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A SURVEY OF TRITERPENOIDS ANTIMALARIALS ISOLATED FROM PLANTS

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ABSTRACT
Malaria is a major parasitic disease in many tropical and subtropical regions of Africa and some parts of the world. It is responsible for more than 1 million deaths each year in Africa. The rapid spread of resistance encourages the search for new active compounds. Nature and particularly plants used in traditional medicine are a potential source of new antimalarial drugs as they contain molecules with great variety of potency and pharmacological activities. A large number of antimalarial compounds with different structures have been isolated from medicinal plants and can play important roles in the development of new antimalarial drugs. Ethnopharmacological approaches appear to be a promising way to find plant metabolites that could be used as templates for designing new derivatives with improved properties. This review focuses on triterpenoids and their derivatives based antimalarial agents sourced from medicinal plants which are used in the treatment of malaria in Africa and other parts of the world. Their activity against malaria parasites in vitro and in vivo (using experimentally infected mice) ranges from promising and excellent to mild/low antiplasmodial activities. The search for new drugs based on medicinal plants is important due to the emergence and widespread of chloroquine-resistant and multiple drug-resistant malaria parasites with ACT which hitherto requires the development of new antimalarials. The use of plants as antimalarials may be a springboard for new phytotherapies that could be affordable and accessible in treating malaria, especially among the less privileged people living in endemic areas of the tropics which are vulnerable and at risk of this devastating disease.

KEYWORDS: *Antimalarials, Triterpenes, Medicinal plants and Malaria.*

INTRODUCTION
Malaria is a serious parasitic disease from tropical regions caused by a species of *Plasmodium* and transmitted by infected female *Anopheles* mosquitoes. It is prevalent in approximately 100 countries in Africa, Southeast Asia and South America, where approximately 2.4 million people are at risk(Kager, 1992). According to the World Malaria Report(WHO,2009a), there are approximately 250 million malaria cases and approximately one million people die from malaria each year. The emergence and rapid spread of multidrug-resistant strains of *Plasmodium*, particularly *Plasmodium falciparum*, represent a major problem for prophylaxis and treatment, which becomes more difficult and limits the choice of drugs used. This has been identified as the current primary cause of control failure.

The well-known use of chloroquine (CQ) and antifolates [sulfadoxine-pyrimethamine (S/P)] for malaria treatment are no longer effective in most endemic areas. Combination therapy has emerged as the best practical solution in overcoming the resistance of selected strains. Therapeutics based on combinations with artemisinin and its derivatives (ACTs), recommended by the World Health Organization (WHO), presently represent the most effective treatment of *P. falciparum* malaria infection(WHO,2008).

There is a broad consensus on the urgent need for new, affordable and efficient compounds that could serve as primary molecules for the treatment of malaria. New highly-efficacious antimalarial drugs that are based on new mechanisms of action or with model structures are urgently needed to overcome the problem of rapid emergence of drug resistance and achieve long-term clinical efficacy.

Medicinal Plant Intervention In Antimalarials
There is a consensus among the scientific community that natural products have a dominant presence in the discovery of new leads for the development of drug treatment for human diseases. In fact, out of the 877 novel medicines that were developed in the period between 1981-2002, 6% were natural products, 27% were derivatives of natural products and 16% were synthetics developed from natural product (Newman, 2003). At least 80% of the world population is estimated to be using traditional medicines in primary health care,

including 40,000-70,000 medicinal plants (Verpoorte *et al.*, 2006).

In malaria therapy, many antimalarial drugs were included in the WHO therapeutic schemes for the treatment of malaria which are natural products or their analogues or were designed based on the pharmacophores from natural products (Bickii, 2007). The great significance of plant-derived drugs for the treatment of the disease is from quinine (derived from Cinchona tree), artemisinin (derived from Artemisia annua) and atovaquone (Malarone), which is a synthetic compound (2-alkyl-3-hydroxynaphthoquinone) analogue of lapachol from the Tabebuia species (Bignoniaceae) (Oliveira *et al.*, 2009).

This paper focuses on the review and compilation of triterpenes and their derivatives based antimalarial agents which are sourced from medicinal plants. The comparison of their antiplasmodial/antimalarial activities and suggestion for the development of novel antimalarial drugs which could be utilized in lieu of existing antimalarial drugs facing resistance by multidrug resistance *Plasmodium falciparum* strains were also highlighted.

Criteria for Activity of Antimalarials

In considering the criteria for *in vitro* antiplasmodial activity of a compound as "good", "moderate", "low" or "inactive", earlier studies by Basco and co-workers (1994) have adopted the following criteria: IC_{50} < 10µgmL^{-1},as good activity; IC_{50} of 10-50µgmL^{-1} as moderate activity; IC_{50} of 50-100µgmL^{-1} as low activity; and IC_{50} > 100µgmL^{-1} as inactive. On the other hand, Muriithi and collaborators(2002) have expressed their IC_{50} values in µM and considered as inactive compounds showing IC_{50} > 100 µM; of limited (moderate) activity, those with IC_{50} of 1–20 µM; and of low activity those displayng IC_{50} of 20–60 µM. In this survey, the existing criteria have been combined in order to establish the following criteria adopted for all triterpenes and their derivatives antimalarial based agents described in this review: IC_{50} < 1 µgmL^{-1} as excellent activity; IC_{50} from above 1-20µgmL^{-1} as having good activity; IC_{50} from above 20-100µgmL^{-1} as exhibiting moderate activity; IC_{50} from 100-200µgmL^{-1} as showing low activity and IC_{50} > 200 µgmL^{-1} as inactive while IC_{50} from above 1-20µM as revealing moderate activity; IC_{50} from above 20-150µM as disclosing low activity; IC_{50} from 150µM as indicating low activity and IC_{50} > 200µM as inactive.

