ACTIVITY OF TERPENOIDS OF HERBAL MEDICINE IN THE THERAPY OF MALARIA

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ABSTRACT

Malaria is disease cause death for large number of the people as affect in economic status in most countries. This disease main obstruction to socioeconomic expansion in the endemic worldwide.

Resistance of the \textit{Plasmodium falciparum} to the drugs encouraged researchers to make herbal medicine as that have molecules with might assortment of the structure and pharmacological activity such as sesquiterpenes and triterpenoid are chemically modulate of the parasite and inhibition several operation within of the molecules then result in parasite death. Terpenes contain several functions in plants such as thermoprotectant, marking function, notable finite for pigments, oregano also solvents.

These review award the significant of the terpenoid as robust compounds with biological effective ready naturally in different plant compounds can be isolated therapeutic competencethrough examined and development promised activities as antimalarial.

Keyword: Terpenoids, Herbal medicine, Antimalarial, Bioactivity, Extract plant.

I. INTRODUCTION

Malaria is protozoan of the common infectious diseases and cause by of the \textit{Plasmodium} genus parasite and killed more than millions individuals of the world \cite{1}. The World Health Organization reported in 2018 through period from 2015-2017 that no fundamental advance was in reduce worldwide malaria cases in this time \cite{2}. There are 4 species from the \textit{Plasmodium} cause malaria in the humans are \textit{P. falciparum}, \textit{P. ovale}, \textit{P. vivax} and \textit{P. malariae}. Consider \textit{P. falciparum} is resulting more in morbidity and mortality mainly with malaria injury \cite{3}. Being the most prevalent malaria by \textit{P. falciparum} and \textit{P. vivax} in subsaharan africa and americas areas are responsible when 99.7% and 74.1% of infected malaria cases at 2017 \cite{4}. The causal agent where transport by Anopheles female mosquito species improved impedance against insecticides like dichlorodiphenyltrichloroethane (DDT) also chemoprophylaxis have not shake expect results \cite{5}. Important symptoms of malaria were high fever, triedness, cephalalgia, muscle ill, abdominal nuisance and copious sweating, in extremist cases without treatment will brain tissue damage, edema pulmonary, kidney fail, anemia, yellow change in color the skin and decrease blood sugar \cite{6}. Resistance most common drug used as antimalarial is menace to mankind \cite{7}. Ethnopharmacology sources funded that plant compounds can be used as template for preparation components as antimalarial \cite{8}. Ease is potent depot of antimalarial substance to plants has chemical repertoire agents with sundry valences \cite{9}. Plants are prosperous by phytochemicals and very active in a treatment of the malaria like sesquiterpenes, sesquiterpene lactones, flavonones, fluoroquinolones, alkaloids and quinones \cite{10}. These active compounds metabolites contain quinine and artemisinin are obtain from and generally antimalarial drugs successful. Artemisinins plant of \textit{Artemisia annua} due to Asteraceae family, actually contain whole part against \textit{P. falciparum} strains combination therapy contributed to treatments \cite{11}. Presence of chemical peroxide connection bridge to the Artemisinin asmost sesquiterpene lactone likely purpose for effect against malarial, split the peroxide connection bridge existence the II iron ions dusty free in forms radicals which bear fast rearrangement compose most steady.
carbon radical so chemically cause parasite modulate and inhibited different operation within the molecules parasite then the death\textsuperscript{[12]} Most families such as Myrtaceae, Rutaceae and Aloeaceae use in malaria treating as plant portions great use in treated malaria were 54.4\% leaves, 17.4\% roots and 16\% bark all herbals and only plant accessories are use\textsuperscript{[13]}.

In these review effort have highlight on antiplasmodial royalty of the antimalarial herbal medicine by different sources.

**Terpenoids**

The terpenoidis natural in progress secondary metabolic existing in plant; the terpenoids are known as isoprenoids is varied category of natural passing organic chemicals obtain from terpenes. Generality are multicyclic frame with oxygen contain functional combination\textsuperscript{[14]}. Terpenoids contain alcohol functional combination is emerge through hydrolysis the carbocation moderate produce of geranyl- pyrophosphate and hydrolysis of the moderate of farnesyl-pyrophosphate grant sesquiterpenoid, hydrolysis of the moderate of geranyl-pyrophosphate grant the diterpenoids\textsuperscript{[15]}. Terpenoids is natural outputs divided into many of Isoprene units these components known with Isoprenoids. Productisoprene units of a biogenetic wherewithal start of acetate mevalonic acid as that each unit push back of 5 carbon have 2 unsaturated chainso have ferrorchid. Number of terpenoids possess from isoprene units connected jointly in head for tail style\textsuperscript{[16]}.

