive control comprising 10 µL of 20% Triton X-100 in distilled water (v/v)+190 µL of 10% RBC were also prepared. Tubes were incubated at laboratory temperature for 60 min followed by centrifugation at 2200 rpm for five min and the supernatants were used for the rest of the experiment. In a 96-well microplate, 150 µL of the supernatant from each concentration and the controls were introduced in triplicate and the absorbances were read at 630 nm. The rate of hemolysis of the various extracts was calculated as a percentage of total hemolysis, using the formula from Haddouchi *et al*.[14]:

$$\text{Hemolysis} = \frac{\begin{array}{c}\text{Absorbance of test-}\\ \text{Absorbance of negative control}\end{array}}{\begin{array}{c}\text{Absorbance from positive control-}\\ \text{Absorbance from negative control}\end{array}}$$

Statical analysis: Excel 2007 spreadsheet (Microsoft office) was employed for data analysis. The percentage of viability was plotted as a function of drug concentrations and the curve fitting was obtained by Nonlinear Regression analysis using a four-parameter logistic method (software Gen5 1.10 provided with the Synergy plate reader [Biotek]). The IC_{50}, which is the dose capable of inducing 50% inhibition of parasite viability, was calculated from the sigmoidal dose-response curve. At least three experiments in duplicate were performed with each investigated parasite stages and/or strains. Data comparison was performed by analysis of variances (One way-ANOVA) using XLSTAT 2019. Values of $p<0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

Phytochemical constituents: Plants were the most important source of substances used in therapy[15]. In Burkina, more than 1000 medicinal plants were used and in the central "Plateau" more than 350 plants[5,15]. Annually, a hundred herbal medicines (category 1) were authorized by the National Pharmaceutical Regulation Agency[16,17]. This promotion of traditional medicine required better phytochemical and pharmacological knowledge of the plants used[18,19]. The preliminary phytochemical screening was shown in Table 1. It was revealed that several phytochemical families with antiplasmodial properties belong. Flavonoids, steroids, saponosides, anthraquinones, alkaloids, polyphenols, terpenes and tannins were detected in leaves and stembark extracts of two plants. These observations were similar to the previous data from the leaves extract of *C. adenogonium*, except for the presence of anthraquinones[20]. Remarkably, *C. adenogonium* was distinguished by the presence of a polar to polar alkaloids in all extracts of leaves and stem bark. The alkaloids were detected in *C. adenogonium* leaves extract, contrary to previous data[20-22]. However, the tests were negative for coumarins, perhaps due to the limits of extraction and/or analysis methods used.

Table 1: Phyto-actives constituents of extracts

Samples	Extracts	Saponosides	Polyphenols	Flavonoids	Alkaloids	Anthraquinone	Coumarin	Terpenoids
Combretum micranthum (stem bark)	Aqueous decoctate	+	+	+	-	+	-	+
Herbarium ID 7027	Aqueous macerate	+	+	+	-	+	-	+
	Methanolic	-	+	-	-	-	-	-
	Chloroformic	+	+	+	+	+	-	+
Combretum micranthum (leaves)	Aqueous decoctate	+	+	+	-	+	-	+
Herbarium ID 7027	Aqueous macerate	+	+	+	+	+	-	+
	Methanolic	+	+	+	-	+	-	+
	Chloroformic	+	+	+	+	+	-	+
Combretum adenogonium (stem bark)	Aqueous decoctate	+	+	+	+	+	-	+
Herbarium ID 7030	Aqueous macerate	+	+	+	+	+	-	+
	Methanolic	-	+	-	+	-	-	-
	Chloroformic	-	+	-	+	-	-	-
Combretum adenogonium (leaves)	Aqueous decoctate	+	+	+	+	+	-	+
Herbarium ID 7030	Aqueous macerate	+	+	+	+	+	-	+
	Methanolic	+	+	+	+	+	-	+
	Chloroformic	+	+	+	+	+	-	+

