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Review: Indole Alkaloids and Antimalarial Activity in the *Tabernaemontana* Species

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Abstract

Background*: Malaria, caused by Plasmodium parasites, is a highly prevalent and lethal illness that shows persistent ability to develop resistance. Antiplasmodial compounds that are indole-based prevent hemozoin formation, exhibiting efficacy against chloroquine-resistant Plasmodium strains. Tabernaemontana is a member of the genus comprised to the Apocynaceae family and has long been known for its efficacy in traditional and herbal tribal medicine. Apocynaceae can be recognized by the existence of indole alkaloids, and Tabernaemontana spp. is widely identifiable for its ability to synthetize a wide variety of indole alkaloids.* ***Objective:*** *This literature review seeks to provide a comprehensive summary of indole alkaloid compounds from Tabernaemontana spp. and the effectiveness of Tabernaemontana spp. as antimalarials.* ***Methods****: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols were followed to explore the PubMed, Sage Journal, ScienceDirect, and Wiley Library databases.* ***Results:*** *23 publications on the antimalarial activity and indole alkaloids of several species of the genus Tabernaemontana were discovered.* ***Conclusion:*** *Various species of Tabernaemontana contain indole alkaloids, and extracts of the plant or parts of the plant and isolates have weak to strong antimalarial activity.*

Keywords*: antimalarial, indole alkaloid, Tabernaemontana spp., Plasmodium spp.*

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INTRODUCTION

Tabernaemontana belongs to the family Apocynaceae. The genus has approximately 100 species that can be found in the tropical and subtropical regions of Asia, Africa, Oceania, and the Americas (Silveira et al., 2017). Tabernaemontana species consist of blooming shrubs and small-to medium-sized trees that typically live in savannahs, rocky outcrops, and forest understories (Marinho et al. 2016). The genus can be identified by its white cylindrical flowers, follicular fruit containing seeds enclosed by a yellow to reddish husk, and the occurrence of milky or watery latex secretion, which is typically observed in wounded plants of this genus (Simões et al., 2010).

Plants belonging to the genus Tabernaemontana generally contain a significant amount of alkaloids, which frequently exhibit pharmacological effects (Silveira et al., 2017). The primary types of alkaloids found in species within the Tabernaemontana genus are monoterpene indole and bisindole alkaloids. Additionally, other chemicals include terpenes, lactones, steroids, phenolics, and flavonoids (Van Beek et al., 1984).

Indole has the chemical formula C_8H_7N and shows weak basicity. The substance is composed of a pyrrole ring connected to the benzene nucleus. It has ten π-electrons that orbit around the form. The fundamental properties of indole alkaloids are ascribed to the dispersion of the unshared pair of nitrogen electrons inside the unconstrained motion of the π electronic system. The indole molecule was protonated at the C-3 position, which is more thermodynamically stable. (Omar et al., 2021).

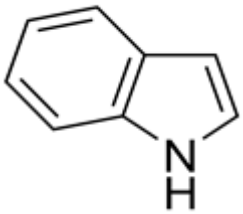

Figure 1. Basic chemical structure of an indole

Indole alkaloids have numerous pharmacological properties. Indole alkaloids have been recorded across multiple important plant families, including Rubiaceae, Apocynaceae, Rubiaceae, Loganiaceae and Nyssaceae, surpassing others in frequency. Indole alkaloids are often identified based on their strong biological effects, including anticancer, anti-inflammatory, antibacterial, antimalarial, antifungal, antidepressant, antiviral, analgesic, hypotensive, anticholinesterase, antileishmanial, antiplatelet, antidiarrheal, spasmolytic, lipid-lowering, antimycobacterial, and antidiabetic properties. (Omar et al., 2021).