**Classification of Terpenoids**

Classified of Terpenoids depending on number from the isoprene units (C5H8)\textsuperscript{[17]}, mingle to specified unsaturated hydrocarbon of terpenoid jot: Monoterpenes are terpenes contain two isoprene units as (C10H16)is molecular formula\textsuperscript{[18]}. Sesquiterpenes are terpenes contain three of isoprene units as (C15H24)is molecular formula\textsuperscript{[19]}. Diterpenoids are terpenes contain four isoprene units as (C20H32) is molecular formula\textsuperscript{[20]}, Triterpenes are chemical compounds contain three terpenes units as (C30H48)is molecular formula\textsuperscript{[21]}. As in Fig. 1

![Terpenoids Classification](image)

**Herbal medicine used in the therapy of Malaria**

Sesquiterpenes they corymbolone (1) and mustakone(2) are isolation by chloroform extracted from rhizomes of the* Cyperus articulatus* due to (Cyperaceae) offer against plasmodiacharacteristic, value IC\textsubscript{50} was (4.53-0.64mM) versus NF54 so IC\textsubscript{50} was 8.14 and 1.15 mM against EN36 \textsuperscript{[22]}. The sesquiterpene lactones to eudesmanolideand germacranolide these genderoffering anti-plasmodial effective versus D10 which separate and specified sivasinolide (3) where IC\textsubscript{50} was 9.9 mM as tatridin A where IC\textsubscript{50} was 1.5 mM versus D10 (4), tanachin value IC\textsubscript{50} was 1.5 mM (5). 3 lactones showed great anti-malaria action versus FcB1 and value IC\textsubscript{50} was (1, 0.19, 0.41mM) this component are toxic to KB cells when IC\textsubscript{50} was 1mM in all injured \textsuperscript{[23]}. Flowers and leaves of the* Artemisia gorgonum* belong to family (Asteraceae) gathered from fogo was phytochemically examined and outcames this isolated from germacranolide and hanphyllin (6) appeared anti-plasmodial action when IC\textsubscript{50} was 9.7mM versus FcB1 solotoxic to vero cell where IC\textsubscript{50} was 111.9 mM\textsuperscript{[24]}. Also sesquiterpene lactones, wedelolides (7) isolated from Wedelia trilobata leaves this compounds show antimalarialeffective with IC\textsubscript{50} was 4.2 and 9.1 mM \textsuperscript{[25]}. Fragments the dichloromethane extracted leaves of the* Vernonia staelhelinoides* (Asteraceae) is isolation of 2 structural linked hirsutinolid these compounds have power anti-plasmodial action contra D10 also have low active contra K1 and 8a-2-methylacryloyloxy-3-oxo-1-desoxy-1,2-dehydrohirsutinolide-13-o-acetate have 0.6 mM.

