The Journal of Phytopharmacology 2024; 13(6):458-463
Online at: www.phytopharmajournal.com

Research Article

ISSN 2320-480X
JPHYTO 2024; 13(6): 458-463
November- December
Received: 18-09-2024
Accepted: 24-12-2024

doi: 10.31254/phyto.2024.13606

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In vitro evaluation of the antiplasmodial activity and phytochemical screening of five plants extracts from the traditional pharmacopoeia in Côte d'Ivoire

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ABSTRACT

The resistance of *Plasmodium falciparum* to current antimalarial drugs, namely artemisinin derivatives associated with a partner molecule, requires the search for new therapeutic alternatives through traditional pharmacopoeia, rich in medicinal plants. The aim of this study is to assess the in vitro anti-plasmodial activity of leaf extracts from five plants selected for their traditional use against malaria. An ethnopharmacological survey was carried out in Agboville to identify plants traditionally used against malaria in this region. The leaves of these plants were harvested, dried and extracted using aqueous and hydroethanolic solvents. The extracts obtained were then subjected to an in vitro anti-plasmodial test using SYBR GREEN to assess their ability to inhibit the growth of *Plasmodium falciparum*. Phytochemical screening and high-performance liquid chromatography-mass spectrometry (LC-MS) was carried out to identify the chemical compounds present in the extracts. In total, ten extracts from the dried leaves of five plants were tested on clinical isolates of *Plasmodium falciparum*. Of these, only *Momordica charantia* extracts showed an $IC_{50} \leq 5$ µg/ml, namely 1.93 µg/ml for the hydroethanolic extract and 4.35 µg/ml for the aqueous extract. The anti-plasmodial activity of these extracts was described as powerful. Extracts from other plants showed IC_{50} values ranging from 16.19 µg/ml to 31.43 µg/ml, indicating moderate anti-plasmodial activity. Phytochemical analyses mainly revealed the presence of flavonoids, alkaloids, polyterpenes and phenolic acids, suggesting that these compounds may be responsible for the anti-plasmodial activity observed. In conclusion, the search for natural products capable of blocking the transmission of malaria must be pursued with determination, and further studies are needed before the formulation of phytomedicines from these plants can be envisaged.

Keywords: Antimalarial, *Momordica charantia*, *Paquetina nigescens*, Plasmodium falciparum, Côte d'Ivoire.

INTRODUCTION

Malaria remains one of the major parasitic diseases in the world, causing considerable morbidity and mortality, mainly in sub-Saharan Africa. In 2022, the World Health Organization (WHO) recorded 249 million cases of malaria, including approximately 609,200 deaths [1]. In Côte d'Ivoire, as in many other African countries, malaria remains endemic, mainly affecting the most vulnerable populations such as children under five and pregnant women [2,3]. Efforts to control and eradicate malaria have intensified in recent decades, with the introduction of dual therapy combining an artemisinin derivative with a partner molecule and the introduction of prevention measures such as long-acting insecticide-treated nets (LLINs) [4-8]. However, the emergence and spread of resistance to antimalarial drugs, particularly artemisinin derivatives, is hampering these efforts and reinforcing the urgent need to find new therapeutic alternatives [9]. Faced with this challenge, medicinal plants, which have been used for centuries by local populations to treat various diseases, including malaria, represent a promising source of new bioactive molecules [10-13]. In Côte d'Ivoire, there is a tradition of using plants to treat malaria. However, scientific studies to validate the efficacy of these plants from a pharmacological, chemical and toxicological point of view are still lacking [14,15]. Based on an ethnopharmacological survey conducted in the Agboville region, five plants were selected. These were *Parquetina nigrescens* (Wennberg) Bullock, *Momordica charantia* L, *Tapinanthus bangwensis* (Engl. & Krause) Danser, *Anthonotha macrophylla* P.Beauv and *Trichilia monadelpha* (Thonn.) J.De Wild. These plants are commonly used to treat a range of conditions including diabetes, parasitic, bacterial and fungal infections, hypertension, asthma, epilepsy, cancer, yellow fever and dysentery [14,16]. There are many issues at stake in this study. On the one hand, it could lead to the discovery of new antimalarial drugs from Côte d'Ivoire's biodiversity to strengthen the available therapeutic arsenal, and on the other, it could preserve and enhance local traditional knowledge by supplementing it with scientific evidence. Ultimately, these investigations should lead to the development of effective and well-tolerated phytomedicines that could

be incorporated into malaria treatment and control strategies. The aim of this work is to screen plant extracts and select those with good activity against *Plasmodium falciparum*, in order to carry out further investigations leading to the development of an improved traditional medicine.