Triterpenes (Triterpenoids)

The term triterpene refers to a class of chemical compounds which consists of three monoterpenes and consequently to 30 carbons grouped in six isoprenyl units. Triterpenes possesses no heteroatom(s). However, functionalized triterpenes which contain oxygen atom(s) enclosed in the ring(s) are known as triterpenoids even though the distinction between triterpene and triterpenoid is not always adhered to in scientific literatures, with the two terms often being used interchangeably. Triterpenoids are compounds with a carbon skeleton based on six isoprene units which are derived biosynthetically from the acyclic C_{30} hydrocarbon, squalene. They have relatively complex cyclic structures, most being either alcohols, aldehydes or carboxylic acids (Breitmaier, 2006).

The terms triterpenes and triterpenoids are often used to describe the same C^{30}-terpene compound. However, they need to be differentiated based upon their occurrence, biosynthesis and biotransformation products. The term 'triterpene' is used to describe naturally occurring terpenes whereas; the broader expression 'triterpenoid' includes natural degradation products (Eggersdofer, 2005). Triterpenoids are widely distributed in the plant kingdom. They are produced in plant as secondary metabolites and have varied biological activities (Hanson, 2003). Triterpenes are originally synthesized by plants as metabolites, and are abundantly present in the plant kingdom in the form of free acids or aglycones (Chappell, 1995;McGarvey Croteau, 1997). Till today, at least 80 distinct types of both the structure and the chemical characteristics of triterpenes have been shown. It is well-recognized that triterpenes have long been used as flavors, pigments, polymers, fibers, glues, and waxes. In many Asian countries, herbal products containing triterpenes are widely prescribed to prevent or treat a variety of diseases by the traditional healers (Wagner and Elmadfa, 2003; Xu et al., 2004).

Chemistry and Classification of Triterpenes

Triterpenes are compounds of natural origin, which have numerously biological activities: anti-malarial properties, anti-cancer properties, anti-inflammatory, anti-oxidative, anti-viral, anti-bacterial and anti-fungal. These substances can be isolated from plants, animals or fungi. Triterpenes exist in a huge variety of structures with nearly 200 different skeletons known from natural sources or enzymatic reactions. These may be broadly divided into subclasses based on the presence or absence and number of rings present in each of its molecule ranging from acyclic, monocyclic, dicyclic, tricyclic, tetracyclic, pentacyclic and hexacyclic triterpenes. Although in general pentacyclic structures (5 rings) tend to dominate(Breitmaier, 2006).

Taking into consideration the structure of triterpenes, triterpenes may be divided into linear ones-mainly derivatives of squalene, tetracyclic and pentacyclic, containing respectively four and five cycles, as well as two- and tricyclic ones (Breitmaier, 2006). A good example could be the betulinic acid and its derivatives which have been investigated for their strong cytotoxic properties (Liu *et al.*, 2014). Other important representatives are the compounds originating from squalene, dammarane, lanostane, oleane (e.g., oleanolic acid), lupane (e.g., lupeol), ursane (e.g., ursolic acid) or triterpenoid sapogenins such as cycloartane, friedelane,

filicane and cucurbitane triterpenoids(Banzouzi, *et al*., 2008).

Most of triterpenic skeletons are tetracycles, containing three six-membered and one five-membered rings, and pentacycles, either with four six membered and one five-membered rings or five six-membered rings(i.e. 6-6-6-5 tetracycles, 6-6-6-6-5 pentacycles, or 6-6-6-6-6 pentacycles types). However, acyclic, mono-, di-, tri-, and hexacyclic scaffolds have also been isolated and identified from natural sources and their structures is said to be derived from squalene, an important intermediate in biogenesis of various plant metabolites (Buckingham, 2002). Ursanes and oleananes such as oleanolic acid, ursolic acid, maslinic acid, uvaol, and erythrodiol are the major triterpene skeletons present in higher plants including commonly consumed plant foods (Abe *et al*., 1993; Connolly and Hill, 2001). Other groups of triterpenes occur widely in edible or inedible plants (Yin M., 2012).

Triterpenoids as Bioactive Compounds Against Malaria

Triterpenoids may contain a variety of functional groups. Many important triterpenoids or triterpenes contain hydroxyl groups and they are considered as important bioactive compounds against malaria because a reasonable number of the triterpenoid compounds have been experimentally investigated (*in vivo* and *in vitro*) and found to eliminate malaria parasites significantly as evidenced in the reported triterpenoid compounds in this review.

Triterpenoids and Their Derivatives Based Antimalarial Agents

Murata *et al*.(2008) isolated two acyclic triterpenoids, namely ekeberin D5[1] and 2-hydroxymethyl-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18 tetracosatetraene[2] from the stem bark of *Ekebergia capensis (Zingiberaceae)*. Compounds **1** and **2** exhibited anti-malarial activity against the chloroquine-resistant K-1 strain, with IC_{50} values of 137µM and 59µM showing low and moderate activity respectively. Compounds **2** exhibited potent anti-malarial activity against the FCR-3 strain of *P. falciparum*, with IC_{50} value of 18µM respectively.