Malaria is a deadly parasitic disease that is spread by the bite of the female Anopheles mosquito acting as the vector for humans. It is caused by five different kinds of Plasmodium parasite species, *Plasmodium falciparum (*the most prevalent), *Plasmodium vivax, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium knowlesi* (Milner, 2018). Globally, in 2022, there were an estimated 249 million malaria cases in 85 malaria-endemic countries and areas, an increase of 5 million cases compared to 2021. Globally, the malaria mortality rate was halved from approximately 29 in 200 to 15 in 2015. In 2020, the mortality rate increased again to 15,2, before slightly decresing to 14,3 in 2022. From 2000 to 2019, the number of reported cases in the WHO African Region decreased from 370 to 226 per 1000 people at risk. However, in 2020, it increased to 233.6 per 1000 people at risk. This rise was primarily due to disruptions in service caused by the Coronavirus Disease 2019 (COVID-19) pandemic in 2020 – 2023. According to the World Health Organization (2023), the number of cases per 1000 people at risk has decreased to 229 by 2022 (World Health Organization, 2023).

In Indonesia, malaria cases are increasing from 2020 to 2022, from 254,055 cases in 2020 to 443,530 cases in 2022. The highest number of cases was in Papua Province, which contributed 356,889 positive cases to the national figure. The fatalities are also linear with the increase in positive cases, where in 2022, the number of deaths is 71, which is the highest in 2018 – 2022 (Kemenkes, 2022).

In 2021, four countries in the African region accounted for nearly half of all malaria cases globally: Nigeria (26,6%), the Congo (12,3%), Uganda (5,1%), and Mozambique (4,1%). Four countries also account for over half of malaria deaths globally: Nigeria (31,3%), Congo (12,6%), Tanzania (4,1%), and Niger (3,9%) (Health Organization, 2023).

Currently, researchers are exploring the extensive possibilities of numerous Tabernaemontana species by examining their plant extracts, fractions, chemical constituents, and isolated compounds (Silveira et al., 2017). This review provides detailed information on several species of Tabernaemontana, focusing specifically on their recently published antimalarial activities.

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MATERIALS AND METHODS

This article follows the principles set forth by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). This study explored the indole alkaloid compounds identified from the genus Tabernaemontana and their effectiveness in combating malaria parasites.

Search methodology

The publications were gathered by an Internet-based search using selective keywords, such as "Tabernaemontana antimalarial activity" and "Indole alkaloid compounds from Tabernaemontana" across numerous databases, including PubMed, ScienceDirect, MDPI, and Google Scholar. The articles were written in either English or Indonesian. The article search covers the period from 2000 to 2023. The papers used relate to the antimalarial properties of plants belonging to the genus Tabernaemontana and the specific indole alkaloids that have been isolated and identified from them.

Data extraction

The authors collected and assessed the articles using standardized protocols. The selected articles included information on malaria in general as well as the characteristics of Tabernaemontana spp. The antimalarial and/or antiplasmodial activity of the extract from Tabernaemontana spp. is discussed, along with the indole alkaloids identified from the plant species and their antimalarial properties. In addition, the mechanism of action of these indole alkaloids as antimalarial agents was examined.

The criteria for data extraction were as follows: 1) all species belonging to the genus Tabernaemontana spp., 2) the article was published from 2000 until 2023, 3) the extract or fraction of the plants has *in vitro* or *in vivo* antimalarial or antiplasmodial activity, 4) isolated and identified compounds are indole alkaloids, and 5) the article is in English or Indonesian. A total of 23 articles were used in this literature review, as displayed in Table 1.

