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Antimalarial Effect and 0ther Properties of *Hoslundia opposita* – A Review

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Abstract

Hoslundia opposita Vahl a plant widely distributed in Africa belongs to the family Lamiaceae and is the only species in the genus Hoslundia. Ethnobotanical and ethnopharmacological knowledge on H. oppositaas effective antimalarial species resemble those of cinchona from South America and qinghao from China. Preliminary biomedical study on *H. opposita* afforded potent antimalarial metabolites. Extending the biomedical work on this plant as well as on other antimalarial plants from Africa might see the continent taking its turn in providing a powerful antimalarial agent after quinine from America and artemisinin from Asia. This paper gives a brief review of *H. opposita* and is a call to researchers to investigate this plant and other potent antimalarial species growing in Africa.

Keywords: Antimalarial; *Hoslundia opposita*; Africa; Ethnobotany; Ethnopharmacology

Introduction

Malaria has been affecting human population for thousands of years and is still among the largest world health burden. Efforts to control malaria can be dated back as early as human started to be affected by this malady but was intensified in the 19th and 20th centuries by wars and colonial expansions in the world tropic and subtropical regions [1]. Top on early endeavor to control malaria was chemotherapy which was later aided by use of insecticide such as DDT to fight mosquito of the plasmodium species that was recognized as the vector for spread of malaria. Eradication of malaria in the developed world due to these efforts and the escalation of costs of development of new pharmaceuticals led to decline in interest in development of new antimalarials since 1970s. However, in the turn of the millennium there has been renewed concern for malaria as global problem and its control has been the focus of many declarations including, United Nations Millennium Declaration, The Abuja Declaration and the Plan of Action on Roll Back Malaria and many more [2]. Notwithstanding, great achievement of those goals in reducing malaria cases and deaths in the last fifteen years, malaria is still a large global health burden. It is reported that 212 million cases of malaria occurred in 2015 and 429,000 individuals died consequently [3]. Thus new innovations are still required in control of this deadly disease.

Chemotherapy has been the mainstay of malaria control. Based on ethnomedical history, terrestrial plants have been the major source of malaria chemotherapeutics. Herbal remedies using cinchona bark and qinghao were used effectively to treat malaria for many years before the discovery of quinine from cinchona bark in 1820 and artemisinin in 1972 [1]. Discovery and development of drugs based on these natural products has previously led to The Nobel Prize in Physiology or Medicine [4]. In addition to these natural products the use of a number of other drugs such as chloroquine has been effective arsenal to fight malaria before the parasite developed resistance to many of the previous regimens.

At present ACT has been the only effective therapy for treatment of malaria and recently there has been reports on occurrence of artmisenin resistant strains. There is therefore a need to initiate investigation aimed on discovery of new antimalarial agents. *H. opposita* is a shrub which is widely used in Africa for treatment of all forms of malaria including chronic variants. Preliminary biomedical study on this species showed the presence of potent antimalarial metabolites with chemical structures that differ markedly from previously known antimalarials. Like cinchona from South America and qinghao from Asia, *H. opposita* might be among potential sources of new antimalarial from Africa. This paper constitutes a general review of this species and its preliminary investigations as a source of new malaria chemotherapeutic agents.

Plant Description

Hoslundia opposite Vahl is an herbaceous perennial shrub that is widely distributed in tropical and subtropical open lands of Africa. It grows up to 3-5m high with slender glabrous or

slightly pubescent branchlets. Leaves opposite, petioled, oblong or oblong-lanceolate, acute, crenate at the base, dentate, 8-10cm long, glabrous above slightly pubescent beneath. Inflorescence an ample lax deltoid terminal panicle; branchlets pubescent; bracts very small; pedicels as long as the flower-calyx. Flowers-calyx pubescent, 0.21cm long teeth deltoid. Fruit-calyx globose, red, edible [5]. It belongs to the family, *Lamiaceae* and is the only species in the genus *Hoslundia*. However, in the literature it is synonymously identified as *Hoslundia paniculata, Hoslundia cornutioides, Hoslundia opposite, Clerodendrum micranthum, Hoslundia verticillata, Hoslundia sp., Orthosiphon physocalycinus, Micranthes menthoides, Hoslundia decumbens* and *Hoslundia* unrecorded [6-8]. H. opposite Vahl is taxonomical classified under Kingdom: Plantae, Phylum: Magnoliophyta, Class: *Magnoliopsida*, Order: *Lamiales*, Family: *Lamiaceae*, Genus: *Hoslundia* and the Species: *Hoslundiaopposita*.