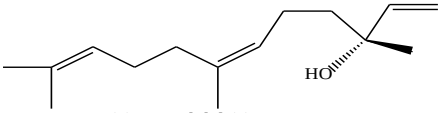
Similarly, Delola *et al* (2008) obtained 2-hydroxymethyl-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene[2] from the stem bark of *Ekebergia capensis*. Compound **2** was screened *in vitro* against chloroquine-resistant (K-1) *P. falciparum* isolates and was found to exhibit good antiplasmodial activity, showing IC_{50} value of 7µM. Compound **2** at a dose of 500 mg/kg indicated moderate parasitemia suppression of 52.9% against *P. berghei* NK65 in a mouse model.

Ayimele *et al.* (2004) isolated (+) S-nerolidol[3] from the seeds of *Aframomum escapum* which is an important constituent of essential oils used in the treatment of malaria. This compound is also discovered in Artemisia herba alba and in lemon grass, and is able to inhibit the development of the intra erythrocytic stages of chloroquine-resistant K-1 strain.

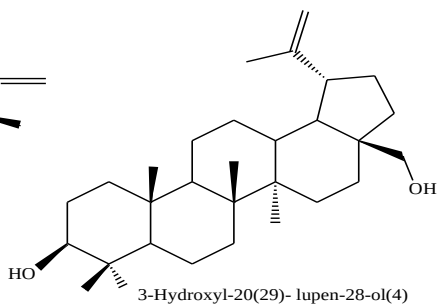
The crude organic (methanol/dichloromethane (1:1)) extract of the leaves of *Schefflera umbellifera (Araliaceae)* exhibits promising anti-malarial activity. Bioassay-guided fractionation of this extract yielded the active compound, 3-hydroxy-20(29)-lupen-28-ol[4] which was isolated by Mthembu (2007) and it was discovered to exhibit good anti-plasmodial activity: IC_{50} of 3.2µgmL^{-1}, when tested against a chloroquine-susceptible malarial strain (D10). The standard compound (chloroquine) gave an IC_{50} of 27.2µgmL^{-1}.

Ekeberin D5 (1)

2-hydroxymethyl-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene (2)



(+) S-nerolidol (3)

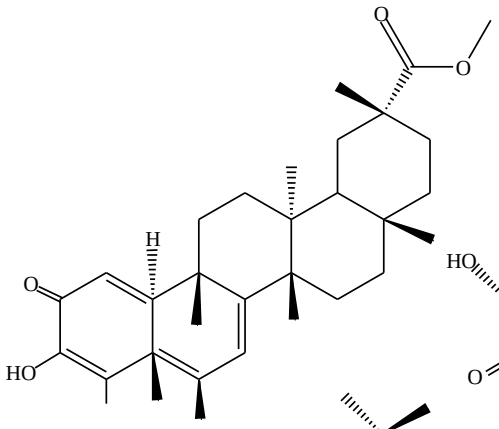


3-Hydroxyl-20(29)- lupen-28-ol(4)

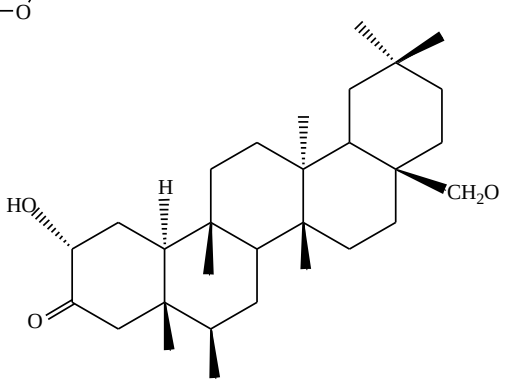
Also, Khalid *et al* (2007) isolated quininemethide triterpene, pristimerin or (20α)-3-hydroxy-2-oxo-24-norfriedela-1(10),3,5,7-tetraen-carboxylic acid-(29)-methylester[5] from the chloroform extract of the root bark of *Maytenus senegalensis (Celasterceae)* harvested from Sudan. The *in vitro* anti-plasmodial activity of the isolated compound[5] against chloroquine-resistant strain (D2) of *P. falciparum* was IC_{50} = 0.5µg mL^{-1}disclosing excellent activity while the cytotoxicity on lymphocyte proliferation model was detected at IC_{50}= 6.8µgmL^{-1}.

In another development, Ngouamegne *et al.* (2008) obtained a novel friedelane triterpenoid named endodesmiadiol[6], as well as three well known compounds friedelin[7], canophyllol[8] and canophyllal[9] were isolated from the ethyl acetate extract of the stem bark of *Endodesmia calophylloides(Guttiferae)*, a tree found in Nigeria, Cameroon, Gabon and Angola, and were assayed against the W2 chloroquine-resistant strain of *P. falciparum*. The IC_{50} of compound endodesmiadiol[6] was found to be 11.8µM, indicating potent antiplamodial/antimalarial activity. Compounds friedelin[7], canophyllol[8] and canophyllal[9] were also found to be active with IC_{50} values ranging from 7.2 to 23.6µM.