+: Detected and -: Undetected

Table 2: Polyphenolic contents of extracts

	Phenolic content (mg GAE/100 mg)		Flavonoid content (mg QE/100 mg)		Flavonols content (mg RE/100 mg)	
	C. micranthum	*C. adenogonium*	*C. micranthum*	*C. adenogonium*	*C. micranthum*	*C. adenogonium*
Leaves extract						
Methanolic	47.53 ± 0.19^{i}	43.10 ± 0.08^{h}	11.49 ± 0.27^{g}	5.30 ± 0.14^{b}	6.14 ± 0.11^{g}	1.50 ± 0.11^{abc}
Aqueous decoctate	27.01 ± 041^{c}	34.95 ± 0.09^{f}	5.67 ± 0.14^{bc}	4.55 ± 0.28^{a}	1.69 ± 0.18^{bcd}	3.15 ± 0.11^{ef}
Aqueous macerated	24.20 ± 0.07^{b}	28.52 ± 0.29^{d}	7.38 ± 0.08^{e}	6.99 ± 0.03^{de}	2.34 ± 0.26^{cde}	2.45 ± 0.19^{cde}
Stembark extract						
Methanolic	47.82 ± 0.25^{i}	32.90 ± 0.09^{e}	7.27 ± 0.05^{de}	9.96 ± 0.27^{f}	2.68 ± 0.34^{def}	3.59 ± 0.30^{f}
Aqueous decoctate	37.55 ± 0.07^{g}	32.37 ± 0.04^{e}	10.21 ± 0.06^{f}	6.80 ± 0.11^{d}	5.50 ± 0.54^{g}	1.00 ± 0.25^{ab}
Aqueous macerated	37.14 ± 0.25^{g}	20.29 ± 0.07^{a}	5.88 ± 0.18^{c}	5.86 ± 0.11^{c}	2.53 ± 0.40^{cde}	0.55 ± 0.07^{a}

Values with different letters (a, b, c, d, e, f, g and h) in the same type of metabolite content were statistically different (p-value <0.0001)

Table 3: Antimalarial and cytotoxicity effects

	3D7 (IC_{50})*		Dd2 (IC_{50})		Cytotoxicity (%)**	
	C. micranthum	*C. adenogonium*	*C. micranthum*	*C. adenogonium*	*C. micranthum*	*C. adenogonium*
Leaves extract						
Methanolic	30.31 ± 5.80	26.87 ± 6.70	ND	ND	1.43 ± 0.02	1.46 ± 0.02
Chloroformic	22.12 ± 0.00	15.93 ± 9.60	>50	>50	1.46 ± 0.02	1.47 ± 0.02
Aqueous decoctate	28.75 ± 1.59	4.47 ± 3.80	ND	ND	1.46 ± 0.02	1.47 ± 0.01
Aqueous macerated	49.38 ± 4.29	>50	ND	>50	1.46 ± 0.02	1.46 ± 0.02
Stembark extract						
Methanolic	>50	27.28 ± 9.70	ND	>50	1.46 ± 0.02	1.47 ± 0.02
Chloroformic	7.98 ± 0.00	17.79 ± 5.60	>50	>50	1.47 ± 0.01	1.46 ± 0.02
Aqueous decoctate	03.07 ± 2.01	02.66 ± 1.40	ND	ND	1.45 ± 0.02	1.47 ± 0.01
Aqueous macerated	39.81 ± 17.80	27.43 ± 2.20	ND	ND	1.45 ± 0.02	1.48 ± 0.01

*Antiplasmodial activity (IC_{50}) of all extracts were statistically unequal for p-value <0.05, **Hemolytic powers of all extracts are statistically equal for p-value <0.0001 and ND: Not determinated

Table 2 shows the total polyphenol, flavonoid and flavonol contents of the extracts. According to this data, in 100 mg of extract, the phenolic content was decreased from 47.53 to 20.29 mg GAE, the flavonoid content was from 11.49 to 4.55 mg QE and the flavonol content was from 6.14 to 0.55 mg RE. It was found that the methanol solvent was the best solvent for extracting metabolites. Interestingly, aqueous extracts (decoction), which were the extraction model in traditional medicine and organic extract possessed similar content of phenolic compounds from the stembark of *C. adenogonium*. In general, *C. micranthum* extracts contained more phenolic, flavonoid and flavonols than *C. adenogonium* extracts, except aqueous extracts from *C. adenogonium* leaves, which presented the best content. The phytoconstituent level in leaf extracts from *C. adenogonium* was more than the stembark phytoconstituent level found previously by Ouoba *et al.*[20]. In recent studies, it was found that *C. micranthum* contained polyphenolic compounds[8,23].