MATERIALS AND METHODS

Fresh leaves of *Parquetina nigrescens* (Wennberg) Bullock, *Momordica charantia* L., *Tapinanthus bangwensis* (Engl. & Krause) Danser, *Anthonotha macrophylla* P.Beauv and *Trichilia monadelpha* (Thonn.) J.De Wild were collected in Agboville from march 2022 to April 2022 (Figure 1). After identification at the National Floristic Center and a sample deposit at the herbarium, plant samples were air dried in shade at room temperature and ground into powder. Two times 100g of the powder were macerated respectively in 1L of distilled water and 1L of 70% ethanol hydroalcoholic solvent using a blender. Macerates were filtered twice on hydrophilic cotton and once on Whatmann filter paper. Filtrates were evaporated through rotary vacuum evaporator and dried in an oven at 45 ºC for 48 h to obtain aqueous and hydroethanolic extracts which were stored at 4 ºC for further use [17,18]. The activity of crude extracts or pure compounds tested *in vitro* on *P. falciparum* is expressed in µg/mL IC_{50} (inhibitory concentration of 50%), for crude extracts and nM for pure compounds. The antiplasmodial activity of the extracts and of the pure compounds was determined according to the following standards: CI_{50} > 50 µg/mL, inactive crude; 15 µg/mL < IC_{50} < 50 µg/mL, moderate effect; 5 µg/mL < IC_{50} < 10 µg/mL, promising effect; CI_{50} < 5 µg/mL, strong effect [19,20].

Malaria parasites

Informed consent was obtained from all patients in this study prior to clinical isolates collection. Fresh clinical isolates of *Plasmodium falciparum* were obtained from symptomatic patients at the Urban Health Unit (FSU-COM) of Anonkoua Kouté in the district of Abobo (Abidjan). The parasites were cultivated and maintained continuously in a human type O positive erythrocyte according to the method described by Trager and Jensen [21].

Determination of antiplasmodial activity

Clinical isolates and reference strains of *Plasmodium falciparum* were cultured in O^+ human red blood cells in RPMI 1640 medium (Roswell Park Memorial Institute) in the presence of different concentrations of extracts from these plants. The extracts were tested at different concentrations (1.56 -100 µg/mL) and added in duplicate to the wells of the culture plates. The reagents and culture medium were then prepared and samples collected (GE and FS positivity with a parasite density of between 0.1 and 0.3%). Preparation of the drugs to be tested (10 mg extract in 10 mL distilled water) and treatment of the parasitized red blood cells (GRP). Preparation of the inoculum (the haematocrit level was set at 5% with 0.6 mL of blood and 11.4 mL of RPMI culture medium, giving 12 mL of inoculum for a 96-well plate). The culture plates were incubated at 37°C in an oven with 5% CO_2 for 72 hours. SYBER GREEN spectrofluorimetry was used to assess inhibition of plasmodial growth. The 50% inhibitory concentration (IC_{50}) was then determined by analysing non-linear regression curves using WWARN's IVART software [22,23].

Phytochemical Screening

Detection of major chemical groups was carried out according to the analytical techniques described by Bagheri *et al*. (2020) [24] and Khan *et al*. (2022) [25]. Phytochemical groups sought are essentially sterols, polyterpenes, alkaloids, tannins, polyphenols, flavonoids, quinones and saponins.

Sterols and polyterpenes

Extracts (0.1 g) were dissolved in 1 mL of hot acetic anhydride in a capsule. The resulted solutions were poured and added with 0.5 mL H_2SO_4. A violet coloration that turned in blue, and then in green revealed triterpenes.