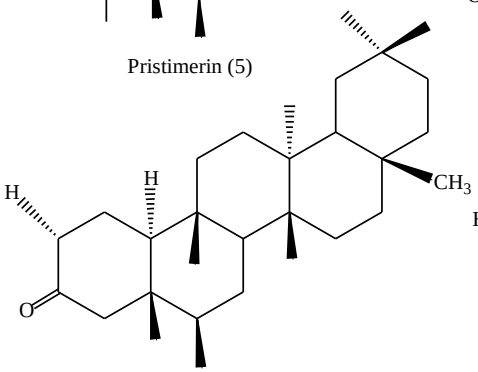
The lupane-type triterpenoids 3-oxolupenal (3-oxolup-20(29)-en-30-al)[10], 3β-hydroxylupenal (3β-hydroxylup-20(29)-en-30-al)[11] and 3-oxolupenol (30-hydroxylup-20(29)-en-3-one)[12] were isolated from the leaves of *Nuxia sphaerocephala (Loganiaceae)*, along with oleanolic acid [14], its acetylated ester[13], lupeol[15] by Mambu *et al.* (2003). Among the compounds isolated from this study, **10** and **11** showed the best inhibitory activity against *P. falciparum* with the IC_{50} values between 1.55 and 4.67µgmL^{-1} *in vitro*, respectively.



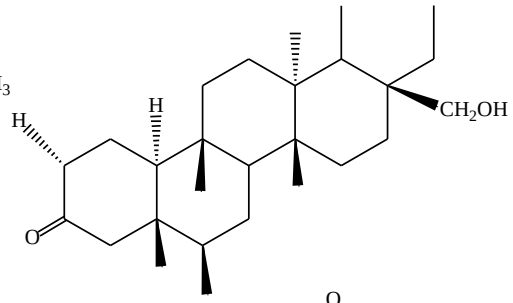
Pristimerin (5)



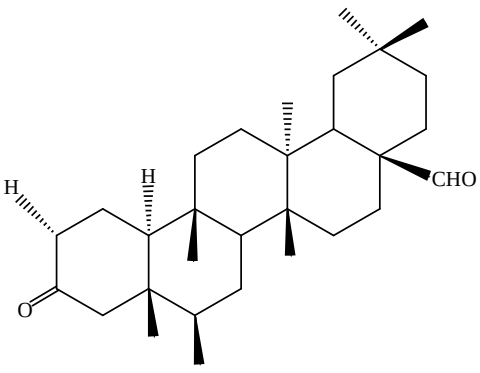
Friedalane (6)



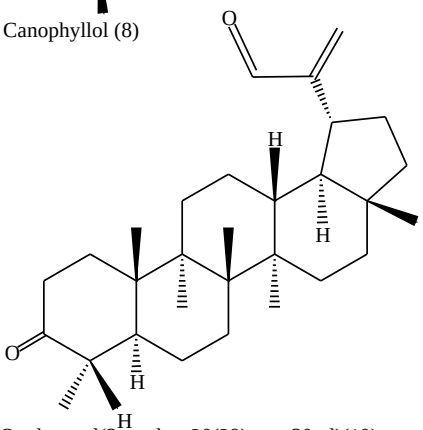
Friedelin (7)



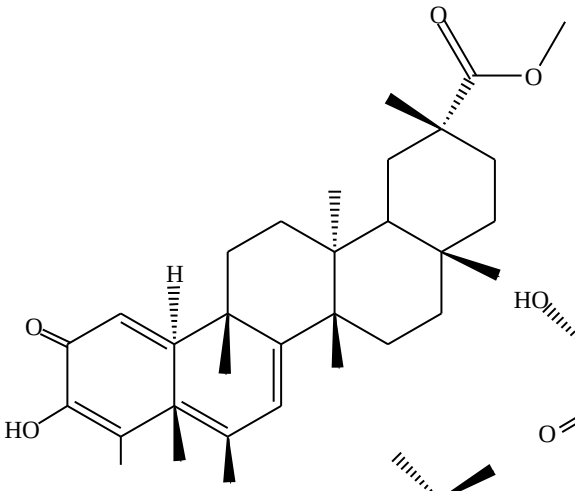
Canophyllol (8)



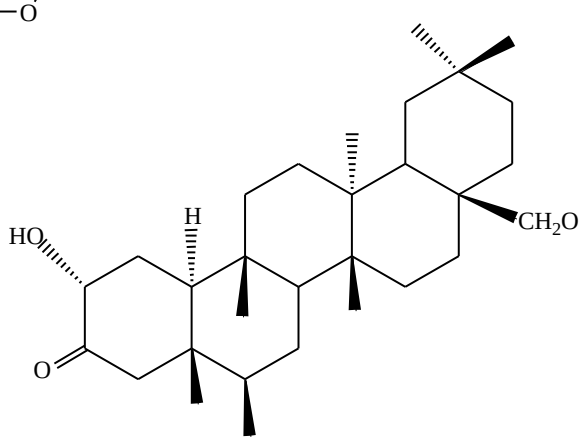
Canophyllal(9)



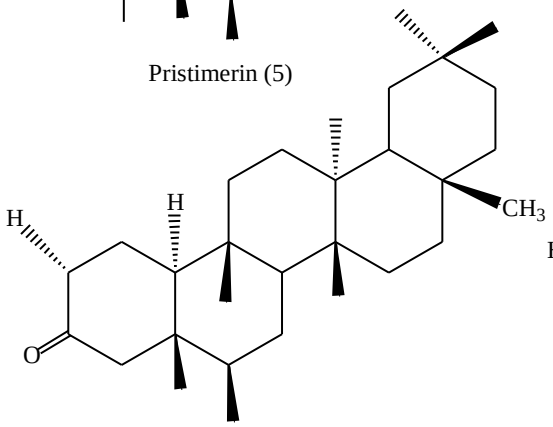
3-Oxolupenal(3-oxolup-20(29)-ene-30-al)(10)



