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REVIEW

Terpenoids from Euphorbiaceae as a source of antimalarial medicines: A literature review

Wiwied Ekasari[1,2], Anisah Mahardiani[1], Nindya Tresiana Putri[1]

[1] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2] Center for Natural Product Medicine Research and Development, Institute of Tropical Diseases, Universitas Airlangga

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Correspondence
Wiwied Ekasari
Department of Pharmaceutical Sciences
Faculty of Pharmacy
Universitas Airlangga
Surabaya
Indonesia
wiwied-e@ff.unair.ac.id

Abstract

Background: Malaria is an infectious disease caused by the *Plasmodium* parasite and transmitted by the *Anopheles* mosquito. *Plasmodium falciparum* is a parasite that causes the most deaths. Currently, there is resistance to various antimalarial drugs. For this reason, it is necessary to search for new antimalarial agents. Medicinal plants have been shown to play an important role in treating malaria for thousands of years. Some of Euphorbiaceae family plants contains terpenoid compounds, which are compounds with antimalarial activity. **Objective:** The present review aims to provide an overview of the terpenoid compounds from Euphorbiaceae family as an antimalarial. **Method:** Comprehensive information on Euphorbiaceae family from 2002-2022 was searched for literature relevant to major science-based data, including Scopus, Science, ScienceDirect, Pubmed, and SciFinder, using appropriate keyword combinations. **Result:** A total of 15 papers were included in this review. The terpenoids isolated from 14 species of Euphorbiaceae family and reported to possess antimalarial activity are presented. **Conclusion:** Terpenoids are found in almost all parts of Euphorbiaceae family plants and are reported to have moderate to high antimalarial activity. Screening of antimalarial terpenoid activity in Ephorbiaceae family plants can be a key step in the source and development of new antimalarial drugs.

Introduction

Malaria is an infectious disease caused by parasites of the genus *Plasmodium* and transmitted by the *Anopheles* mosquito. Malaria transmission occurs mostly in tropical as well as subtropical countries and occurs in many temperate regions. It is estimated that around 300-500 million clinical cases of malaria and around 2.5 million deaths occur each year. According to the World Malaria Report 2017, there were 216 million new malaria cases worldwide in 2016, with 90% occurring in Africa (World Health Organisation, 2017). *Plasmodium falciparum* is the parasite that causes the most deaths, followed by *Plasmodium vivax* (Miller *et al.,* 1994; Naing *et al.,* 2014; Bassat et al., 2016).

Currently, there is antimalarial drug resistance to chloroquine, sulfadoxine-pyrimethamine, and so on. Cases of chloroquine resistance to P. *falciparum* were first reported in Columbia in 1961 (Moore & Lanier, 1961). The presence of the first-line antimalarial drug resistance (front-line antimalarial compound) and there has not been a successful attempt to find an ideal malaria vaccine, and it would require the discovery of an effective antimalarial drug (Ministry of Health Republic of Indonesia, 2014). For this reason, researchers need to find new antimalarial agents.

The plant of the Euphorbiaceae family has many medicinal properties. The existence of secondary metabolites as medicinal substances in this plant can be caused by stress factors of the habitat in which it grows, such as temperature, salinity, drought, and genetic factors. Euphorbiaceae is one of 25 plant families that have an important role economically. The characteristics of the Euphorbiaceae are generally a milky sap (if any), unisexual flowers, superior ovaries and generally trilocular, axile placentation, collateral ovaries, fraying with ventral raphe, and usually a

carunculate (Bennett, 2011). There are three main classes of antimalarial substances, namely alkaloids (31.9%), terpenoids (30.8%), and polyphenols (17.4%) (Bero *et al.,* 2009).

This review discusses the terpenoid compounds isolated from Euphorbiaceae with malaria activity. The journals chosen are research from 2002-2022. Terpenoids are compounds found in almost all parts of plants, such as flowers, stems, leaves and roots. Terpenoids are composed of the smallest component, called isoprene, with the general formula $(C_5H_8)_n$. Collection of isoprene can form various molecules such as hemiterpene (C_5H_8), monoterpene ($C_{10}H_{16}$), sesquiterpene ($C_{15}H_{24}$), terpene ($C_{20}H_{32}$), triterpene ($C_{30}H_{48}$), tetraterpene ($C_{40}H_{64}$), and polyterpene $(C_5H_8)_n$.

