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Review Article

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African Traditional Antimalarials: A Review

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Abstract Traditional herbal medicines have been used to treat malaria for thousands of years in various parts of the world especially Africa. This review addresses medicinal plants used to treat malaria in traditional medicine from many Africa countries and compare popularly used native species, antimalarial activity of extracts and isolated substances. New drugs have to be developed to replace those compromised by parasite resistance. The identification of novel anti-malaria pharmacophores requires the scientific evaluation of relevant medicinal plants used in traditional health care.

Keywords Africa, medicinal plants, traditional antimalarial, *Plasmodium falciparum*

Introduction

Malaria remains a major public health problem in the world and Africa is said to be having the highest burden of malaria, this is due to the fact that *Plasmodium falciparum* (which is the most deadliest specie) occurs more in Africa and have led to an increased mortality rate (of about 600,000 deaths yearly) as well as morbidity[1]. It has been estimated that out of the over one million deaths caused by malaria world-wide, 90% occur in sub-Saharan Africa [2]. It is a public health problem of global concern because of its high economic burden on the nation, high prevalence of mortality in children, pregnant women and non-immune individuals [3]. The rapid increase of resistance to most of the available antimalarial drugs, as well as resistance of vectors to insecticides [4] led to the reemergence of malaria in many parts of the world. Drug resistant strains of *P. falciparum* have been found in many endemic areas of the world and the well-known chloroquine (CQ) and antifolates [sulfadoxine-pyrimethamine (S/P)] have been associated with treatment failure. This is also compounded by the difficulty of creating efficient vaccines and also adverse side-effects of the existing antimalarial drugs, this highlights the urgent need for novel, well-tolerated antimalarial drugs [5] for both prophylaxis and treatment of malaria. Plant-derived compounds played crucial roles in drug discovery and development for the treatment of malaria, the isolation of new bioactive compounds from medicinal plants based on traditional use or ethnomedical data appears to be a very promising approach [6, 7].

In WHO therapeutic schemes for malaria treatment, 11 antimalarial drugs are natural products or their analogues or were design-based on the pharmacophores from natural products [8]. Traditional medicines continue to be natural, cheaper and most affordable means of treatment methods for malaria and they have also proven to be a source of major drug lead for synthetic counterpart. Therefore this review focuses on medicinal plants used in traditional medicine in the treatment of malaria infections in some countries of the community of Africa, which includes Nigeria, Cameroon, Ghana, Kenya, Mali, Tanzania, Uganda, and involved the comparison of popularly used antimalarial activity of extracts and isolated substances and may be some of these plant metabolites could be used as templates for designing new derivatives with improved properties.

Traditional Treatment of Malaria

The use of traditional antimalarial drug plays an important role in daily health care in Africa, herbal remedies are even preferred to modern medicines in both urban and rural areas of Africa community. Traditional antimalarial drugs are commonly sold in markets and public places or administered by healers in traditional clinics [9, 10] Whole plants or parts of them are prepared and administered as oral decoction, steam baths, infusion or enema. Most remedies are a concoction of two or more plant species and solvents used include water, palm wine or oils [11].

Africa has as much as three hundred thousand medicinal plants, [12], approximately 80% of population in Africa use traditional medicines in primary health care, including 40,000-70,000 medicinal plants, approximately 20% of all higher-plant species [13].

