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ANTIMALARIAL PHENOLIC COMPOUNDS IN AFRICA: A REVIEW

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ABSTRACT
Malaria is currently a public health problem due to many factors such as parasite resistance, mosquito vector resistance, non-availability of vaccine and adverse reactions of antimalarial drugs. Traditional herbal medicines have been used to treat malaria for thousands of years in various parts of the world especially Africa. This article reviews focuses on African medicinal plants by discussing *in vivo* and *in vitro* phenolic compounds derived from plant extracts.

KEYWORDS: Antimalarials, Traditional medicine, Phenolic compounds, Extracts, Fractions.

INTRODUCTION

Malaria remains a major public health problem in Nigeria and Africa at large. It has been estimated that out of the over one million deaths caused by malaria world-wide, 90% occur in sub-Saharan Africa (Rathod *et al*., 1997). 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 (Benjamin *et al*., 2004). The reemergence of malaria in many parts of the world is due to the rapid increase of resistance to most of the available antimalarial drugs, as well as resistance of vectors to insecticides (Zirihi *et al*., 2005) Drug resistant strains of *P. falciparum* have been found in many endemic areas of the world and many of conventional antimalarial drugs have been associated with treatment failure. Furthermore, the difficulty of creating efficient vaccines and also adverse side-effects of the existing antimalarial drugs highlight the urgent need for novel, well-tolerated antimalarial drugs (Ridley, 2002) for both prophylaxis and treatment of malaria.

In some communities in Africa excessive mortality due to the disease has been reduced by the ability of the local traditional medicinal practitioners to manage the disease (Okigbo and Mmeka, 2006). The plant kingdom remains a major target in the search of lead compounds and new drugs to treat this debilitating parasitic disease (Builders, 2015).

The article is a compilation of African plant species, extracts, fractions and phenolic antimalarial activity with reference to some recent literatures aim at identifying new and effective antimalarial candidates which are isolated phenolic compounds from medicinal plants based on traditional use or ethnomedicinal data.

Plant species

Plants from different botanical sources have been used by various traditional medicinal practitioners (TMPs) for the treatment and cure of malaria (Asase *et al*., 2005; Jullian *et al*., 2006). For example quinine and artemisinin have been derived from traditional medicine and plant extracts (Wagner and Bladt, 2004). Artemisinin derivatives are now recommended by the World Health Organization worldwide, in combination with other drugs, such as lumefantrine, amodiaquine, mefloquine, sulphadoxine-pyrimethamine (SP), as the first-line treatment of malaria (Builders, 2013).

About 80% of the populations of many developing countries still use traditional medicines for their health care. Over 90% of Nigerians in rural areas and about 40% of the population living in urban areas depend partly or wholly on traditional medicines (Shriner *et al*., 1979). Due to economic reasons, most of the people in developing countries are precluded from the luxury of access to modern therapy. This has made the people to rely on plant and animal resources for their health care over centuries (Builders, 2015). Figure 1 indicates plant species with antimalarial phenolic activities.

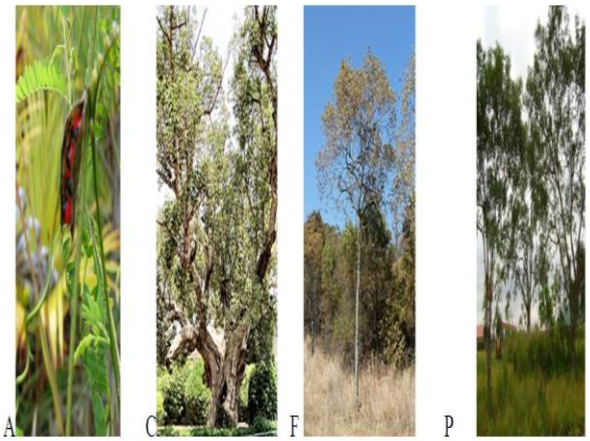


Figure 1: A= *Abrus precatorius, C= Combretum molle,* F= *Ficus mucuso,* P=*Parkia biglobosa*

Extracts and fractions: Extraction is carried out to remove impurities or recover a desired products, this involves dissolving the plant materials in a solvent which have certain selectivity for the extracted materials (Builders *et al*., 2012). In fractionation, sequential solvent extraction involves successive extraction with solvents of increasing polarity from a non polar (hexane) to a molar polar solvent (methanol) in order to extract compounds with wide range of polarity for the isolation of the most active fraction (Builders *et al*., 2012).