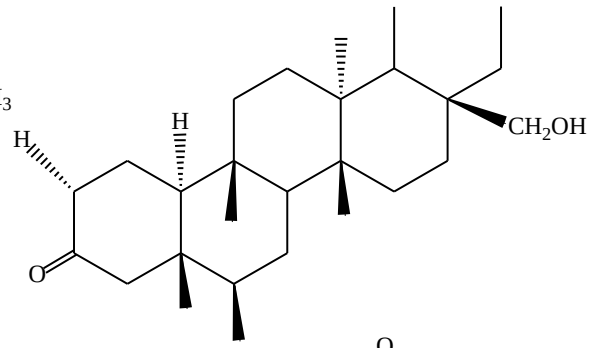
Pristimerin (5)



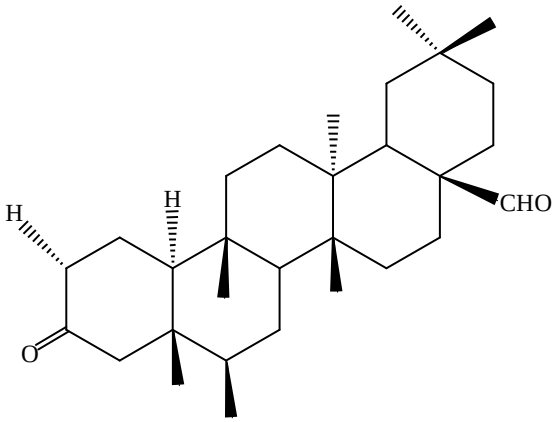
Friedalane (6)



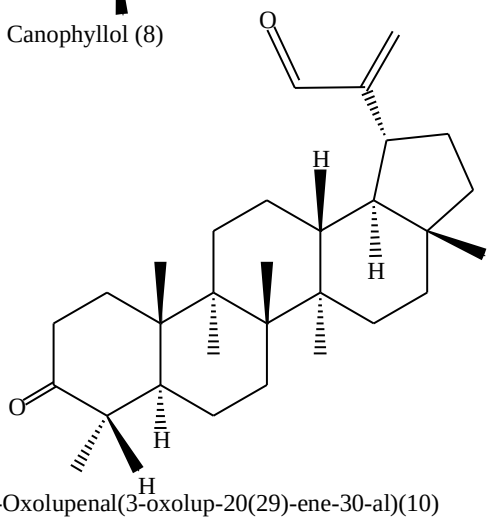
Friedelin (7)



Canophyllol (8)



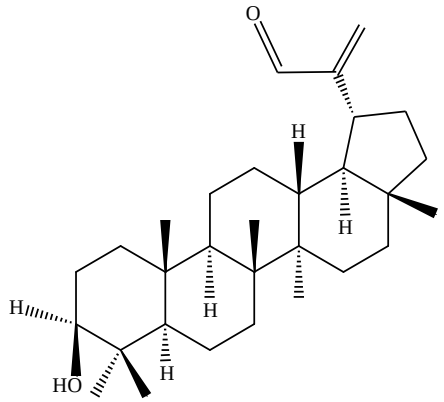
Canophyllal(9)



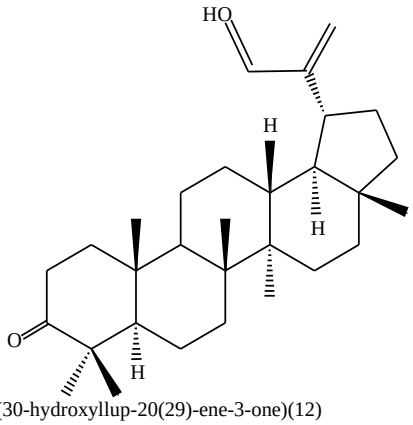
3-Oxolupenal(3-oxolup-20(29)-ene-30-al)(10)

Another lupane-type triterpene, lupeyldocosanoate[16], was isolated from the bark extract of *Hymenocardia acida (Phyllanthaceae)* collected in Chad, along with lupeol[15] by Mahmout *et al.* (2008).The anti-malarial property of compound[16] justifies the ethnobotanic use of the plant in the treatment of malaria. *Cassia siamea (Fabaceae)* was identified from an ethnobotanical survey of southwest Nigeria as a remedy for febrile illness. Bioassay-guided fractionation of stem bark of the plant extract, using the parasite lactate dehydrogenase assay and multi-resistant strain of *P. falciparum* (K1) for assessing *in vitro* anti-malarial activity led to the isolation of lupeol[15] from the ethyl acetate extract. The compound[15] was found to be one of the active principles responsible for the anti-plasmodial property with IC_{50} value of 5µgmL^{-1} revealing good antiplasmodial activity. The compounds 22-hydroxyhopan- 3-one[17] and 24-methylene cycloartenol[18] were isolated by Bickii *et al.*(2007) from the stem bark of *Entandrophragma angolense(Meliaceae)* had moderate activities against *P. falciparum* W2. Zofou *et al.*(2011) evaluated the anti-plasmodial activity of betulinic acid[19] from the ethyl acetate of the stem bark of the African St John's wort, *Hypericum lanceolatum (Hypericaceae)*.The compound had an $IC_{50}$of 2.05µgmL^{-1}.Lenta et al (2008) have identifted betulinic acid[19] and friedelan-3-ol[20] from n-