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16611
isIC50 on D10 and IC50 was 4.5 mM K1 and (8), 8a-50-acetoxysenecioyloxy-3-oxo-1-desoxy-1,2-dehydrohirsutinolide-13-o-acetate have IC50 was 0.5 mM / D10, IC50 was 5.5 mM / K1 compound, these component were exist to be toxic for mammalian cells in same concentrated [26]. Chemically, the Camchaya calcarea due to family (Asteraceae) where isolated from 8 type sesquiterpene lactones offered modest antiplasmodial action versus K1 like goyazensolides (9) value IC50 was 3.3 mM, 5-epi-isocentratherin (10) where IC50 was 8.0 mM [27]. Bioactivity planned where isolation of the chloroform from Carpesium rosulatum of the sesquiterpene lactone, inepua-torolide A (11) found great anti-plasmodial effective versus D10 with 19 nM value IC50 [28]. Linear sesquiterpene lactone 4-Hydroxyanthecotulide (12) isolated of Anthemis auriculata, was rectify versus K1 and was 7.6 mM value IC50 [29]. 3 new indolo-sesquiterpene are 8α-Polyveloinone (13), N-Acetyl-8α-Polyveloinone (14) N-Acetyl-Polyveloine (15) these compounds isolated from Polyalthea oliveri (Annonaceae) in stem bark these act on mild antiplasmodial effective against NF54 strain P. falciparum with cytotoxicity on myoblast (L6) [30]. Reported by [31] where isolation 2 sesquiterpene are polythlenol (16) and N-acetyl-polyveloine (17) from tree of Greenwayodendron suaveolens (Annonaceae) observed that these compounds led to activity contra K1P. falciparum with value 2.8 μM was IC50. 2 sesquiterpenic lactones secluded from Acanthospermum hispidum reaped isolated 15-Acetoxy-8β-2-methylbutyryloxy-14-oxo-4,5-Cis-Acanthospermolide (18) and 9α-acetoxy-15-hydroxy-8β-(2-methylbutyryloxy)-14-oxo-4,5-trans-acanthospermolide (19) noted antiplasmodial activity in vitro compare to cytotoxic contra human fibroblasts cell line with IC50 was 2.9 and 2.23 μM [32]. In standard phytochemical analysis techniques used thin layer and column chromatography solvent extraction isolate eudesmanolide sesquiterpene lactone type dehydrobrachylaenolide (20) of Dicoma anomala of south Africa in vitro with IC50 was 1.865 μM strain (D10) of antimalarial activity. [33][34] demonstrated that Warburgia ugandensis belong family (Canellaceae) of Ethiopia across Trypanosoma brucei and P. falciparum with in vitro refer activity of antimalodial the existence coloratan and drimane sesquiterpene were 4-13, 7-Coloratadiene-12,11-Olide (21), 11α-(Hydroxymuzigadiolide) (22), Muzigadiol (23), 6α,9α-Dihydroxy-4,13,7-Coloratadiene-11,12-Dial (24), Cinnamolide(25), Cinnamolide-3β-Acetate (26), Mukaadial(27) also Ugandensidial (28) with IC50 was 114 μM. As in Fig.2
Isolated from leaves and stems of Croton lobatus (Euphorbiaceae) is geranylgeraniol(29) consider medicine plant used in Africa in treatment malaria, dysentery and pregnancy problems these compound reasonable antiplasmodial effective against K1 and IC50 was 3.7 mM \[35\]. Steenkrotin A (30) is diterpenoid isolated from by ethanol leaves extract of Croton steenkampianus belong to (Euphorbiaceae) and examined contra D2, D6, D10 and W2 showed mild effectivewas 15.8, 30, 9.4 and 9.1 mM value IC50\[36\]. 3-deoxyaulacocarpin A (31) is labdane diterpenoid isolated from the Aframomum zambesiacum seeds(Zingiberaceae) have antimalariaactivity versus FcB1 and was 4.97 mM value IC50\[37\]. from the fruits wereisolated of Juniperus seravschanica to (Cupressaceae) showed hopeful antimalarial activity are cedrol (32) and IC50 was 265 mM, sugiol (33) and IC50 was 1.6 mM and 13-Dien-19-O-Acid (34) and IC50 was 2.2 mM against D6, W2 and TM91C235\[38\]. Bioassay planned fractionation of the stem bark extracted of the Laetia procera from family (Flacourtiaiceae) which deposition of diterpenoids, Casearlicin A, Clerodane (35) and Casamembrol A (36) that diterpenoids display antiplasmodial activity and IC50 was 6.04 mM on F32 and FCB1 strain but most cytotoxic to laeiaprocerine (37)\[39\]. Bioactivity planned fraction of hexane extraction for Casearia grewiifolia bark (Flacourtiaiceae) bear 4 clerodane diterpenes are caseargrewiins A(38), D (39) andrel-2S,5R,6R,8S,9S,10R,19R-18,19-Diacetoxyl-18,19-Epoxo-2-Methylbutanoyloxy- Cleroda-3,13,14-Triene (40) these component show anti-malaria effective versus K1 when IC50 was 5.6, 3.7, 5.3, 7.8 and 6.1 mM, consider cytotoxic\[40\]. Isolated diterpenes from CH2C12 Caesalpinia crista extract (Caesalpiniaceae) from Indonesia were fated versus FCR-3-A2 rewrite and antimalarial activity. Caesalpins-MA (41), Norcaesalpins-MC (42), MD (43), Caesalpins-C (44) and P (45), norcaesalpins E (46), caesalmins B (47), caesaldekarin E (48), 2-acetoxyl-3-deacetoxylcaesaldekarin E (49), bonducellins B (50) 1-Deacetoxyl-1-Oxocaesalamin-C (51) showed anti-malarial effective IC50 of 3.6, 3.7, 4.2, 7.0, 0.65, 3.1, 1.0, 6.5, 0.65, 0.40, 1.7 mM\[41\], 3 cassane furano diterpenoids isolated of the EtOAc extract Caesalpinia bonduc (Caesalpiniaceae), Bonducellins G (52) offeredactivity of antimalarialin K1 strain and IC50 was 1.6, 3.8 and 5.8 mM respectively \[42\]. 