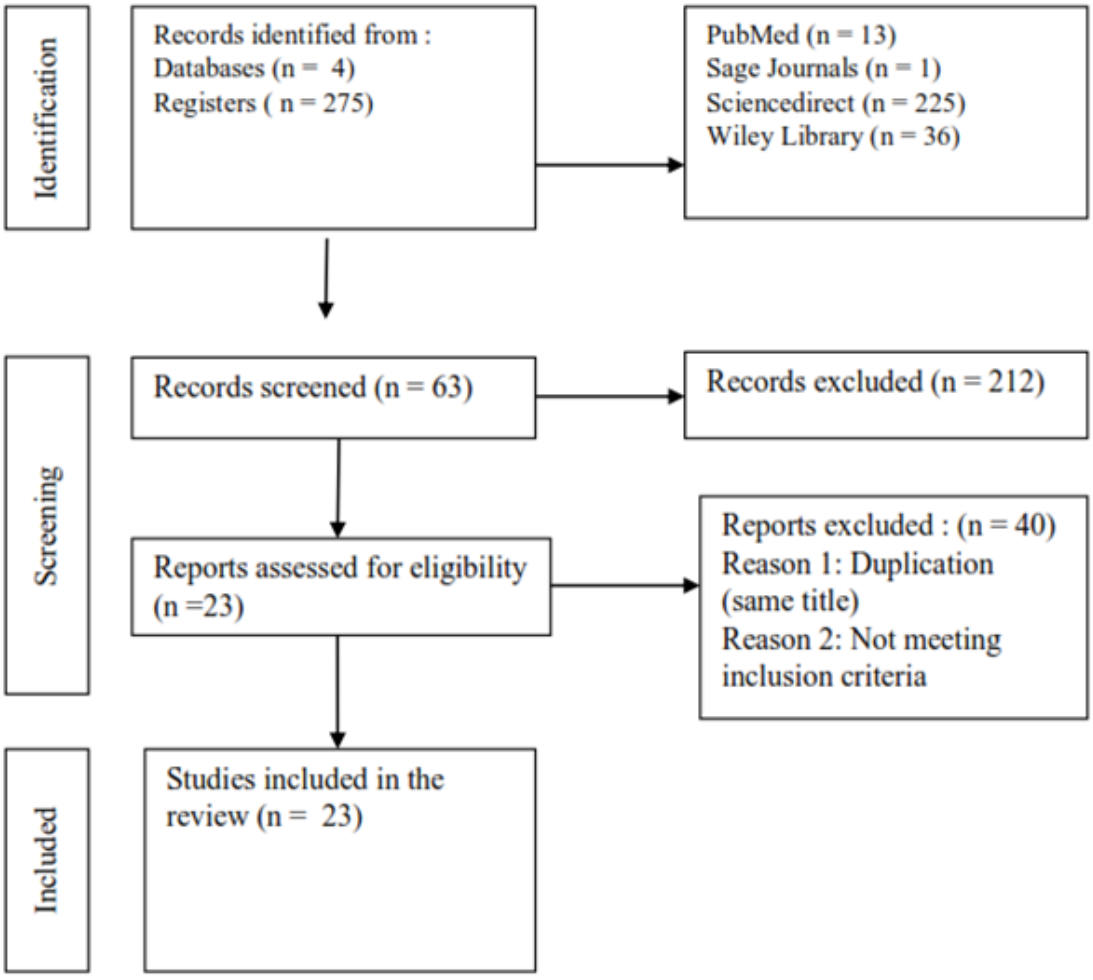

Figure 2. Flow chart of PRISMA guidelines in article collection

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Table 1. Systematic review data table

Source	Indole Alkaloids Isolation and Identification	Antimalarial Activity Evaluation (*in vitro*)
Nge, et.al., 2016	√	
Kam & Sim, 2002	√	
Lim, et.al., 2015	√	
Qu, et.al, 2016	√	
Yuwen, et.al, 2016	√	
Sim, et.al., 2014	√	
H. Zhang, et.al, 2007	√	
Cai, et.al., 2018	√	
Ingkaninan, et.al, 2006	√	
B. J Zhang, et.al., 2015	√	
Hirasawa, et.al, 2019	√	√
Xu et.al., 2019	√	
Pereira, et.al, 2008	√	
Foudjo Melacheu, et.al, 2019	√	
Yu, et.al, 2019	√	
Bitombo, et.al., 2021	√	√
Masuda, et.al, 2000	√	
Bapela, et.al., 2018	√	
Federici et.al, 2000	√	√
Noguchi, et.al, 2016	√	√
Amelia, et.al, 2019	√	√
Ramalhete et.al., 2008		√
Muthaura, et.al, 2015		√

RESULTS AND DISCUSSION

Indole alkaloids antimalarial mechanism of action

The efficacy of the drug against drug-resistant *Plasmodium spp*. remains high even when it possesses a distinct or additional mode of action. It should be emphasized that the presence of the indole nucleus alone does not ensure antimalarial action. Covalently linking the pharmacophore units of hemozoin and PfATP4 inhibitors to an indole backbone using molecular hybridization has the potential to create antiplasmodial medicines that act on both targets simultaneously (Surur et al., 2020).