Traditional Uses

H.opposita is a popular herb in Sub-Saharan Africa used as remedy for various diseases. It is reported to be used for treatment of resistant malaria, fever, stomach pain, cough, wounds, sores, chest pain, liver damage, gonorrhea, cystitis, conjunctivitis, epilepsy, stomach trouble, and mental disorders as well as prevention and as an antidote for snake bites. There are several reports in the literature describing the use of different part of *H. opposita* in African traditional medicine; the following paragraphs are briefly summarizing the use of *H. opposita* in treatment of various diseases in different part of Africa. In Tanzania, one of East African countries, infusion of root bark of *H. opposita* has been locally used in Tanzania to fight chloroquine resistant strains, especially before the advent and commercialization of artemisinin based medicines. Furthermore, different parts of *H. opposita* are traditionally used for gonorrhoea, cystitis, coughs, wounds, liver disease, blennorrhoea and hookworms as well as for control of epilepsy in Tanzania [9-11].

In the neighboring Kenya and Uganda, concoction or infusion of *H. opposita* are also used as antimalarials. Other uses of this species in Kenya include remedies for colds, coughs, sore throat, gonorrhea, convulsion, stomach pains, constipation, ringworms and parasitic skin infection [12,13]. While in Uganda it is used for colic pain, enema, headache, miscarriage splenomegaly, stomachache syphilis uterine pains, and wounds [14,15]. Furthermore, preparations of *H. opposita* are used in Uganda traditional medicine for postnatal health, vomiting during fever and jaundice [16]. In Southern part of the continent there is no report on the use of H. opposite as antimalarial. However, the species has been used as remedy for various complications. For instance, in Zimbabwe extract from the leaves of *H. opposita* is dropped into eyes as cataract medicine and the root infusions are used to treat fits and epilepsy [17,18].

In Western Africa countries such as Cameroon, infusions from leaves of *H. opposita* are reported to be used as a purgative, diuretic, febrifuge, antibiotic, and antiseptic as well as for anaemia and skin diseases by traditional healers [19]. In Eastern Nigeria *H. opposita* is widely used in folk medicine for the treatment of cough, chest pain, fever, hookworm, stomach disorders, wounds, liver diseases and mental disturbances [20]. Leaves or root of *H. opposita* are used oral or topical to treat chronic and deep wounds, stomach ulcer, as well as dermatitis in some regions of Ghana [21,22]. Furthermore, Essential oils from the leaves of *H. opposita* are extensively used as insect repellents [23]. Leaves infusion is used as antidiabetic in Guinea [24].

Pharmacological Properties

Biomedical investigations of organic extracts obtained from various parts of *H. opposita* have revealed that this plant possesses diversified pharmacological activities. Reported biological activities include antimalarial, antimicrobial, antioxidant, CNS depression, hepatoprotective, and insecticidal properties. The evaluated biological properties are further described below.

Antimalarial

Organic extracts from root bark of *H. opposita* collected from Tanzania were shown to have high *in vitro* antimalarial activity against multidrug resistant K1 strain of *Plasmodium falciparum* Hexane extract was the most effective(IC50=5.6µg mL^{-1}). It also showed a 26% inhibition of growth of *P. berghei* in mice, at a daily dose of 190mg kg^{-1} body weight, for four days [25]. Quinonesisolated from these extracts showed significant *in vitro* activity against the multidrug-resistant K^{-1} strain and the chloroquine-sensitive NF54 strain of *P. falciparum*, with IC50 values of 0.4 and 0.22µg mL^{-1}, respectively [10]. Furthermore, different parts of *H. opposita* collected in Kenya displayed strong antiplasmodial activity against CQ sensitive (D6) and CQ resistant (W2) *Plasmodium falciparum* strains with IC50 values 2-4µg mL^{-1}[12].

Antimicrobial

Crude extracts of the entire plant collected from the coast of Tanzania showed strong antibacterial activity against a series of gram positive and gram negative bacteria [9]. However, ethanolic extract of *H. opposita* collected from hinterland of Tanzania showed poor antimicrobial activity [26]. Extracts from H.opposita collected from Mozambique demonstrated good antimicrobial activity against strains of *Mycobacterium tuberculosis*. Subsequent phytochemical investigation on these extracts afforded isolation of several compounds including euscaphic acid and 5,7-dimethoxy-6-methylflavone. The former compound was found to inhibit the growth of drug-sensitive *M. tuberculosis* at concentration of 50µg mL^{-1} while the latter was shown to inhibited the HIV-1 reverse transcriptase enzyme by 52% at a concentration of 100 µg mL^{-1} [27].