Methods

This paper is compiled based on literature review, journal reviews and reports results. The method used to search the relevant literature to explore the major scientific databases, including Scopus, Science, ScienceDirect, PubMed, and SciFinder, using appropriate keyword combinations. This review discusses 30 Euphorbiaceae family plants. Materials obtained from the results of the heirloom study by the meta-analysis method. Meta-analysis is a method of combining the results of various similar studies obtained from various articles and other scientific publications so that this study will obtain a combination of data and information describing terpenoid compounds from various types of plants that can be used in the treatment of malaria.

Results

Several plants from Euphorbiaceae family are known to have antimalarial activity (Table I). In the present review, there are 14 plants of Euphorbiaceae family have been investigated for their active antimalarial compounds.

Table I: An overview of Euphorbiaceae family plants with terpene compound as an antimalarial agent

Species	Part used	Terpenoid compound(s)	Antimalarial activity (IC_{50} and strains used)	References
Croton gratissimus Burch.	Leaves	**Cembranolide:** (+)-(1R*,4S*,10R*)-4-hydroxycembra-2E,7E,11Z-trien-20,10-olide (+)-(1S*,4S*,7R*,10R*)-7-acetoxy1,4-dihydroxycembra-2E,8(19),11Z-trien-20,10-olide	20.8 µg/mL (D10) 13.5 µg/mL (D10)	Langat *et al.*, 2011
Croton kongensis Gagnep	Leaves	8,9-secokaurane diterpene derivatives	1.0–2.8 µg/mL (K1)	Thongtan *et al.*, 2003
Croton lobatus L.	Stems and leaves	Geranylgeraniol Betulinic acid	1.07 mM (K1) 1.45 mM (K1)	Attioua *et al.*, 2007
Croton megalocarpoides Friis & M.G. Gilbert	Roots	Crotocorylifuran ***Ent*-clerodane diterpenoid:** Megalocarpoidolide A – H 2-Epi-crotocorylifuran 8β-Hydroxy-crotocorylifuran Crotocorylifuran-2-one 7,8-Dehydrocrotocorylifuran **Abietane diterpenoid:** Isolophanthin E	4.76 µg/mL (D6 and W2)	Ndunda *et al.*, 2016
Croton steenkampianus Gerstner	Leaves	Steenkrotin A Steenkrotin B	9.4 µg/mL (Dd2) 9.1 µg/mL (W2), 15.8 µg/mL (D10)	Adelekan *et al.*, 2008
Croton zehntneri Pax & K. Hoffm.	Leaves	Essential oils consisting monoterpenoids and sesquiterpenoids	15.20 µg/mL (K1)	Mota *et al.*, 2012
Euphorbia esula L.	Twigs	**Pre-segenate-type diterpenoid:** Euphorbesulin A Euphorbesulin B – C **Jatrophane-type diterpenoid:** Euphorbesulin D – E, G – K, M – N Euphorbesulin F Euphorbesulin L	2.41 µM (Dd2) >5 µM (Dd2) >5 µM (Dd2) 0.12 µM (Dd2) >10 µM (Dd2)	Zhou *et al.*, 2016
Jatropha integerrima Jacq.	Roots	2α-hydroxyjatropholone Jatropholone A	4.1 µg/mL (K1) 5.4 µg/mL (K1)	Sutthivaiyaki *et al.*, 2009