Polyphenols

A drop of alcoholic solution of 2% ferric chloride was added to 2 mL of extracts. A blue-blackish to green darkish coloration indicated a positive reaction.

Flavonoids

In a tube containing 3 mL of extract, a few drops of 10% NaOH were added. Appearance of yellow-orange color indicated the presence of flavonoids.

Catechic tannins

Two milliliters of water and few drops of 1% ferricchloride were added to 1 mL of extract. The appearance of a blue, blue- black or black coloration indicated the presence of gallic tannins, the green or dark presence of catechic tannins.

Gallic tannins

Previous solution was filtered and saturated with sodium acetate. Addition of 3 drops of 2% FeCl3 causes appearance of an intense blue-black color denoting gallic tannins presence.

Quinonic substances

An aliquot (0.1 g) of extract was dissolved in 5 mL of diluted HCl (1/5) and heated in a boiling water bath for 30 minutes, and then extracted with 20 mL of CHCl3 after cooling. To the organic phase was added 0.5 mL of 50% NH4OH diluted solution. The positivity of the reaction was indicated by a red to violet color.

Alkaloids

Two drops of Bouchard's reagent (reagent of iodine-iodide) were added to 1 mL of each extract. A red-brown precipitate indicated a positive reaction.

Saponins (foam index)

Samples (0.1 g of dry extract) were dissolved in 10 mL of distilled water. The samples were shaken vigorously up and down for 30-45 seconds and then left for 15minutes. The height of the foam was measured. Persistent foam for more than 1 cm high indicated the presence of saponins.

LC-MS protocol

Phytomolecules were analysed using the high-performance liquid chromatography-mass spectrometry (LC-MS) technique [26,27]. Column chromatography was carried out using two glass columns of different sizes. In practice, the silica powder was suspended in a solvent and then poured down the column to the desired height. After stabilising the silica gel, the crude extract was dissolved in acetone and ethyl acetate and deposited at the top of the column. The brown precipitate was fractionated with the hexane/ethyl acetate ($CH_3(CH_2)_4CH_3$ /AcOET) solvent system (90-10 to 0-100) for gradient elution. Bio-guided purification was carried out using a hexane/ethyl acetate ($CH_3(CH_2)_4CH3$ /AcOET) elution gradient (90-10 to 0-100). The molecules were therefore more or less easily carried away by the solvent, depending on their affinity for it. Finally, the fractions were collected in test tubes, then thin layer chromatography (TLC) was carried out to bring together the different tubes forming each molecule. The fractions were then concentrated in a rotary evaporator. The structure of the purified bioactive compounds was

determined using spectroscopic methods, namely mass spectrometry (MS). Mass spectra were performed on the BRUKER MAXIS II ETD with electrospray ionisation at a voltage of 5200 Ev in positive mode. The mass spectra were analysed using Compass Data Analysis 4.3 software.

Statistical analysis

Graphics were performed using Graphpad prism 5 software (Microsoft, San Diego California, USA). All values were expressed as mean ± Standard of deviation. Data analysis were performed using one way analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparisms test using Graphpadinstat® software. Values were statistically significant at $p<0.05$.

Ethical approval

The patient's selections were carried out in accordance with the provisions of the Helsinki Declaration of 1964, revised in 2013 and the relevant regulatory provisions. All the study participants were well informed about the purpose, nature, and outcomes of the study prior to the process of getting informed consent forms. A consent form was signed by them before any inclusion in the study.

RESULTS

Extraction yield

Aqueous and hydroethanolic extracts were prepared from the fine powder of each plant to obtain ten extracts. Table 1 shows a yield of 26.72%, 13.76% and 25.36% for the aqueous extracts of *Mormordica charantia*, *Parquetina nigrescens* and *Trichilia monadelpha* compared with 21.64%, 8.76% and 18.42% for the hydroethanolic extracts.