A part from that, essential oil from leaves of H.opposita collected from Central Africa showed significant antimicrobial activity against *Aspergillus niger, Acinetobacter calcoacetica,*

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Brochothrix thermosphacta and Flavobacterium suaveolens. [28]. Moreover, the results on the investigation of antimicrobial activities of aqueous, methanol and ethyl acetate extracts of leaves of H.opposita showed antibacterial activities against strains of gram positive and negative bacteria at concentration of 20µg/mL with zone of inhibition ranging from 6.5-11.0mm [29].

Insecticidal

Crude methanolic extract from leaves of *H. opposita* as well as pet.ether, ethyl acetate and aqueous fractions partitioned from the methanolic extract were found active against the larvae of the cattle tick, *Amblyomma variegatum*, However, all extracts were less potent than the control, malathion. LC_{50} values of the active extracts were more than 500 times higher than that displayed by malathion (1.14×10^{-4}mg/ml). Furthermore, ursolic acid isolated from ethyl acetate fraction showed weaker acaricidal effects (LC_{50}=1.13mg/ml). This result is an indication that the overall acaricidal effect of *H. opposita* might be due to synergistic effect of individual principles within the extracts [23]. In a similar investigation extracts from leaves, stem and root barks of *H. opposita* collected from Tanzania showed significant larvicidal activity against *A. gambiae* larvae under laboratory trials [30]. Furthermore, essential oil from *H. opposita* showed insecticidal activity against the red follower beetle *Tribolium castaneum* [31].

Hepatoprotective

Organic extract of *H. opposita* showed hepatoprotective effect against carbon tetrachloride (CCl4) and paracetamol-induced liver damage in rats. Treatment of affected animals with methanol extract and methanol and ethyl acetate fractions of *H. opposita* (100mg/kg) ameliorated the effects of the hepatoxins and significantly reduced the elevated levels of the biochemical marker enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) as well as bilirubin. The extracts showed good toxicity profile with an LD_{50} value above 5000mg/kg for the methanol extract [20].

Antioxidant

In determination of antioxidant activity of some wound healing plants growing in Ghana Agyare et al. [21] found that ethanolic extract from leaves of *H. opposita* has strong DPPH radical scavenging activity (RC50=9.8µg/ml) [21]. However, ethanol extract from stem of *H. opposita* collected from Zimbabwe showed poor antioxidant activity in similar investigation conducted by Muchuweti & coworkers [32].

CNS Depression

The chloroform extract of the dried root of *H. opposita* showed depression of central nervous system (CNS). It significantly potentiated the phenobarbitone sleeping time in mice and produced a 60% protection against leptazol-induced convulsion [33]. In addition, ethanolic extracts from leaves of *H. opposita* collected from South Africa showed dose-dependent GABAergic activity in the GABAA-benzodiazepine receptor binding assay [34,35].

Chemical Constituents

Basic phytochemical screenings of organic extracts from *H. opposita* have revealed the presence of secondary metabolites that could be grouped as sterols, terpenoids, saponins, flavonoids and tannins [13,20]. Individual natural products that have so far been isolated from various parts of *H. opposita* include terpenoids, flavonoids and quinones. Four quinones, including the hosloppones, 3-O-benzoylhosloppone (Figure 1), 3-O-cinnamoylhosloppone (Figure 2), as well as 3-O-benzoylhinokiol (Figure 3) and 3-O-benzoylhosloquinone (Figure 4) were afforded from root bark of *H. opposita* collected from Tanzania. Hosloppone, Figure 1 showed *in vitro* antimalarial activity against the multidrug-resistant K-1 strain and the chloroquine-sensitive NF54 strain of *P. falciparum* (IC_{50}=0.4 and 0.22µg mL−1, respectively). The remaining compounds were not assayed because only limited quantity was available [10]. Based on ethnobotanical and ethnopharcological use of *H. opposita* it would have been interesting to evaluate antimalarial property of these compounds as well as to prepare and evaluate extra analogs of compound Figure 1 to reveal SAR of the hosloppones for further development of new antimalarials.

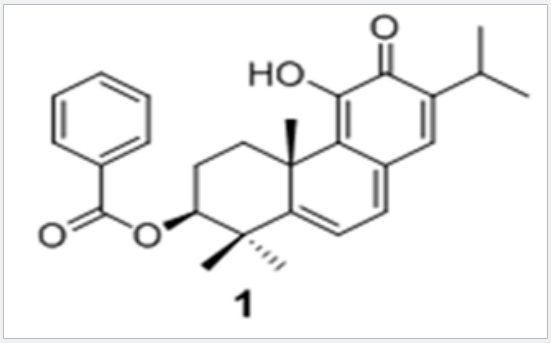

Figure 1: Interface behavior: a) Mohr-Coulomb slip model; b) Behavior under uniaxial loading.