Species	Part used	Terpenoid compound(s)	Antimalarial activity (IC_{50} and strains used)	References
Jatropha isabellei Müll.Arg.	Rhizomes	Jatrophone diterpene derivatives	5.8 µM (3D7); 6.0 µM (K1)	Hadi *et al.,* 2013
Neoboutonia macrocalyx Pax	Stem barks	Mellerin B	9.6 µg/mL (FcB1)	Namukobe *et al.,* 2014
		Cycloartane triterpene:		
		Neomacrolactone	1.1 µg/mL (FcB1)	
		22α-acetoxyneomacrolactone	1.4 µg/mL (FcB1)	
		6-hydroxyneomacrolactone	0.8 µg/mL (FcB1)	
		22α-acetoxy-6-hydroxyneomacrolactone	1.6 µg/mL (FcB1)	
		6,7-epoxyneomacrolactone	5.1 µg/mL (FcB1)	
		22α-acetoxy-6,7-epoxyneomacrolactone	6.7 µg/mL (FcB1)	
		4-methylen-neomacrolactone	1.0 µg/mL (FcB1)	
		Neomacroin	1.7 µg/mL (FcB1)	
		22-de-O-acetyl-26-deoxyneoboutomellerone	1.1 µg/mL (FcB1)	
		Neoboutomacroin	4.9 µg/mL (D6); 3.6 µg/mL (W2)	
		Daphnane diterpenoid:		Namukobe *et al.,* 2015
		Montanin	3.9 µg/mL (D6); 2.3 µg/mL (W2)	
Pedilanthus tithymaloides (L.) Poit.	White latex	**Poly-O-acylated jatrophane diterpene:**		Mongkolvisut & Sutthivaiyakit, 2007
		1a,13b,14atrihydroxy-3b,7b-dibenzoyloxy-9b,15b-diacetoxyjatropha-5,11 E-diene	5.9 mM (K1)	
		1a,8b,9b,14a,15b-pentaacetoxy-3b-benzoyl-oxy-7-oxojatropha-5,12-diene	4.9 mM (K1)	
		7,8b,9b,14a,15b-pentaacetoxy-3b-benzoyl-oxy-1a,5b-dihydroxyjatropha-6(7),12-diene	6.0 mM (K1)	
		1a,7,8b,9b,14a,15bhexaacetoxy-3b-benzoyl-oxy-5b-hydroxyjatropha-6(7), 12-diene	5.8 mM (K1)	
Strophioblachia fimbricalyx Boerl.	Roots	9-O-demethyltrigonostemone	8.7 µM (K1)	Seephonkai *et al.,* 2009
		3,6,9-trimethoxyphenanthropolone	9.9 µM (K1)	
Uapaca nitida Müll-Arg.	Root barks	Betulinic acid	19.6 mg/mL (K1); 25.9 mg/mL (T9-96)	Steele *et al.,* 1999
Uapaca paludosa Aubrév. & Landri	Trunk barks	Squalene	0.7 µg/mL (FcM29)	Banzouzi *et al.,* 2015
		Betulinic acid	1.7 µg/mL (FcM29)	
		Betulin	3.0 µg/mL (FcM29)	
		Samvisterin	7.5 µg/mL (FcM29)	

Discussion

Medicinal plants have been shown to have an important role in malaria treatment for thousands of years (Rukunga & Simons, 2006; van Wyk *et al.,* 2009). In addition, the structural diversity of secondary metabolites in plants is a rich biogenetic source for the discovery of new drugs when compared to synthetic molecules (Shen, 2015). Some new compounds isolated medicinal plants, among others of alkaloids, terpenoids, flavonoids, coumarin, lignans, chalcone, and xanthone, have antimalarial activity in vitro and in vivo (Saxena *et al.,* 2003). From a literature study, it is proven that the terpenoid content in the Euphorbiaceae family can be used as an antimalarial drug. This review focuses on the research journal approach to guided isolation throughout the life of antimalarial with a wide variety of structures. The standard reference of terpenoids used the sesquiterpene lactone class of compounds derived

from artemisinin. It is known that artemisinin comes from the Artemisia annua plant from the Asteraceae family. Most of the terpenoid compounds obtained from this family are highly cytotoxic. Therefore, it is necessary to search for compounds from other families.