In vitro antiplasmodial tests

The best results were obtained with *M. charantia* with an IC_{50} = 4.35 ± 1.4 µg/mL for the aqueous extract and IC_{50} = 1.93 ± 0.56 µg/mL for the hydroethanolic extract, followed by *P. nigrescens* with an IC_{50} = 19.06 ± 3.2 µg/mL for the aqueous extract and IC_{50} = 19.19 ± 2.4 µg/mL for the hydroethanolic extract, and *T. monadelpha* with an IC_{50} = 29.5 ± 2.2 µg/mL for the aqueous extract and IC_{50} = 28.89 ± 3.2 µg/mL for the hydroethanolic extract (Table 2). In addition, IC_{50} values of 21.93 µg/mL and 28.44 µg/mL were observed for the aqueous extracts of *T. bangwensis* and *A. macrophylla*, and IC_{50} values of 31.43 µg/ml and 19.46 µg/ml for the hydroethanolic extracts.

Phytochemical socreening

Phytochemical sorting of the extracts showed results that varied from one plant to another. They were rich in flavonoids, polyphenols, alkaloids and polyterpenes but low in gall tannins. Generally speaking, extracts from the five plants are rich in secondary metabolites (Table 3). High-performance liquid chromatography coupled to mass spectrometry (LC-MS) confirmed the presence of flavonoids, alkaloids, phenolic acids and terpenoids in extracts from *M. charantia*, while extracts from *P. nigrescens* showed a good presence of terpenoids and diterpenoids, alkaloids and phenolic acids. The presence and abundance of these compounds make these plants ideal sources of antimalarial drugs and/or antioxidants.

Table 1: Yields of aqueous and hydroethanol extractions

Plants	Organs	Extracts	Yield (%)
Parquetina nigrescens (Wennberg) Bullock	Leaves	Aqueous	26.72%
		Ethanolic	21.64%
Momordica charantia L.	Leaves	Aqueous	13.76%
		Ethanolic	8.76%
Tapinanthus bangwensis (Engl. & Krause) Danser	Leaves	Aqueous	11.86%
		Ethanolic	7.71%
Anthonotha macrophylla P.Beauv.	Leaves	Aqueous	9.65%
		Ethanolic	6.46%
Trichilia monadelpha (Thonn.) J.De Wild	Leaves	Aqueous	25.36%
		Ethanolic	18.42%

Table 2: *In vitro* sensitivity testing of *Plasmodium falciparum* to plant extracts

		IC_{50} (µg /mL) or nM						
Plant	Code	IS1	IS2	IS3	IS4	IS5	IS6	IC_{50} mean
TRI	TRI_{aq}	1.53	45.63	3.19	13.12	82.58	30.96	29.50
	TRI_{he}	3.48	46.16	3.13	13.17	72.36	35.02	28.89
TAP	TAP_{aq}	2.9	50.78	1.53	12.1	ND	ND	21.93
	TAP_{he}	9.57	65.29	13.99	14.98	77.52	7.21	31.43
MOM	MOM_{aq}	1.45	2.86	1.51	14.41	ND	1.54	4.35
	MOM_{he}	2.29	2.92	1.4	1.57	ND	1.46	1.93
PAR	PAR_{aq}	69.29	ND	11.6	11.51	1.35	1.55	19.06
	PAR_{he}	83.88	6.2	0.92	3.28	1.34	1.53	16.19
ANT	ANT_{aq}	73.22	7.3	1.4	23.43	63.8	1.48	28.44
	ANT_{he}	18.98	8.95	15.83	18.53	45.51	8.95	19.46
LUM		584.26	13.2	595.25	26.42	486.21	110.07	302.57
QUIN		603.64	24.9	556.7	71.25	135.49	12.28	234.04

ND : not determined; **TRI** : *Trichilia monadelpha* ; **TRI_{aq}**= aqueous extract of TRI ; **TRI_{he}**= hydroethanolic extract of TRI; **TAP** : *Tapinanthus bangwensis* ; **TAP_{aq}**= Aqueous extract of TAP; **TAP_{he}**= hydroethanolic extract; **MOM** : *Momordica charantia* ; **MOM_{aq}**= Aqueous extract of MOM ; **MOM_{he}**= hydroethanolic extract; **PAR** : *Parquetina nigrescens* ; **PAR_{aq}**= Aqueous extract of PAR ; **PAR_{he}**= hydroethanolic extract of PAR ; **ANT** : *Anthonota macrophylla* ; **ANT_{aq}**= Aqueous extract of ANT ; **ANT_{he}**= hydroethanolic extract of ANT.