For many years, traditional medicine has proven to be the surest source of effective antimalarial, the alkaloid quinine was extracted from the bark of cinchona, and this was the first antimalarial drug used by the inhabitants of Peru to control malaria. Three other antimalarial compounds, namely, quinidine, cinchonine, and cinchonidine had also been isolated from this plant. [14] Quinine served as a lead structure for the synthesis of several antimalarial drugs such as chloroquine, mefloquine, pyrimethamine, proguanil, atovaquone (sold together with proguanil as "Malarone"), or primaquine. Quinine (alone or in combination with doxocycline, tetracycline or clindamycin) is still used today to treat acute cases of severe *P. falciparum* infections [15].Another plant-based antimalarial drug isolated from the Chinese plant *Artemisia annua* in seventies [16].World Health Organization recommended the use of artemisin in based combination therapy (ACT) for the treatment of uncomplicated malaria in endemic regions of the world since ACT greatly reduced the morbidity and mortality due to acute severe malaria in endemic Africa countries [17]. Currently available ACT has some limitations which include high cost beyond what the average African rural dweller can afford, unavailability of the raw materials and toxicity [18]. Clinical resistance to these combinations has been recently reported in Cambodia [19], suggesting that *P. falciparum* parasites have already developed the ability to grow in the presence of these antimalarials, which strongly suggests the need for further research into new antimalarials.

African Medicinal Plants for Malaria Treatment

African traditional treatment of malaria is a comprehensive knowledge system, which comprises the utilization of herbal drugs, dosages and practices based on socio-cultural norms, and religious belief as well as witnessed experience and observation of a specific group [20]. The knowledge of treatment of malaria with herbal medicines in Africa is currently transmitted from one generation to another principally by verbal medium without concise documentation; therefore there is availability of only minute documented information about traditional herbal medicine in Africa [21].

In various African countries, several plants have been reported to be having antimalarial effects and are being applied traditionally as antimalarial agents. A wide variety of plants illustrated in table 1found in African nations, belonging to several families have been identified through ethnobotanical and ethnopharmacological studies as antimalarial medicinal plants [4, 9,11, 21-25].

Table 1: Indigenous medicinal plants used for malaria treatment in Africa

No	Plants	Parts	Common names	Preparations	Countries
1	*Allium sativum*	Bulbs	Garlic	Decoction	Cameroon, Nigeria, Uganda Ivory coast, Nigeria
2	*Alstoniaboonei*	Leaves, root, stem barks	Stool wood	Decoction	Kenya
3	*Ajugaremota*	Leaves	Ajuga	Decoction	Burundi, Nigeria
4	*Artemisia annua*	Leaves, seeds	Sweet wormwood	Decoction	Nigeria
5	*Aspiilia africana*	Stem barks	Wild sun flower	Decoction	Nigeria
6	*Azadirachta indica*	Barks, leaves	Dogoyanro, neem	Decoction,	

			Mitzeerie	infusion	Nigeria, Ghana, Tanzania,
7	*Bridelia ferruginea*	Barks, leaves, roots		Decoction	Uganda
		Leaves, roots	Pigeon pea		Nigeria, Togo
8	*Cajanus cajan*			Decoction	
		Leaves, fruits, roots	Paw paw		Cameroon, Nigeria, Uganda
9	*Carica papaya*	Barks		Decoction,	Burkina Faso, Ghana,
			African bark	infusion	
10	*Crossopteryx febrifuga*	Leaves		Decoction	Central Africa
		Whole plant, root	Lemon grass		Cameroon, Nigeria
11	*Cymbopogon citratus*		Hairy spurge	Decoction	
12	*Euphorbia hirta*	Barks, leaves		Decoction	Ivory coast, Cameroon,
			Broad leaf fig		Togo
13	*Ficus platyphylla*	Barks		Decoction	Cameroon, Nigeria
		Leaves	Bitter kola		Nigeria
14	*Garnicia kola*	Stem barks	Easter tree	Decoction	Kenya
15	*Holarrhena pubescens*		Mahogany	Decoction	
16	*Khaya grandifoliola*	Leaves,stem barks,		Decoction,	Cameroon, Nigeria
		roots	African mahogany	infusion	
17	*Khaya senegalensis*	Barks, leaves	Mango	Decoction,	Cameroon, Nigeria
				infusion	
18	*Mangifera indica*	Barks, leaves, roots	Brimstone tree	Decoction	Cameroon, Ghana, Uganda
		Leaves, stem bark,			
19	*Morindalucida*	root	Moringa	Decoction,	Ghana, Nigeria
		Leaves, roots		tincture	
20	*Moringa oleifera*		African peach	Decoction	Ghana, Uganda
		Leaves			
21	*Nuclea latifolia*	Leaves	Tea bush	Decoction	Ghana, Nigeria
			Opilia		Nigeria, Uganda
22	*Ocimum gratissimum*	Leaves, stembarks,		Decoction	
23	*Opilia celtidifolia*	roots,	African locust bean	Decoction	Burkina Faso, Togo,
		Barks, leaves	tree		Cameroon, Ghana, Nigeria
24	*Parkia biglobosa*		Guava	Decoction	Cameroon, Nigeria
		Leaves			
25	*Psidium guajava*		Bitter wood	Decoction	Nigeria
		Leaves, stembarks,			
26	*Quassia amara*	roots	Serpent wood	Decoction	Nigeria
		Aerial parts			
27	*Rauvolfia vomitoria*		Broom weed	Infusion	Kenya, Ivory coast, Nigeria
		Leaves			
28	*Sida acuta*		Bitter leaf	Decoction	Ghana, Nigeria, Tanzania,
		Leaves, roots			Uganda
29	*Vernonia amygdalina*		Ginger	Decoction,	Cameroon, Nigeria
				infusion	
30	*Zingiber officinale*			Decoction	