The most promising approach is to inhibit the detoxification of the plasmodial pathway to become hemozoin. The breakdown of hemoglobin within the parasite's food vacuole results in the release of a significant amount of free haem (ferriprotoporphyron IX). The abundance of free heme is believed to be deadly to the Plasmodium parasite because of its ability to block membranes, cause lipid peroxidation, and induce oxidation of proteins and DNA. *Plasmodium spp*. employs a heme detoxification mechanism known as bio-crystallization, which transforms heme into an insoluble substance called hemozoin. Hemozoin has been proposed to be composed of chains of Fe^{III}-protoporphyrin units, connected to form a polymer. The collection of a substantial amount of free hematin and the complex formed between hematin and antimalarial drugs impairs the parasite's capacity to maintain cationic gradients. This, in conjunction with the harmful effects of free heme, results in parasite death (Kgokong et al., 2005). Certain indole compounds can directly attach to ferriprotoporphyrin IX, thereby interfering with heme polymerization into hemozoin (Surur et al., 2020).

PfATP4 is a P-type ATPase found in *P. falciparum* and serves as a target for the sporoindolone class of antiplasmodial drugs. Sporoindolones disrupt the growth of parasites by disturbing the balance of sodium ions, which is weakened in Plasmodium species with acquired mutations in PfATP4 that confer resistance. PfATP4 has been identified as a critical mechanism for the antimalarial action of new chemotypes, aminopyrazoles, and dihydroisoquinolines, in addition to sporoindolones, which have been used in preclinical studies (Spillman & Kirk, 2015).

By targeting the melatonin receptor, research has revealed the potential for generating therapeutic candidates that target several targets and are based on indole. Melatonin is crucial for the coordination of the cell cycle of malaria parasites. The ubiquitin/proteasome system plays a vital role in regulating genes in Plasmodium, which is essential for maintaining cell cycle and transcriptional activity. This regulation ultimately contributes to the percentage of mature schizonts. Malaria stimulates hepatocyte death by inducing mitochondrial diseases and oxidative stress.

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However, this detrimental effect can be mitigated by administering a large dose of melatonin, as demonstrated by Surur et al. (2020). Bagnaresi et al., 2008 demonstrated that luzindole, an indole-based melatonin antagonist, effectively suppressed trophozoites by disturbing the rhythmicity of the cell cycles of the parasite.

As described above, various modes of action are responsible for their efficacy against chloroquine-resistant strains. Indeed, it is important to note that the indole nucleus alone does not guarantee antimalarial activity, such as alkaloids from *Pandaca*, *Bonafusia*, or *Rauvolfia*, which contain indole nuclei but are not active against Plasmodium parasites (Passemar et al., 2011). Molecular hybridization that covalently links the pharmacophore units of hemozoin inhibitors and PfATP4 inhibitors to an indole structure may lead to dual-acting antimalarial action (Surur et al., 2020).

Indole alkaloids showed synergistic/additive interactions with conventional antimalarial agents, as shown by Bagnaresi et al. (2008), in which mice treated with luzindole (15 mg kg^{-1}) and chloroquine (suboptimal dose at 1.5 mg kg^{-1}) worked synergistically, which reduced the number of intraerythrocytic parasites. Cryptolepine in combination with a 4 mg kg^{-1} dose of artemisinin showed no significant biochemical and histopathological index variations compared to the control group, which ensured an acceptable safety profile (Forkuo et al., 2017).

Toxicity profiles of indole-alkaloid-rich extracts generally show no genotoxicity, cardiotoxicity, or respiratory issues (Surur et al., 2020). However, some compounds such as luzindole and cryptolepine have specific toxic effects, including reduced cardioprotection and cytotoxicity (Gopalan et al., 2011). Cryptolepine showed *in vivo* toxicity in mice and embryonic malformations in zebrafish; however, in *P. berghei*-infected mice, it did not alter the histopathology of the liver, spleen, stomach, or kidney (Forkuo et al., 2017). The observed toxicity of indole alkaloids has partly hindered further preclinical development of indoles. Most of the reported side effects are associated with long-term exposure to indoles; thus, the chronic toxic effect of indole derivatives could be avoided as long as the malarial treatment regimen extends only for a short time (Forkuo et al., 2017).