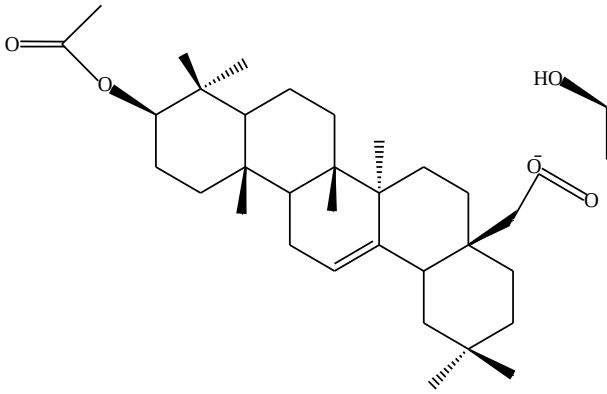
hexane extract of *Psorospermum glaberrimum* from Cameroon which showed excellent anti-plasmodial activity against the *P. falciparum* W2 strain, with IC_{50} of 0.87µg mL^{-1}. The quantified *in vitro* activity of compound[19] against the *P. falciparum* W2 strain gave an IC_{50} of 2.33µgmL^{-1} indicating good activity. Mbah *et al.* (2011) isolated 3-O-betulinic acid p-coumarate[21] from ethylacetate/hexane extract of the stem bark of *Baillonella toxisperma*, with an IC_{50} of 1.65µM indicating potent antiplasmodial activity against W2mef strain of *Plasmodium falciparum*.



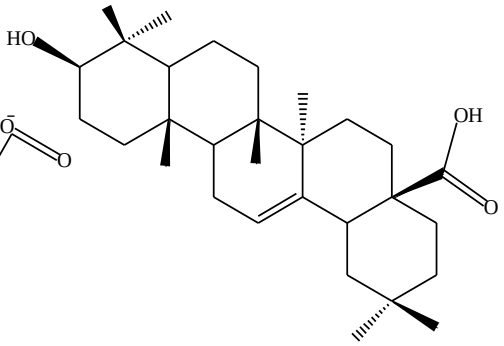
3βhydroxyllupenal(3β-hydroxylup-20(29)-ene-30-al)(11)



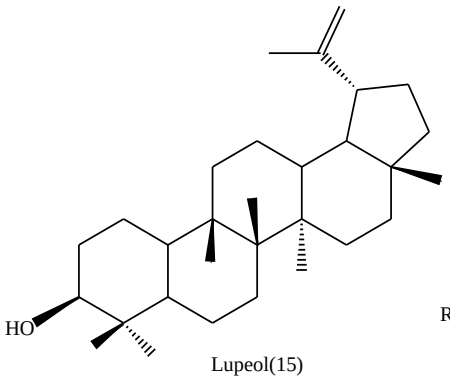
3-Oxolupenol(30-hydroxyllup-20(29)-ene-3-one)(12)



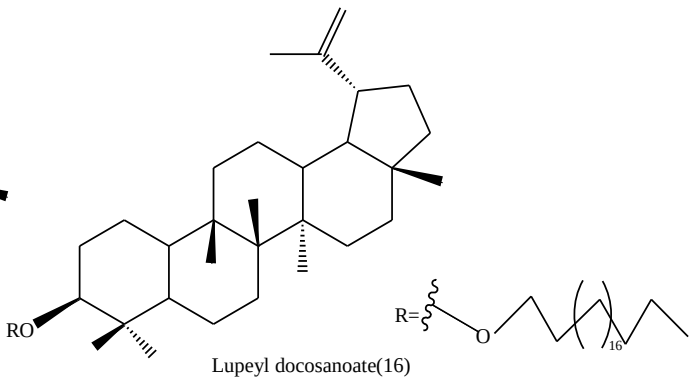
3β - Acetyloleanolic Acid (13)



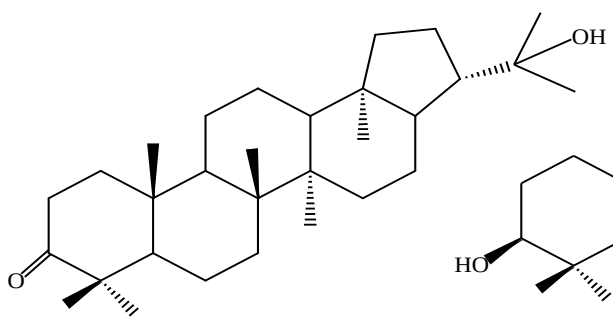
Oleanolic Acid (14)



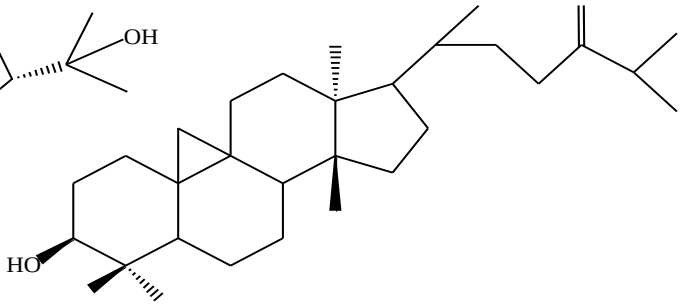
Lupeol(15)