The Euphorbiaceae family has a characteristic feature, namely the sap on the stem. Parts of plants used as antimalarials from Euphorbiaceae include the leaves, fruit, rind and bark. Antimalarial compounds come from various groups, one of which is terpenoids. Terpenoids are compounds with moderate antimalarial activity. Moreover, when compared with other genera, Euphorbiaceae is a potential genus (Bero *et al.,* 2009). The active ingredients for drugs can come from extracts, fractions, subfractions, or isolates. Before being developed into an antimalarial drug, it is necessary to know the content of the active antimalarial ingredient, which functions to inhibit the growth of the P. *falciparum* parasite. In the search for new antimalarial drugs, several in vitro screening tests were carried out using several types of P. *falciparum* strains. The in vitro test for malaria was carried out by growing parasites on red blood cell cultures under controlled environmental conditions. The antimalarial activity of the drug was evaluated from the results of inhibition of parasite growth by serial dilution of the concentration in the test culture (Trager & Jensen, 1976; Krettli *et al.,* 2009).

Through in vitro testing, it is possible to evaluate the occurrence of prevention of sporozoite infection (prophylactic effect), and cessation of parasite growth and development (schizonticidal effect). Some strains of the P. *falciparum* parasite that are sensitive to chloroquine are 3D7, D6, D10 NF54, NF54/64, F32, HB3, FCC1-HN Ghana; resistant to chloroquine were FcB1, W2, FCM29, BHz26/86, Dd2, EN36, ENT30, FCR3, FCR-3/A2; and resistant to multidrug, namely K1 and TM91C235 (Mokgethi-Morule & N'Da, 2016).

The standard drugs used as antimalarials are chloroquine and artemisinin. IC_{50} chloroquine was 2.9 ng/mL against strains NF54 (range 1.6–4.5 ng/mL) and 48 ng/mL (range 19–66 ng/mL) against strains K1. Meanwhile, IC_{50} artemisinin was 1.9 ng/mL (range 0.8–2.4 ng/mL) against strain NF54 and 0.8 ng/mL (range 0.4–1.5 ng/mL) against strain K1.

Plant extracts with an IC_{50} value of ≤10 µg/mL can be considered active as antimalarial, IC_{50} with a range of $10<IC_{50}≤25$ µg/mL is considered moderately active, and IC_{50} >25 µg/mL is classified as inactive. Extracts with IC_{50} <50 µg/mL and fractions with IC_{50} <25 µg/mL were classified as effective antimalarials (Köhler *et al.,* 2002). Several researchers explained that compounds with IC_{50} values of >100 mM were active antimalarial compounds. While other criteria use stricter limits, which compounds are worthy of further investigation must have an IC_{50} value of <25 mM (Cos *et al*., 2006). In addition to the IC_{50} value, you must consider the SI (selectivity index) value, which is the ratio between CC_{50} and IC_{50} so that the antimalarial lead compound must have an IC_{50} value of <1 mM and SI >10 times (Katsuno *et al.,* 2015).

Terpenoids have an important role in producing antimalarial activity. The terpenoid compounds known as antimalarials include limonene, nerolidol, farnesol, perillyl alcohol, linalool, and modified terpenes of s-farnesylthiosalicylic acid (Gabriel *et al.,* 2018). Terpenes are formed in plants through two biosynthetic pathways, namely the mevalonate pathway and the 2C-methyl-D-erythritol-4-phosphate pathway (Abdallah & Quax, 2017). According to Hamilton (2004), the terpenoid class compounds as antimalarials inhibit the stage of the *Plasmodium* parasite from the ring stage to the trophozoite. Terpenoids inhibit the intake of nutrients needed by the parasite by inhibiting the permeation pathway. Inhibition of this pathway occurs in the food vacuole of the malaria parasite in the presence of a process of haemoglobin degradation and heme detoxification (Widyawaruyanti *et al.,* 2014).

This review is intended to provide an overview of current knowledge regarding the use of terpenoids from Euphorbiaceae family plant as an antimalarial. They belong to a great structural diversity including ent-clerodane, abietane, pre-segenate, daphnane, jatrophane and poly-O-acylated jatrophane diterpenoids, as well as cembranolide and cycloartane triterpenes. Many of the compounds with interesting antimalarial properties were reported for the first time within this period, and they present a show strong antimalarial properties with low IC_{50} values.

Conclusion

Terpenoids from Euphorbiaceae family have potential antimalarial activity. Screening of antimalarial terpenoid activity in Euphorbiaceae family plant can be a key step in the source and development of new antimalarial drugs.

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