Indole alkaloids compounds and antimalarial activities of *Tabernaemontana* species

The Tabernaemontana genus possesses an abundance of monoterpene indole alkaloids (MIAs), which are synthesized from tryptophan (an aromatic acid) and secologanin (an iridoid terpene) (Athipornchai, 2018). Various skeletal types have been identified in MIAs, such as seco-tabersonine, bis-vobtusine, and bis-vobsinyl-ibogan indole alkaloids. (Marinho et al., 2016). Heterodimeric bisindole alkaloids are another important family of alkaloids in this plant (Athipornchai, 2018). Table 2 presents a summary of the indole alkaloids identified from the taxa in the genus Tabernaemontana.

Table 2. Summary of indole alkaloids identified from tabernaemontana

No	Species	Plant Part	Reported MIAs	Class Type	Reference
1	*Tabernaemontana corymbosa*	Stem Bark	Conodusine A	Iboga	(Nge et al., 2016)
			Conodusine B	Iboga	(Nge et al., 2016)
			Conodusine C	Iboga	(Nge et al., 2016)
			Conodusine D	Iboga	(Nge et al., 2016)
			Conodusine E	Iboga	(Nge et al., 2016)
			Apocidine A	Aspidosperma	(Nge et al., 2016)
			Apocidine B	Aspidosperma	(Nge et al., 2016)
			Conoduzidine A	Vincamine	(Nge et al., 2016)
			Tabernamidine A	Vobasine-Iboga	(Nge et al., 2016)
			Tabernamidine B	Vobasine – Iboga	(Nge et al., 2016)
			19'(S)-Hydorxytabernamine	Vobasine – Iboga	(Kam & Sim, 2002)
			19'(R)-Hydorxytabernamine	Vobasine – Iboga	(Kam & Sim, 2002)
			16'-Decarbomethoxyvoacamine	Vobasine – Iboga	(Lim et al., 2015)

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No	Species	Plant Part	Reported MIAs	Class Type	Reference
2	*Tabernaemontana litoralis*	Fruits	Isokuammiline	Corynanthe	(Qu et al., 2016)
			18-Hydroxypseudovincadifformine	Iboga	(Qu et al., 2016)
			3,19-Oxidocoronaridine	Iboga	(Qu et al., 2016)
			Strictosidine	Strictosidine	(Qu et al., 2016)
3	*Tabernaemontana divaricata*	Leaves and twigs	Tabervarine A	Iboga	(Yuwen et al., 2019)
			Tabervarine B	Iboga	Yuwen et al., 2019)
			Vobasidine C	Vobasine	(Sim et al., 2014)
			Ervadivaricatine B	Vobasine – Iboga	(H. Zhang et al., 2007)
		Stems	Flabellipparicine	Flabelliformide – Appariicine	(Cai et al., 2018)
			19,20-Dihydrovobparicine	Vobasine-Appariicine	(Cai et al., 2018)
			10'Demethoxy-19,20-Dihydrovobatemsine D	Vobasine-Iboga	(Cai et al., 2018)
			3'-(2-Oxopropyl) Ervahanine A	Sarpagine – Iboga	(Cai et al., 2018)
			19,20-Dihydrotabermine	Vobasine-Iboga	(Ingkaninan et al., 2006)
			Taberdivarines E	Vobasine-Iboga	(B. J. Zhang et al., 2015)
			Hydroxy-3-(2-Oxopropyl) Coronaridine Indolenine	Iboga	(Ingkaninan et al., 2006)
			Deoxytubulosine	Corynanthe bisindole	(Cai et al., 2018)
		Root	Divaricamine A	Vobasine – vobasine – iboga	(Hirasawa et al., 2021)
4	*Tabernaemontana bufalina*	Branches and leaves	(3R,7S,14R,19S,20R)-19-Hydroxypseduovincadiffromine	Iboga	(Xu et al., 2019)
			Voachalotine	Akuammidine	(Pereira et al., 2008)
			12-Methoxyl-Voaphylline	Aspidosperma	(Perera et al., 1984)
			Conophylline	Apsidosperma-Aspidosperma	(Perera et al., 1984)
5	*Tabernaemontana contorta*	Fruits	5,6-Dioxo-11-Methoxy Voacangine	Iboga	(Foudjo Melacheu et al., 2019)
			(-)-Apparicine-21-One	Apparicine	(Foudjo Melacheu et al., 2019)
6	*Tabernaemontana bovina*	Leaves	Tabernabovine A	Corynanthe bisindole	(Yu et al., 2019)
			Tabernabovine B	Aspidosperma	(Yu et al., 2019)
			Tabernabovine C	Iboga	(Yu et al., 2019)
7	*Tabernaemontana penduliflora* K. Schum	Trunk bark	Penduliflorines A		(Bitombo et al., 2021)
			Penduliflorines B		(Bitombo et al., 2021)
			Penduliflorines C		(Bitombo et al., 2021)
			Penduliflorines D		(Bitombo et al., 2021)
			Penduliflorines E		(Bitombo et al., 2021)
			Tabernaemontine		(Bitombo et al., 2021)