6a-7diacetoxylvouacapane compound (53) isolated from Bowdichia nitida seeds (Leguminosae) showed hopeful activity of anti plasmodial and against 3D7 where IC50 was 969 nM and perfect selective indicator with cytotoxic when IC50more than 250 mM \[43\]. Bioactive navigable partition of petroleum ether extracted for leaves from Hypitis suaveolens due to (Lamiaceae) use in classical medical where isolated of a betaine diterpenoid type ofendo-peroxide and 13a -Epoxiabiet-8-en-18-Ol (54) offering rise antiplasmodial effective against D10and IC50 was 344 nM \[44\]. Bioactivity of the Juniperus procera, (Cupressaceae) berries and nuts harvest fresh compounds, Abieta-7,13-Diene (55) so ferruginoll (56) explained anti-malarial effective versusw2, D6 strainandwas 7.0 value IC50and 7.4 mM \[45\]. The activity against antimalarial of ferruginol at IC50 was 6.8 mM seclusion of Fuerstia africana (Lamiaceae) was cytotoxic action andunfavorable anti-malarial \[46\]. Isolated of the Pedilanthus thithymaloides white latex belong to (Euphorbiaceae) werederterpenes Poly-O-Acylated-Arrophe, 1a, 8b, 9b, 14a, 15b-Pentaacetoxyl-3b-Benzoxyloxy-7-Oxojatropha-5,12-Diene (57) and 1a, 8b, 9b, 14a, 15-Bhexaacetoxyl-3b-Benzoxyloxy-5b-Hydroxyjatropha-6(7),12,Diene (58) shown high oxygenated diterpenes have scarce O-Acetyl-enol-Moiety as explain anti-plasmodial effective versus K1 line when IC50 was 5.9 mM) and IC50 was 5.8 mM \[47\]. Isolated two diterpene caesalminines A (59) and caesalminines B (60), have tetracyclic cassane diterpenoid typeof Caesalpinia minax (Fabaceae) seeds, found these compounds act as antiplasmodial with IC50 were 0.42 and 0.79 μM \[48\]. By \[49\] where isolated diterpenes compound, deoxycaesaldekalin C (61) and caesaldekarin C (62) by used chloroform and ethyl acetate extracts
*Caesalpinia volkensii* root bark these two act as antiplasmodial activities with IC50 was 25.67 and 30.33 μg mL-1. As in Fig.3.
Triterpenoid derivative bleakness of *Ekebergia capensis* from stock bark (Meliaceae) against K1 so FCR-3 strains, 2,4,23,24-tetrahydroxy-3,7,11,16,19,23-hexa-methyl-6,11,15,18-tetra-cosatetraene (63) explain that IC50 was 18 and 8 mM as noted in vivo parasite in blood extinction 33.9% by giventhere intraperitoneal[56]. Isolated by ethyl acetate extract from *Nuxia sphaerocephala* leaves Buddlejaceae 3b-hydroxy-lupenal (64) and 3-oxolupenal (65) has the superior activity against FcB1 with IC50 was 3.6 and 7.2 mM [51]. Ceanothane and lupine are triterpenes isolated from *Ziziphus cambodianus* (Rhamnaceae) root bark, 3-O-vanillylceanothic acid (66) and zizyberenallic acid (67) these compounds revelation prominent antiplasmodial activity and IC50 was 5.8 and 6.6 mM[52]. Bioassay fraction due to bleakness of the Betulinic acid-3-caffeate (68) from arid twigs and andeleves of the *Diospyros quaesitadue to (Ebenaceae)* display these compounds effectiveness as antimalarial against W2, D6 and IC50 was 1.40 and 0.98 mM[53]. Phytochemical research of the *Erythrina stricta* (Leguminosae) the CH2Cl2 extracts from roots and stems of *Erythrina subumbrans* (Leguminosae) where isolation of one triterpene and soyasapogenol B (69) which offered effective against plasmodial when IC50 was 10.0 mM[54]. Garcinane (70) is isolated from *Garcinia polyantha* (Clusiaceae) roots also notable activity of antimalarial against NF54 and IC50 was 4.1 mM [55]. Bioassay partition due to deposition of 2a,3b-Dihydroxyolean-12-En-29-Oic acid (71) so *Grewia bilamellata* belong to (Tiliaceae) noted that as anti-malarial versus D6 and W2 with IC50 was 21.1 and 8.6 mM and without cytotoxicity effect [56]. Bioassay partition from leaves of *Morinda lucida* (Rubiaceae) and Satureja parvifolia (Lamiaceae) isolation of triterpenic acid(72), oleanolic acid and ursolic acid compound showed rectify in vitro studies noted activity with IC50 was 6.7 and 10.6 mM tofrolic acid and 32.4 and 19.7 mM to oleanolic acid dose daily of 200 mg/kg[57]. Isolated 3 triterpenes of *Cogniauxia podolaena* belong family (Cucurbitaceae) was Cucurbutin-B (73), Cucurbutin-D (74) also 20-Epibryonolic acid (75) these component examined withaction as antiplasmodial and cytotoxic with IC50 was 2.8, 7.6 and 3.8 mM [58]. The *Picrolemma sprucei* (Simaroubaceae) from roots and stems isolated quassinoid (76) and neoerogeloleide (77) shown inhibited effect on malaria with IC50 was 2 mM [59]. Azadiradione (78) and Dukunolide-C (79) where seclusionof *Lansium domesticum* due to (Meliaceae) seeds offered effected as anti-malarial versus K1 and IC50 was 4.1 and 9.6 mM [60]. Used *Chisochetoniansensis* (Meliaceae) in examined for antimalarial by isolated two limonoids from seeds are dysobinin (80) and mahonin (81) notable have inhibitory effect versus plasmodium so IC50 were 4.4 and 5.8 mM [61]. *Pseudocedrela kotschyi* (Meliaceae) by dicholoromethane extract from root used in Malian herbal medicine where isolation 7,deacetylgedunin (82) 7,deacetyl-7-oxogedunin (83) haveaction versus *P. falciparum* with IC50 was 3.1 and 4.1 mM [62]. Reform the versus plasmodia action of the Betulinic acid (84) of the *Hypericum lanceolatum* (Hypericaceae) from stem bark the compound has IC50 was 2.05 μg mL−1. **Fig3** showed diterpenes with promising effective against different of *P.falciparum* strains.
is 2β,6β,19α-trihydroxy-urs-11-20-en-28-Onic acid compound (85) isolated of *Kigelia africana* (Bignoniaceae) stem bark with IC50 was 0.91 μg mL⁻¹ notable activity versus W2 line of *P. falciparum* as in Fig. 4.