The next generation of antimalarial may be found in plants currently used in Africa, artemisinin has been discovered in Asia, Latin American has offered quinine to humanity. Many researchers believe that it is Africa's turn to offer a new antimalarial drug to humanity [26].

Figure 1, indicates the medicinal plants employed as antimalarial in Africa as a promising source for the development of new and better antimalarial drugs. This is however very important due to the current urgent need for novel antimalarial drug development so as to curtail the challenges being faced currently in the treatment/control of malaria [27].

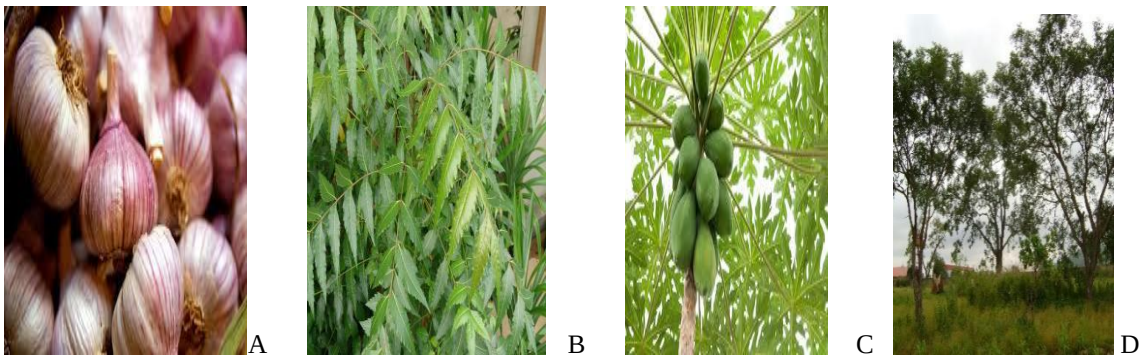

Figure 1: Medicinal plants used to treat malaria in Africa
A= *Allium sativa*; B=*Azadirachta indica; C= Carica papaya ; D=Parkia biglobosa*

Preparation of Plant materials

Traditional antimalarial drugs may be collected from wild or cultivated plants, it is known that the active constituents of medicinal plants are affected by many factors such as time of the year, time of the day, stage of maturity and age and these may vary during the course of plant growth. Proper time of collection is very important to obtain a drug of good quality [28]. Identification of plant material is the key to all following steps in antimalarial natural products isolation, in the medicinal plant area the awareness of necessity of authentication of biological material has been given a boost by significantly increasing emergence of herbal drugs from traditional medicine [29]. The method of identification involves keeping of the track of investigated material of each study, a voucher specimen is kept locally and also stored in a major herbarium [30]. Other steps are as pre-washing, drying of plant materials or freeze drying, grinding to obtain a homogenous sample and often improving the kinetics of analytic extraction and also increasing the contact of sample surface with the solvent system [31].