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No	Species	Plant Part	Reported MIAs	Class Type	Reference
			10-Hydroxycoronaridine		(Masuda et al., 2000)
			Voacangine		(Masuda et al., 2000)
8	*Tabernaemontana elegans*	Stem bark	Tabernaemontine	Vobasine	(Bapela et al., 2018)
			Dregamine	Vobasine	(Bapela et al., 2018)
9	*Tabernaemontana hystrix*	Stem bark	Voacangine	Vobasine – Iboga	(Federici et al., 2000)
			Coronaridine	Iboga	Federici et al., 2000)
10	*Tabernaemontana dichotoma*	Leaves	16-Hydorxy-16,22-dihydroappariicine	Vobasine – vobasine – Iboga	(Noguchi et al., 2016)
11	*Tabernaemontana macrocarpa*	Bark	16-demethoxycarbonyl voacamine	Vobasine – Iboga	(Amelia et al., 2019)

MIAs: Monoterpene indole alkaloids

Tabernaemontana Species with Antimalarial Activity

***Tabernaemontana penduliflora* K. Schum**

The botanical nomenclature assigned to this plant is *Tabernaemontana penduliflora*. K. Schum, previously named as *Conopharyngia penduliflora* (K. Schum), is a sleek-stemmed bush or little tree indigenous to the woodlands of Cameroon and the southern part of Nigeria (Bitombo et al., 2021). The ethanol extract of *T. penduliflora* exhibits potent antibacterial effects against gram-positive bacteria, as discovered by Van Beek et al. in 1984. *T. penduliflora* root is also used as a traditional treatment for malaria (Titanji et al., 2008).

The trunk bark ethanol of *T. penduliflora* extract was prepared by subjecting the dried plant part to extraction using 90% ethanol under decreased pressure. Subsequently, the extract was combined with a 5% hydrochloric acid solution and subjected to extraction using n-hexane. The remaining portion was treated with NH4OH and subsequently extracted with $CHCl_3$ to yield a crude alkaloid extract. The material was subjected to phytochemical examination using repeated column chromatography (CC) and liquid chromatography (LC), along with high-resolution mass spectrometry (HRMS) (Bitombo et al., 2021).

From the trunk bark of *Tabernaemontana penduliflora*, six new zwitterionic monoterpene indole alkaloids, penduliflorines (A-E), and tabernaemontine, were extracted, along with eight alkaloids that had been identified previously. The *in vitro* activity of penduliflorines A-E and tabernaemontine against 3D7 and Dd2 strains of *Plasmodium falciparum* demonstrated IC_{50} values ranging from 1.85 to 26.69 µg/ml, respectively. Penduliflorine A-B exhibited strong antiplasmodial action against 3D7 and Dd2 strains, with the IC_{50} value of 7.88 and 5.32 µg/ml, respectively. Penduliflorine C and Penduliflorine D-E demonstrated *in vitro* IC_{50} values ranging from 15.71 to 26.69 and 14.41 to 15.87 µg/ml, respectively, against the two strains of *P. falciparum* (Bitombo et al., 2021).