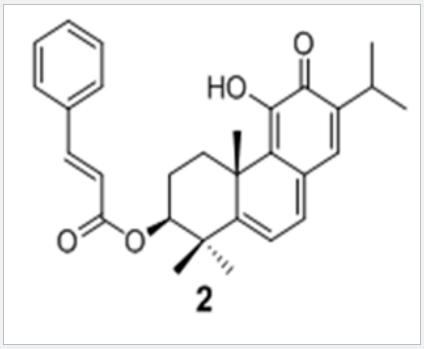

Figure 2: 3-O-cinnamoylhosloppone.

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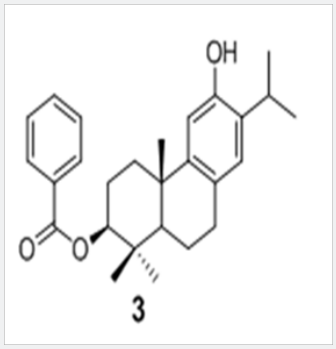

Figure 3: 3-O-benzoylhinokiol.

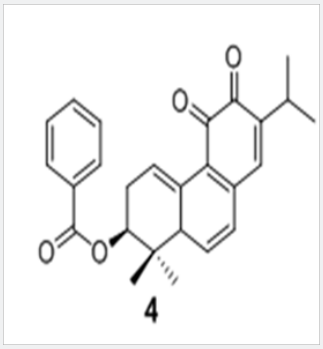

Figure 4: 3-O-benzoylhosloquinone.

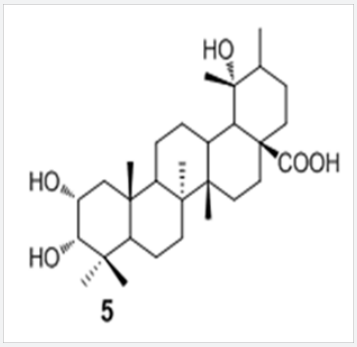

Figure 5: Euscaphic acid.

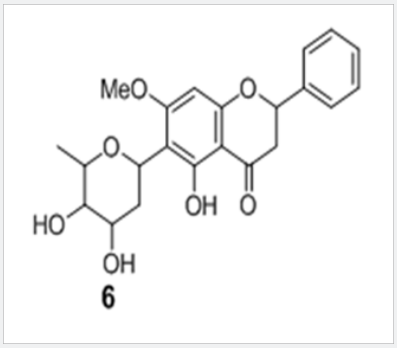

Figure 6: Hoslunddiol.

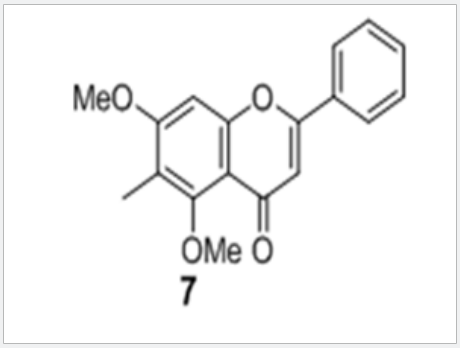

Figure 7: 5,7-dimethoxy-6-methylflavone.

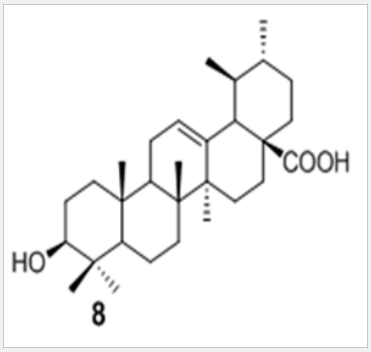

Figure 8: Ursolic acid.

In 2009 Mujovo [27] reported isolation of three compounds including, euscaphic acid (Figure 5), hoslunddiol (Figure 6) and 5,7-dimethoxy-6-methylflavone (Figure 7) from leaves of *H. opposita* collected from Mozambique. Euscaphic (jacarandic acid, Figure 5) acid was found active against drug sensitive strains of *Mycobacterium tuberculosis* (MIC~50mcg/ml). Compound 7 inhibited HIV-1 reverse transcriptase enzyme by 52% at 100µg/ml [30]. More recently, Annan and his group reported isolation of ursolic acid (Figure 8), from the leaves of *H. opposita* [23].

Conclusion

Ethnopharmacological information as well as preliminary biomedical data on *Hoslundia opposita* growing in East Africa shows that this species might be a potential source of new chemical entities with desirable pharmacological properties for development of new malaria chemotherapeutic agents.

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