Table 3: Phytochemical Screening

Plants	Extracts	Alkaloids		Sterols Et Polyterpenes	Polyphenols	Flavonoids	Quinones	Saponosides	Tannins	
		B	D						Cat	Gal
PAR	PAR_{aq}	+ +	+ +	+	+	+	+	-	+	-
	PAR_{he}	+ +	+ +	+ +	+ +	+ +	+	-	+ +	-
MOM	MOM_{aq}	+ +	+ +	+ +	+	+	+	+ +	+	-
	MOM_{he}	+ +	+ +	+ +	+	+	-	-	-	-
TAP	TAP_{aq}	+	+	+ +	+	+	+	+	-	-
	TAP_{he}	+	+	+ +	+ +	+	+ +	+ +	-	-
ANT	ANT_{aq}	+ +	+ +	+ +	+ +	+ +	+	+ +	+	-
	ANT_{he}	+ +	+ +	+ +	+ +	+ +	+	+ +	+	-
TRI	TRI_{aq}	+ +	+ +	+	+ +	+ +	+ +	+ +	+	-
	TRI_{he}	+ +	+	+ +	+ +	+	+	-	+ +	-

TRI : *Trichilia monadelpha* ; **TAP** : *Tapinanthus bangwensis* ; **MOM** : *Momordica charantia* ; **PAR** : *Parquetina nigrescens* ; **ANT** : *Anthonota macrophylla* ; +++=abondance ; ++=présence ; -=abscence

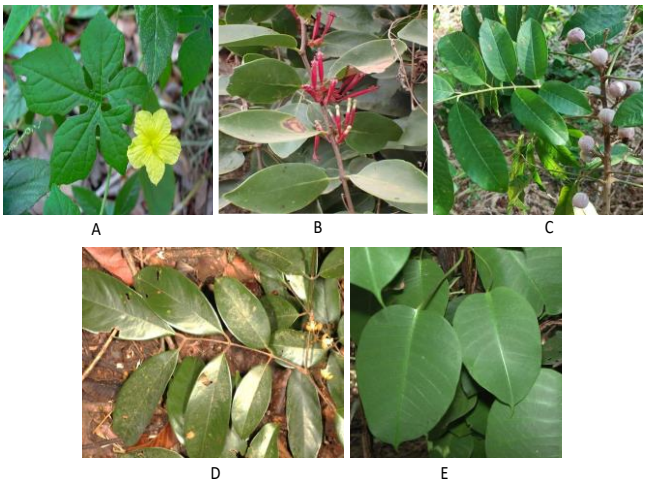

Figure 1: Pictures of fresh leaves from selected plants. a- *Momordica charantia* (Cucurbitaceae), b- *Tapinanthus bangwensis* (Loranthaceae), c- *Trichilia monadelpha* (Meliaceae), d- *Anthonota macrophyla* (Caesalpinaceae), e- *Parquetina nigrescens* (Periplocaceae)

DISCUSSION

These results indicate that aqueous extracts have a better yield compared to extracts. These same observations were made by Houngbedji *et al* (2015) [2] who showed that aqueous extracts had a better yield compared to hydroethanolic extracts. The extraction yield allowed a better appreciation of the quantity of total extracts that can be extracted from each species and to consider the quantity of organs to be sampled if needed for a similar study.