Several studies have been undertaken to evaluate not only the inhibitory effects of various plant extracts on *P. falciparum* using *in vitro* culture, but also *in vivo* anti-malarial properties on *Plasmodium berghei*-infected mice (Builders, 2016). The most significant advance in antimalarial testing followed the development of a method for the continuous *in vitro* culture of the human malaria parasite, *P. falciparum*. In 1979, a technique for the quantitative assessment of *in vitro* anti-*P. falciparum* activity was described and modified, but still relies on the ability to inhibit the incorporation of 3H-hypoxanthine into plasmodia (Mojab, 2012).

Four stages were described in the Guidelines for antimalarial screening of drugs established by WHO (WHO, 1973). Primary screening establishes whether compounds are active against malaria parasites whereas secondary screening sets out to further qualify and quantify antiparasitic activity and to determine safety and comparative activities of analogues. The purpose of tertiary screening is to study nonhuman and human parasites in primates other than man prior to the fourth stage of the clinical testing. In assessing the activity of plant extracts for the presence of compounds with antimalarial activity, the techniques of primary and secondary screening can be utilized. For initial screening, both *in vivo* and *in vitro* techniques may be employed (Phillipson, 1991).

Although many crude plant extracts with *in vitro* and *in vivo* antiplasmodial activities have been reported in the recent literature, the results often show only modest activity against the parasites *in vitro* or against malaria in mice, suggesting that the species in question probably have only a limited effect in man and that cure of the disease is unlikely. However, this may not necessarily mean that medicines made from these species are of no value, since partially effective treatments might be beneficial in those cases that the course of the disease is shortened by reducing anaemia and lowering the risk of death or serious illness from other anaemia-related diseases. Moreover, benefits may also include the alleviation of symptoms such as pain and fever and immunomodulation leading to increased immunity (Wright, 2005). Also, plant extracts with phenolic activities could also be effective against the parasite on hepatic stage (Batista et *al*., 2009). The plant species with antimalarial phenolic activities is illustrated below.

Table. 1: Plant species with antimalarial phenolic activities.

S/No	Plant species	Family	Plant parts	Country	References
1.	*Abrus precatorius*	Leguminosea	Stem bark	Kenya	Yenesew *et al*., 2004
2.	*Allanblackia monticola*	Guttiferaceae	Stem bark	Cameroon	Lannang *et al*., 2008
3.	*Alchornea cordifolia*	Euphorbiaceae	Leaves	Ivory Coast	Banzouzi *et al*., 2002
4.	*Anogeissus leiocarpus*	Combretaceae	Stem bark	Nigeria	Adebayo and Krettli, 2011
5.	*Combretum molle*	Combretaceae	Stem baark	Ethiopia	Maroyi, 2017
6.	*Croton macrostachyus*	Euphorbiaceae	Stem bark	Ethiopia	Maroyi, 2017
7.	*Derris trifoliate*	Leguminosea	Seed pods	Kenya	Yenessew *et al*., 2004
8.	*Erythrina sacleuxi*	Leguminosa	Stem bark	Kenya	Yenessew *et al*., 2004
9.	*Ficus mucuso*	Moraceae	Figs	Cameroon	Bankeu *et al*., 2011
10.	*Garcinia polyantha*	Gutiferae	Roots	Cameroon	Lannang *et al*., 2008
11	*Kigelia Africana*	Bignoniaceae	Stem bark	Cameroon	Zofou *et al*., 2011
12.	*Morus mesozygia*	Moraceae	Stem bark	Cameroon	Zelefack *et al*., 2012
13.	*Parkia biglobosa*	Fabaceae	Stem bark	Nigeria	Builders *et al*., 2012
14.	*Polygonum senegalense*	Polygonaceae	Aerial parts	Kenya	Midiwo *et al*., 2007
15.	*Sida acuta*	Malvaceae	Leaves	Nigeria	Lawal *et al*., 2015
16.	*Sorindeia juglandifolia*	Anacardiaceae	Fruits	Cameroon	Boyom *et al*., 2010
17.	*Vepris uguenensis*	Rutaceae	Roots	Kenya	Cheplogoi *et al*., 2008

Secondary metabolites

Chemicals derived from higher plants have played a central role in the history of mankind. Efforts to develop new, clinically effective pharmaceutical agents have relied primarily on one of five approaches, most of which utilize existing agents in some manner as follows:

i. Derivatization of existing agents.
ii. Synthesis of additional analogs of existing agents.
iii. Use of combination therapy of existing agents with other drugs.
iv. Improvement of delivery of existing agents to the target site.
v. Discovery of new prototype pharmaceutical agents.

Natural products can offer an alternative to established therapy because they act at a different stage in malaria treatment and be useful in combination therapy. Investigation into plant extracts have produced a wide range of phenolic compounds with various modes of action that result in antimalarial activities (Mukherjee, 2002).