Antiplasmodial activity and hemolytic extracts: Nowadays, the development of resistance of plasmodium to drugs has become recurrent[1,24]. Thus, the discovery of new antimalarials and the development of new alternatives have become urgent[1,24]. The antiplasmodial activity and cytotoxicity of the various extracts are shown in Table 3. The different extracts were non-cytotoxic and did not inhibit Dd2 growth (IC_{50} >50 µg/mL). The highest antiplasmodial activity was found in the decoctate of *C. micranthum* stem bark (IC_{50} = 3.07±2.01 µg/mL), the decoctate of *C. adenogonium* stem bark (IC_{50} = 2.66±1.4 µg/mL) and leaves (IC_{50} = 4.47±3.8 µg/mL). The aqueous macerate of *C. adenogonium* leaves and the methanolic extract of *C. micranthum* barks were non-active on plasmodial strains with IC_{50} >50 µg/mL. All the other extracts showed moderate antiplasmodial activity (15 µg/mL<IC_{50}<50 µg/mL). The chloroquine with 14.98±3.03 ng/mL was more active than all extracts. Interestingly, the aqueous extracts (maceration and decoction), the traditional mode of extracting, presented the best antiplasmodial effect. The 3D7 growth inhibition by *C. micranthum* extract could partially support the *in vivo* antimalarial data from previous studies by Namadina *et al.*[25]. Additionally, 3D7 growth inhibition by *C. adenogonium* could complete the antimalarial found in K1 growth inhibition[26]. These pharmacological data found in this study could be from the presence of an amount of active compounds[8,9].

The cytotoxic study revealed very weak hemolytic properties against isolated red blood cells. Cytotoxicity towards red blood cells showed values around zero for all extracts at a concentration of 100 µg/mL (Table 3). These results support a toxicity study that showed non-toxicity of an oral dose of up to 5000 mg/kg of *Combretum micranthum* leaf extracts in rats[27]. The level of risk assessed in this study supported the use of these plants in traditional medicine.

According to Ouédraogo *et al.*[28], evaluations *C. micranthum* were a threatened species since 2018[28]. This was due to the overexploitation of Kinkeliba across West Africa[8,29-31]. The presented findings suggested that *Combretum adenogonium* could be used in supplying to contribute to the good management of *C. micranthum*.

CONCLUSION

The present study provided an overview of the phytochemical profile and anti-plasmodial properties of extracts from *Combretum adenogonium* and *Combretum micranthum*, used in the treatment of malaria. The results showed that both the barks and leaves of the plants contained numerous and diverse bioactive substances with pharmaceutical interest. The *in vitro* study of the antiplasmodial activity and cytotoxicity of each leaf and stem root extract showed a wide range of activity, from non-active to highly active against plasmodial strains. Of all the plant extracts evaluated, decoctions from two plants and *Combretum micranthum* leaves were the most active on asexual forms of *Plasmodium falciparum* strain 3D7.

SIGNIFICANCE STATEMENT

The objective was to develop an alternative for the safe production of Kinkéliba, whose main ingredient was disappearing. The results showed that *Combretum adenogonium* leaves were as usable as those of *Combretum adenogonium* in the management of malaria. The use of *Combretum adenogonium* as a substitute for *Combretum micranthum* or a combination of the two plants, could reduce overexploitation of *Combretum micranthum* and promote ecological plant management. The production of antimalarial drinks was also guaranteed. These results are very useful for traditional healers in Burkina Faso.

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