Extraction of Plant materials

Extraction is the crucial first step in the analysis of medicinal plants, the desired chemical components from the plant materials must be extracted for further separation and characterization. The potential active constituents must not be lost, distorted or destroyed during the preparation of the extract from plant samples therefore proper actions must be taken. If necessary, the method of preparation of extract by the traditional healer may be replicated in order to mimic as closely as possible the traditional antimalarial herbal drug [31].

The extraction of the compounds depends on the specific nature of the bioactive compound being targeted, these include the polarity, stability of the extractives and the solvents, the toxicity, volatility and purity of the extraction solvent, the probability of artefact formation during extraction process and the amount of bulk material to be extracted. Hydrophilic antimalarial compounds are extracted with polar solvents such as methanol, ethanol or ethyl-acetate, dichloromethane or a mixture of dichloromethane/methanol in ratio of 1:1 are used for extraction of lipophilic compounds. In some instances, extraction with hexane is used to remove chlorophyll [32]. The various methods of extraction for non-polar to polar and thermally labile are maceration, percolation, soxhlet extraction, ultrasound assisted extraction and turbo extraction [30]. The filtrate is concentrated by rotary evaporation to obtain the crude extract, the extract is then tested in various systems mainly *in vitro* incubation with *Plasmodium* parasite or *in vivo* in a malaria animal model. It is worth mentioning that several *Plasmodium falciparum* strains, which have been successfully adapted to *in vitro* culture, are employed in testing, while a number of animal and human models are also used for *in vivo* studies [33]. Several extracts derived from plants used as African traditional antimalarial [9, 33-41) are illustrated in Table 2

Table 2: Antimalarial activities and toxicities of indigenous medicinal plant extracts

No.	Plants	Extracts	*In vivo* (%)	*In vitro* (µg/ml)	LD_{50} (mg/kg)
1	*Allium sativum*	AQ	-	0.5	3034
2	*Alstonia bonnei*	AQ, EOH	66.4, 100	0.2, 3.2,	>5000
3	*Ajuga remota*	CHCL, MOH, H_2O	77.5	22.1, > 100	>2000
4	*Artemisia annua*	AQ, HOH, HX	52.8, 94.3	3.27,4.95	2750
5	*Aspilia africana*	AQ, EOH, MOH	92.2	9.3,22.7	894
6	*Azadirachta indica*	AQ, EA, EOH	79.6	2.50, 11.5	6200
7	*Bridelia ferruginea*	AQ	95	-	> 5000
8	*Cajanus cajan*	DM, EA, EOH	40.0	15.6, 31.3	>3000
9	*Carica papaya*	PE, MOH	100	15.2, 16.8	2000
10	*Crossopteryx febrifuga*	CHCL, EOH	84.7	>10	774
11	*Cymbopogon citratus*	DM, EA, PE	87.2	9.1, 12.1	2500
12	*Euphorbia hirta*	EOH, MOH	59.1	4.33, 10.7	3800
13	*Ficus platyphylla*	EOH, PE	43.5	13.8, 15.3	3800
14	*Garnicia kola*	CHCL, MOH	-	1.6, 2.9	358
15	*Holarrhena pubescens*	HX, MOH, MCD	43.0	5.7, 28	2000
16	*Khaya grandifoliola*	MOH	>80	0.84, 1.40,	5500
17	*Khaya senegalensis*	EOH	< 80	<5.00	>3000
18	*Mangifera indica*	DM, EOH	67.7,100	14.0, 24.3	18400
19	*Morinda lucida*	PE, MCD, MOH	55.0	3.9, 5.2	5000
20	*Moringa oleifera*	EOH	100	15.1	6617.00
21	*Nuclea latifolia*	AQ, DM	63.8	0.60	1183
22	*Ocimum gratissimum*	AQ, MOH	88.0	1.84	4240
23	*Opilia celtidifolia*	AQ, DM	-	2.8	636