Natural phenolic products have traditionally provided most of the antimalarial drugs in use, with the achievements of synthetic chemistry and the advances towards rational antimalarial drug design, herbal antimalarial drugs continue to be essential in providing antimalarial medicinal compounds and as starting points for the development of antimalarial synthetic analogues (Builders, 2016).

Many secondary plant substances had been assessed either for *in vitro* activity against *P.falciparum* or *in vivo* activity against *P.berghei* (Builders, 2015). The step taken in the isolation of phenolic compound from natural sources is shown in Figure 2.

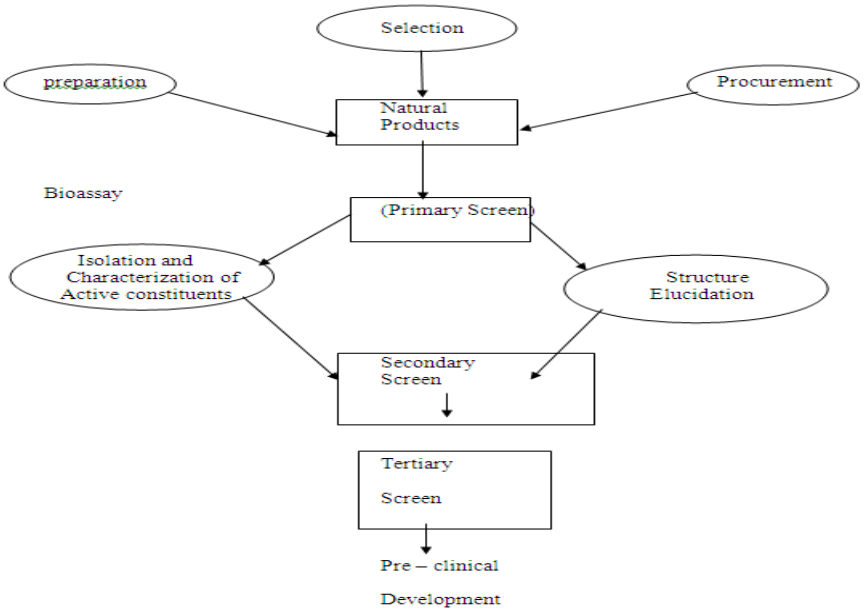


Figure. 2: Various strategies for the discovery of drugs from natural resources (Mukherjee, 2002).

Table. 2*: In vitro* antimalarial phenolic compounds.

S/No	Plant species	phenolic compounds	*In-vitro* activity (ug/ml)	References
1.	*Abrus precatorius*	7,8,3',5'-tetramethoxyioflavanol	8.9	Lawal *et al*., 2015
2.	*Albizia zygia*	3',4',7-trihydroxyflavonone	0.08	Lawal *et al*., 2015
3.	*Alchornea cordifolia*	Ellagic acid	0.08	Lawal *et al*., 2015
4.	*Arrabidaea patellifera*	Mangiferin	18.1	Silva *et al*., 2011
5.	*Artemisia indica*	Exiguaflavone	50	Sudhanshu *et al*., 2003
6.	*Artoccarpus rigidus*	Artonin	4.8	Bero *et al*., 2009
7.	*Bauhinia purpurea*	Flavanone	9.5	Bero *et al*., 2009
8.	*Campnosperma panamensis*	Lanaroflavone	0.48	Bero *et al*., 2009
9.	*Erythrina fusca*	Flavonoids	12.5	Bero *et al*., 2009
10.	*Garcinia livingstonei*	Biflavanone	6.7	Silva *et al*., 2011
11	*Ochna intergerrima*	Flavonoids	157	Sudhanshu *et al*., 2003
12.	*Parkia bigobosa*	Phenol	0.51	Bero *et al*., 2009
13.	*Piptadenia pervillei*	(+)-catechin 3-gallate	1.0	Builders *et al*., 2014
14.	*Siparuna andina*	(-)-cis-3-acetoxy-4c,5,7-trihydroxy	50	Bero *et al*., 2009

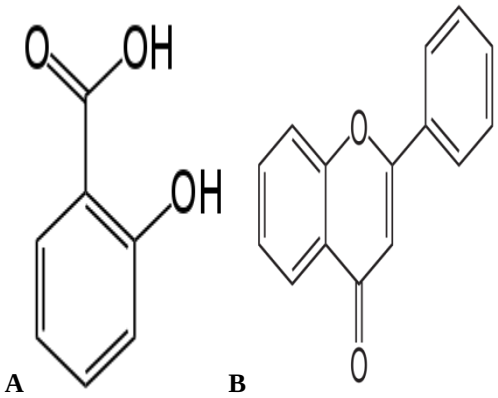
Phenolic compounds: Phenolics are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants. Plant polyphenols have drawn increasing attention due to their potent antioxidant properties and their marked effects in the prevention of various oxidative stress associated diseases such as malaria (Dai and Mumper, 2010). Structurally, phenolic compounds comprise an aromatic ring, bearing one or more hydroxyl substituents, and range from simple phenolic molecules to highly polymerised compounds (tannins) (Bravo, 1998).