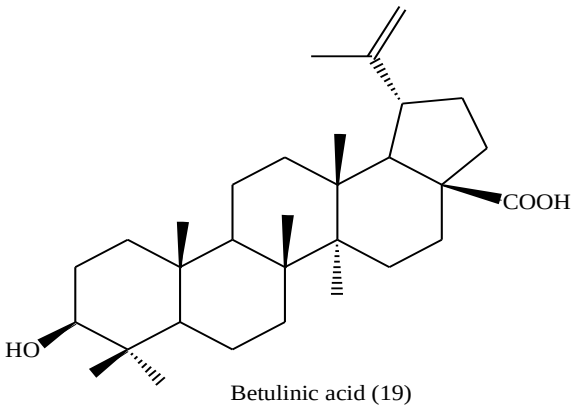
Lupeyl docosanoate(16)



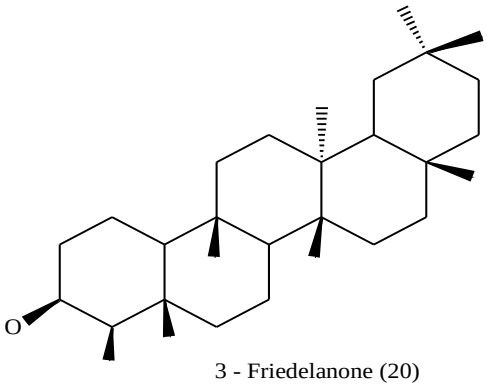
22-Hydroxylhopan-3-one(17)



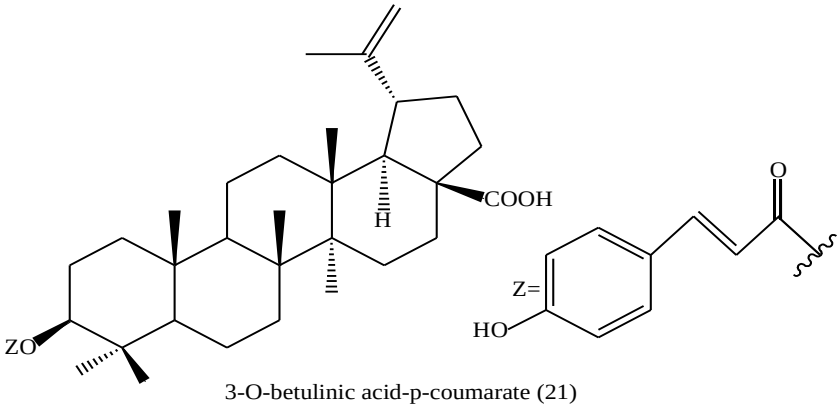
24-Methylene cyloatenol(18)



Betulinic acid (19)



3 - Friedelanone (20)

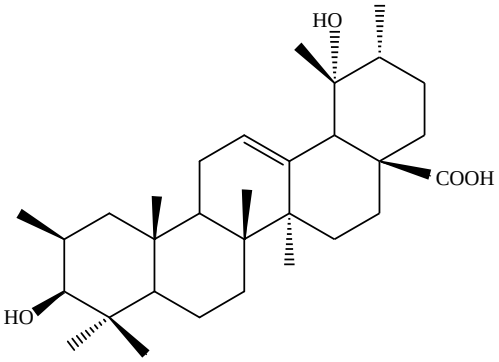


3-O-betulinic acid-p-coumarate (21)

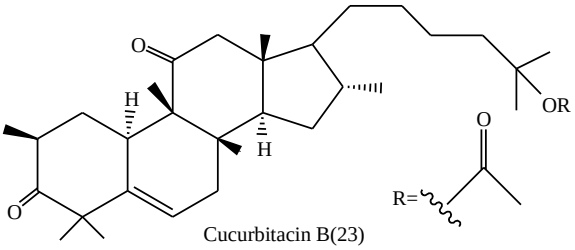
The triterpenoid 2β,3β,19α-trihydroxy-urs-12-20-en-28-oic acid[22] was isolated by Zofou *et al.* (2012) from the stem bark of *Kigelia africana (Bignoniaceae)*. This compound exhibited an IC_{50} of 1.86µM against the W2mef strain of *P. falciparum* revealing good activity.

Banzouzi *et al.*(2008) isolated three compounds i.e. Cucurbitacin B.[23], Cucurbitacin D[24] and 20-epibryonolic acid[25] from *Cogniauxia podolaena (Cucurbitaceae)* which were evaluated for anti-plasmodial activity(on FcM29, a chloroquine-resistant strain of *P. falciparum*) and cytotoxicity (on KB and Vero cell lines). The compounds indicated IC_{50} values of 1.6, 4.0 and 2.0µgmL^{-1} on FcM29 respectively exhibiting strong activities. Compounds **23** and **24** both revealed high cytotoxicity where as compound **25** showed a better selectivity index. The respective IC_{50} values of 1.6, 4.0 and 2.0µgmL^{-1} on FcM29 scientifically validated the traditional use of *Cogniauxia podolaena (Cucurbitaceae)* in Congo Brazzaville for the treatment of malaria.