**II. CONCLUSIONS**

In this present review the terpenoids components scelusion from herbal medicinal and explored recently for antimalarial possession. There are great structural variety including monoterpenes, sesquiterpenes, diterpenes and triterpenes. Almost of these action compounds is examined for they

Fig. 4: showed triterpenes with promising effective against different of *P. falciparum* strains.
cytotoxic as antimalarial activity in vivo. In traditional medicine used aqueous decoction from plant for treatment to combat malaria. As consider mechanism of the terpene activity which connect to the hemin portion of erythrocytes infection where hemin synthetic of iron consider needful the plasmidium expansion in the erythrocytes and act on kills this parasite. Alasoterpenoids can effect on carbohydrate metabolic of this parasite due to lysis of the parasites; so, terpenes can be styling for be auspicious drug to malaria. The increased in anti-plasmodial action in cumin seed oil from pinene alsoraise in the percolation time concluded that favorable percolation time for raised antimalarial action is 5-7.5 min. The almost plentiful terpene and caryophyllene have the capactity both prevented and healing malaria the caryophyllene so consider effective compound of insect repelled particularly to mosquitoes also to other blood nutrition diptera. Other new studies include silver nanoparticles synthesizing of the caryophyllene consider very activity versus Plasmodium falciparum. They, terpenescan be secure and price effectivenesses satisfactory to the malaria treatment.

REFERENCES