Phenolic compounds can basically be categorized into several classes, these include phenolic acids, flavonoids and tannins, and they are regarded as the main dietary phenolic compounds (King and Young, 1999).

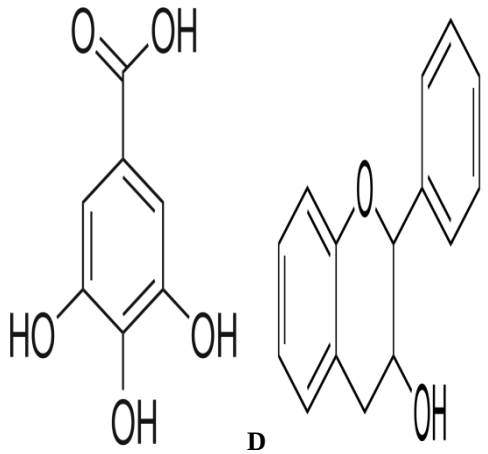
Phenolic acids can be subdivided into hydroxybenzoic and hydroxycinnamic acids. Hydroxybenzoic acids include gallic, p-hydroxybenzoic, protocatechuic, vanillic and syringic acids, which in common have the C6–C1 structure. Hydroxycinnamic acids, on the other hand, are aromatic compounds with a three-carbon side chain (C6–C3), with caffeic, ferulic,p-coumaric and sinapic acids being the most common (Bravo, 1998).

Flavonoids constitute the largest group of plant phenolics, accounting for over half of the eight thousand naturally occurring phenolic compounds (Harborne *et al*., 1999). Variations in substitution patterns to ring C result in the major flavonoid classes, i.e., flavonols, flavones, flavanones, flavanols (orcatechins), isoflavones, flavanonols, and anthocyanidins (Hollman *et al*., 1999), of which flavones and flavonols are the most widely occurring and structurally diverse (Harborne *et al*., 1999).

Tannins, the relatively high molecular weight compounds which constitute the third important group of phenolics may be subdivided into hydrolysable and condensed tannins (Balasundram *et al*., 2006). The former are esters of gallic acid (gallo- and ellagi-tannins), while the latter (also known as proanthocyanidins) are polymers of polyhydroxyflavan-3-ol monomers (Balasundram *et al*., 2006). Structure of antimalarial phenolic compound is shown in figure 2.



A B



C D

Figure 2: A=Phenolic acid, F=Flavonoid, H=Hydrolysable tannin, C= Condensed tannin.

Mechanism of action

Plant phenolics are a major group of compounds that act as primary antioxidants or free radicals scavengers (Builders *et al*., 2014). The antioxidant activity of phenolic compounds is mainly due to their redox properties, which can play an important role in adsorbing and neutralising free radicals, quenching singlet and triplet oxygen, or decomposing peroxides (Builders *et al*., 2014). The antioxidant phenolic compounds have also been shown to exert antiplasmodial activity by elevating the red blood cell oxidation and inhibiting the parasite s protein synthesis and also counteract the oxidative damage induced by the malaria parasite (Builders *et al*., 2014).

Toxicity

The phenolic antimalarial drugs should cause less harm than the malaria itself, this is normally achieved by balancing the toxicity of the drug with the efficacy of the drug and the risk from malaria. Therefore, patient compliance is the most important determinant of drug use and its effectiveness, also the doses given to the patients should be taken into account in determining the treatment of malaria. Phenolic antimalarial compounds should be assessed for safety by evaluating adverse drug reactions, side effects, and drug-related toxicity (Sharma and Awasthi, 2015). Finally phenolic antimalarial drug combinations will go a long way to prevent resistance or have properties that do not facilitate development or spread of resistant parasites.

CONCLUSION

Phenolic compounds are found in plants, these are phytochemicals that are responsible for the antiplasmodial activities due to their antioxidant properties. These therapeutic activities may be as a result of a single compound or a combination of phenolics present in the plant extracts. The antimalarial activities of several phenolic compounds isolated from plant species have provided interesting leads which require further investigation. However, for the efficacy and safety of antimalarial phenolic drug to be validated, there must be

adequate information on the contra-indications, drug interactions and toxicities of these drugs and there should also be proper standardization and clinical trials of these plant products.

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