24	*Parkia biglobosa*	AQ	55.6, 100	12.9, 56.2	>5000
25	*Psidium guajava*	EOH	<80	6.0	> 5000
26	*Quassia amara*	EOH, H_2O	-	8.9	>2000
27	*Rauvolfia vomitoria*	EA, DM	-	1.0, 2.5	> 5000
28	*Sida acuta*	AQ, MOH	-	0.92, 3.90	3400
29	*Vernonia amygdalina*	MOH	97.8	4.1	>5000
30	*Zingiber officinale*	AQ, EOH	<60	15.9	5000

AQ: Aqueous, CHCL: Chloroform,: DM: Dichloromethane, EOH: Ethanol, EA: Ethyl acetate, HX: Hexane, HOH: Hydro alcoholic : MOH: Methanol, PE: Petroleum ether, H_2O : Water

Identification and Characterization of Active antimalarial compounds

Antimalarial plant extracts usually occur as a combination of various types of bioactive compounds or phytochemicals with different polarities, therefore the separation of active antimalarial compounds still remains a big challenge for the process of identification and characterization. A number of different separation techniques such as TLC, column chromatography, flash chromatography, Sephadex chromatography and HPLC, are used to obtain pure compounds. The pure compounds are then used for the determination of structure and biological activity. Also non-chromatographic techniques such as phytochemical screening assay, Fourier-transform infrared spectroscopy (FTIR), can also be used to obtain and facilitate the identification of the bioactive antimalarial compounds [29].

Thin layer chromatography (TLC) is a simple, quick, and inexpensive procedure, this is used to determine the number of components in a mixture. TLC is also used to support the identity of a compound in a mixture when the Rf of a compound is compared with the Rf of a known compound. Other tests such as spraying of phytochemical screening reagents, which cause colour changes according to the phytochemicals existing in a plants extract; or viewing the plate under the UV light can also be carried out. This has also been used for confirmation of purity and identity of isolated antimalarial compounds [29].

Another widely used technique for the isolation of natural antimalarial products is High performance liquid chromatography (HPLC). Currently, this technique is an analytical technique for fingerprinting study for the quality control of herbal antimalarial plants [29]. Natural products are frequently isolated following the evaluation of a relatively crude extract in a biological assay in order to fully characterize the active entity. The biologically active entity is often present only as minor component in the extract and the resolving power of HPLC is ideally suited to the rapid processing of such multicomponent samples on both an analytical and preparative scale [42].

Non–chromatographic techniques such as Immunoassays, which use monoclonal antibodies (MAbs) against drugs and low molecular weight natural bioactive antimalarial compounds, are becoming important tools in bioactive compound analyses. They show high specificity and sensitivity for receptor binding analyses, enzyme assays and qualitative as well as quantitative analytical techniques. Enzyme-linked immunosorbent essay (ELISA) based on MAbs are in many cases more sensitive than conventional HPLC methods [43].

Phytochemical Screening Assays

Phytochemicals are large number of secondary metabolic compounds found in plants, these are chemically obtained from plant. Phytochemical screening assay is a simple, quick, and inexpensive procedure and is used for the determination of the various types of secondary metabolites in a mixture and an important tool in bioactive compound analyses. After obtaining the crude extract or active fraction from plant material, phytochemical

screening can be performed with the appropriate tests as indicated in the Table 3 to get an idea regarding the type of phytochemicals existing in extract mixture or fraction [29].