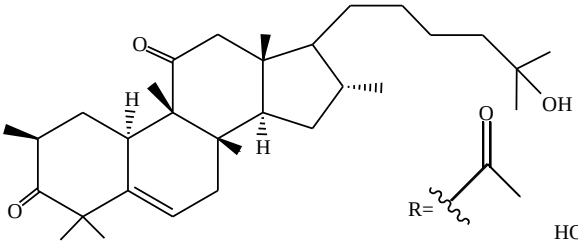
Barthélemy *et al.* (2012) have obtained the following compounds, 16-β-hydroxylupane-1,20(29)-dien-3-one[26], (3β)-3-hydroxyolean-12-en-28-oic acid[27] and 3β-hydroxy-olean-5,12-dien-28-oic acid[28] from the methylene chloride crude extract (PeBMc) of the stem bark of *Parinari excels* with IC_{50} values of 28.3µM, 69.9µM and 77.9µM against *Plasmodium falciparum* (K-1) strain respectively, of which these three triterpenes showed moderate activities. Thiem *et al.* (2005) isolated 20-epi-Isoiquesterinol[29] from the pet-ether extract of the root bark of *Salacia madagascariensis DC(Celestraceae)* with IC_{50} value of 0.16µgmL^{-1} showing excellent and significant activity against both strains of *Plasmodium falciparum* D6 and W2.



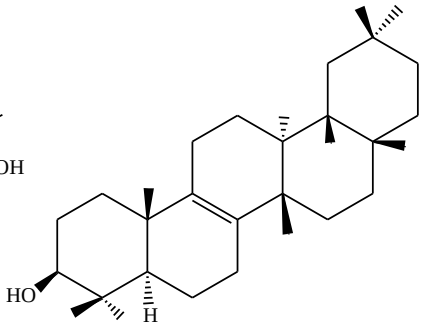
2β, 3β, 19α -Trihydroxyl-urs-12-20-en-28-oic acid (22)



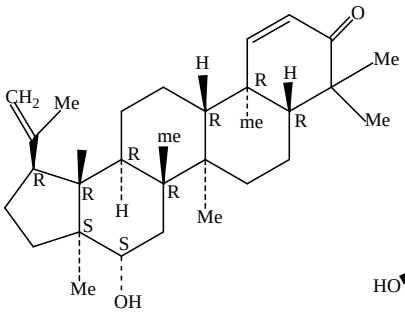
Cucurbitacin B(23)



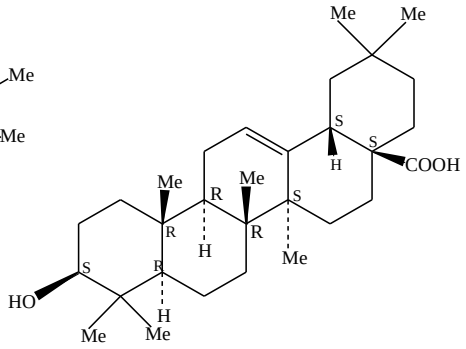
Cucurbitacin D(24)



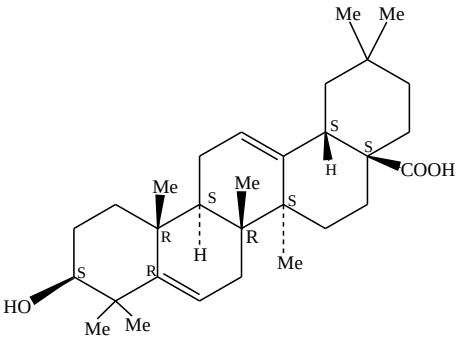
20- Epibryonolic acid (25)



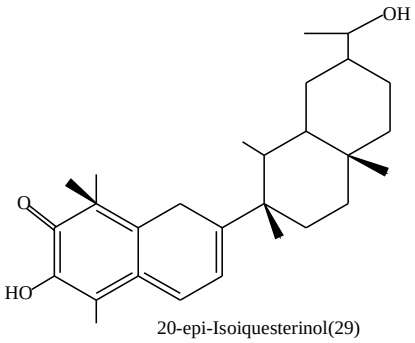
16β- hydroxylupane-1,20(29)-diene-3-one (26)



3β -3- hydroxyolean - 12-en-28-ioc acid (27)



3β- 3- hydroxyolean -5,12- dien - 28 - ioc acid (28)



20-epi-Isoiquesterinol(29)

DISCUSSION

Based on available and reported antiplasmodial activities IC_{50} data on triterpenes and their derivatives reviewed in this survey and compared with indices/criteria for interpretation of antiplasmodial activities stated earlier, compounds **5, 20** and **29** displayed excellent antiplasmodial activities, compounds **4,10, 11, 15, 19, 21, 22, 23, 24** and **25** indicated good antiplasmodial activities, compounds **2, 6, 7, 8, 9**, **17, 26, 27 and 28** exhibited moderate antiplasmodial activities, only compound **1** showed low antiplasmodial activity. However, IC_{50} values of compounds **3, 12, 13, 14** and **18** were not reported due to inaccessibility of their empirical data in the abstracts of the published articles which were reviewed.

Compounds **4, 5, 10, 11, 15, 19, 20, 21, 22, 23, 24, 25** and **29** revealed promising, interesting and significant antiplasmodial activities against various strains of *Plasmodium falciparum*, despite the fact that compounds **2, 6, 7, 8, 9, 17, 26, 24** and **25** displayed moderate antiplasmodial activities against specific strain of *Plasmodium falciparum*, their activities could be improved via appropriate structural modifications or in synergy with either already existing synthetic antimalarials or isolated antiplasmodial compound(s) which may not necessarily be triterpenes and their derivatives but other antiplasmodial compounds of interesting activities with little or no cytotoxicity belonging to any class of organic compounds.

CONCLUSION

In this survey, attempt has been made to review twenty nine (29) triterpenes and their derivatives based-antimalarial compounds isolated from medicinal plants and investigated for their antimalarial property. Many of the triterpene compounds and their derivatives possess interesting antimalarial property and may present an array of potential lead compounds towards development of novel antimalarial drugs.

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