With a view to selecting the most active extracts, the maximum inhibitory concentration 50% (IC_{50}) was set at 50 µg/. Under these conditions, the tests were unable to select extracts with an IC_{50} greater than 50 µg/mL. On the basis of these results, the activities of *M. charantia* extracts are said to be potent, and moderate for extracts of *P. nigrescens, T. monadelpha, T. bangwensis* and *A. macrophylla*, according to the standards for classifying the activity of plant drugs mL [28,19,20]. The antimalarial activity is thought to be due to the presence of alkaloids, as the majority of antimalarial molecules are from this chemical family. In addition, various studies have shown that polyphenols have antioxidant potential, and this antioxidant activity is thought to be due to the ability of these compounds to trap free radicals and chelate metal ions [29]. Terpenoids and tannins are thought to have analgesic and anti-inflammatory activities. Phenolic compounds are recognised for their properties against various pathologies, including parasitic diseases and atherosclerosis, and also as natural antioxidants to combat cell ageing [30,31]. Lumefantrine and quinine, used as reference molecules, gave IC_{50} values of 302.57 ± 5.2 nM and 243.04 ± 4.3. The plasmodial isolates showed good sensitivity to the reference molecules. These results are similar to those found in the literature [32]. In addition, studies by Johnson et al. (2016) [33] and Duquesne (2006) [34] showed the presence of steroids, alkaloids, flavonoids and triterpenes in *M. charantia* extracts. The anti-plasmodial activity observed with *M. charantia* extracts is better than those reported by Menan in 1997, who found IC_{50}s ranging from 7 µg/ml to 23 µg/ml [35]. Several studies have been carried out on *Parquetina nigrescens*, as this plant is widely used in traditional pharmacopoeia in many African countries, including Ghana, Nigeria and Senegal [36]. Studies on its pharmacological activities have shown that the plant has antioxidant, anti-inflammatory, haematological, cytotoxic, antimicrobial, antipyretic, sympathomimetic, uterotonic, haematopoietic, analgesic and antiulcerogenic properties [37,38]. Other studies involving phytochemical screening of the ethanolic extract of the leaf and stem of *Parquetina nigrescens* revealed the presence of flavonoids, saponins, terpenoids and cardiac glycosides, alkaloids and are consistent with our data [39,40]. Another study conducted on albino Wistar rats reported that the aqueous extract of *P. nigrescens* leaves reduced parasitaemia by 86% after an 18-day treatment of infected animals. Anti-anaemic properties were also attributed to this plant by Gui et al. (2019**)** [41] and that gavage of Wistar rats at doses of 2000 mg/kg and 2500 mg/kg bw increased haemoglobin and red blood cell count while decreasing red blood cell count. Extracts of *T. monadelpha*, *T. bangwensis* and *A. macrophylla* contain saponosides, quinones and flavonoids, compounds known to have a wide range of pharmacological properties. Saponosides are known for their ability to disrupt the cell membranes of parasites, leading to their lysis. Flavonoids play a role in inhibiting enzymes essential to cell metabolism, while quinones are responsible for the free radicals that

damage Plasmodium cells. However, the absence of catechic tannins in *T. bangwensis* does not appear to significantly affect anti-plasmodial activity, suggesting that these compounds have no direct anti-plasmodial activity. The pharmacological activities observed indicate that these extracts have the same molecular targets on the parasite.

CONCLUSION

The results of anti-plasmodial tests and phytochemical screening partly explain the enthusiasm of traditional practitioners for using these plants as antimalarial agents. The therapeutic activities are thought to be induced by various chemical compounds such as alkaloids, flavonoids, polyphenols, polyterpenes, saponosides, sterols and catechic tannins, which form the scientific basis for the traditional therapeutic use of the plants studied. *In vivo* studies and the biotolerance of these crude extracts will enable us to deepen our scientific knowledge of these plants before considering their formulation as phytomedicines.

Conflict of interest

The authors declared no conflict of interest.

Financial Support

None declared.

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HOW TO CITE THIS ARTICLE
Alfred KA, Abibatou KT, Dominique TK, Jeanne KA, Brice BK. *In vitro* evaluation of the antiplasmodial activity and phytochemical screening of five plants extracts from the traditional pharmacopoeia in Côte d'Ivoire. J Phytopharmacol 2024; 13(6):458-463. doi: 10.31254/phyto.2024.13606