Fourier-transform infrared spectroscopy (FTIR) is a valuable technique for the characterization and identification of compounds or functional groups (chemical bonds) present in an unknown mixture of antimalarial plants extract [44]. Also FTIR spectra of pure compounds are usually so unique that they are like a molecular "fingerprint". For most common antimalarial plant compounds, the spectrum of an unknown compound can be identified by comparison to a library of known compounds [29].

A large number of antimalarial compounds with a wide variety of structures have been isolated from plants and can play a role in the development of new antimalarial drugs. The pure product is further tested for antimalarial activity *in vitro* and *in vivo* [34-35, 39- 40, 45-48] as mentioned below as shown in table 3.

Table 3: Antimalarial activity and cytotoxicity of phytochemicals from African indigenous plants

No	Plants	Phytochemicals	*In vivo* (%)	*In vitro* (µg/ml)	Cytotoxicity (µg/ml)
1	*Allium sativum*	Ajoene, alliacin	94.0,100.0	-	100
2	*Ajugaremota*	Ajugarin-1	-	23.0	-
3	*Artemisia annua*	Artemisinin	100	1.00, 5.10	28.3
4	*Azadirachtaindica*	Gedunin	-	0.020, 0.039	2.300
5	*Cajanuscajan*	Cajachalcone	-	2.00	<50
6	*Cymbopogoncitratus*	Terpenoids, aldehyde	-	4-10	>2000
7	*Garnicia kola*	Kolaviron	92.6	-	<1500
8	*Khayagrandifoliola*	Gedunin	-	1.25	21.6, 37.6
9	*Khayasenegalensis*	2,6-dihydroxylfissinolide	-	0.120	61.1
10	*Mangiferaindica*	Saponins, tannins	-	20	15-30
11	*Morindalucida*	Urosilic acid	-	3.1	>2000
12	*Ocimumgratissimum*	TOG 1-7	-	0.32-0.52	>2000
13	*Parkiabiglobosa*	Phenol	100	0.51	. -
14	*Quassiaamara*	Similikalactone D, E	-	0.010-0.068	22.6
15	*Sidaacuta*	Cryptolepines	-	0.13,0.17	9.000
16	*Vernoniaamygdalina*	Sesquiterpene lactones	-	< 4.0	>1000

Toxicity of African traditional antimalarial drugs

Clinical studies conducted to validate the efficacy and safety of African traditional antimalarial are few [29, 49] studies have shown that some African traditional antimalarialmay produce low rates of parasite clearance but higher rates of adequate clinical response [50]. Information on the toxicity of African indigenous antimalarial is provided in

table 2, the Lethal Dose (LD_{50}) values are required to predict the safety associated before the use of these herbal antimalarial [25, 51-75]. A number of cases of toxicity were reported by patients taking herbal antimalarial, minor side effects such as diarrhoea, bitter taste were observed with many herbal preparations. Literature review has revealed that many African indigenous antimalarials displayed significant cytotoxic effects [48, 76- 80] on mammalian cells as shown in table 3, therefore screening for inhibitors against parasite-specific targets in organelles like the apicoplast and pathways such as heme degradation and type II fatty acid biosynthesis is recommended to identify active leads with highly selective antiplasmodial action so that reliable quality controls can be established.[26, 50].

Conclusion

African traditional knowledge and medications play a large role in primary healthcare, rural and urban setting, however African indigenous antimalarials are not without drawbacks. Lack of clinical studies on safety and efficacy, poor toxicological data, concentration and seasonal variation of active ingredients, conservation of biodiversity, problems with plant species, patent and inadequate standardized preparations and dosages reduce the interest of large funding organization in African tradition medicine. Indigenous medicinal plants in many of these African countries used in combating malaria are yet to be projected in conferences as the foreign plants in spite of our rich flora diversity, it is essential to establish the efficacy and safety of African indigenous antimalarials which are used to fight the malaria. Therefore, it is hope that some of these active compounds generated from rich Africa flora will replace and control drug-resistant *P. falciparum* parasites in regions where ACT is less effective.

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