Tabernaemontana elegans

Tabernaemontana elegans (IC_{50} of dichloromethane extract = 26,9 ±3.1 µg/ml), widely utilized for malaria treatment in Mozambique, revealed moderate or no significant activity. It is worth mentioning that plants are commonly used in the treatment of fever, particularly in cases related to malaria (Ramalhete et al., 2008). The absence of *in vitro* antimalarial inactivity in *T. elegans* may be attributed to its potential role as an antipyretic or an enhancer of the immune system, rather than its direct antiparasitic activity. (Ramalhete et al., 2008).

Tabernaemontana hystrix

Tabernaemontana hystrix (formerly *Peschiera fuchsiaefolia*) is indigenous to South America. The use of the stem bark of *T. hystrix* as an antimalarial traditional medicine led Federici et al. (2000) to investigate its basic extract, which showed good *in vitro* activity using the D6 strain of *P. falciparum*, which exhibited an IC_{50} value of 0.495 µg/ml, and W2, which exhibited an IC_{50} value of 0.817 µg/ml. Voacamine, identified from *T. hystrix*, shows the most active antimalarial activity, with IC_{50} values of 0.238 and 0.290 µg/ml against the D2 and W2 strains, respectively (Federici et al., 2000).

Tabernaemontana pachysiphon

The fruit of *Tabernaemontana pachysiphon* has historically been used to prevent miscarriages and cure sores and lesions in Nigeria. (Duru & Mbata, 2010). The plant is believed to exhibit antibacterial properties, and investigation of the leaf extract concluded the existence

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of bioactive phytochemical components, including alkaloids, resins, saponins, flavonoids, polyphenols, and carbohydrates. (Duru & Mbata, 2010). Muthaura et al. (2015) investigated water and methanol extracts from *T. pachysiphon* fruit and leaves and found that the extracts yielded IC_{50} values against D6 and W2, respectively, of 4,8 and 4,4 µg/ml (fruit water extract), 3,9 and 53,7 µg/ml (fruit methanol extract), 25,3 and 70,8 µg/ml (water leaves extract) and 14.7 and 25,4 µg/ml (leaf methanol extract).

Tabernaemontana dichotoma

Tabernaemontana dichotoma exhibits vasorelaxant activity. Zaima et al. (2013) reported the vasorelaxant activity of a methanol extract of the bark of *T. dichotoma* in the rat aorta. Furthermore, a total of eight indole alkaloids were identified, namely 10-methoxyalstonerine, 10-methoxyaffisinine, lochnerine, cathafoline, (-)-alstonerine, 19,20-dehydro-10-methoxyalcarpine, alstonisine, and alstonal.

In 2019, Noguchi and colleagues conducted a study to examine the antimalarial activity of *T. dichotoma* methanol leaf extract. The main constituents of the methanol extract derived from the leaves of *T. dichotoma* are primarily 16-Hidroxy-16,22-dihydroapparacine, which is a 5-nor stemmadenine alkaloid. It exhibits antimalarial properties. The methanol extract of *T. dichotoma* leaf exhibited strong *in vitro* antimalarial activity, with a measured IC_{50} value of 0.59 µg/mL against K1, a chloroquine-resistant strain of *P. falciparum* and 0.35 µg/mL against FCR3 which is a chloroquine-sensitive strain of *P. falciparum*.

Tabernaemontana divaricata

Tabernaemontana divaricata (L) R. Br ex Roem & Schult is a plant native to Asia and Australia, both tropical and subtropical. Currently, it is primarily recognized as a decorative tree found in gardens. However, in Thailand and China, it has long-standing traditional use for alleviating fever and pain (Naidoo et al., 2021). *T. divaricata* is known for its ability to synthesize a diverse range of indole alkaloids. In their study, Hirasawa et al., (2021) discovered a novel trimeric monoterpene alkaloid named divaricamine A. Divaricamine A exhibited strong *in vitro* antimalarial activity against the 3D7 strain of *P. falciparum*, with IC_{50} measured at the value of 1.9 µM.

Tabernaemontana macrocarpa

Tabernaemontana macrocarpa Jack, a tree species found in Borneo, Indonesia, is traditionally used to treat dental diseases such as herpes and dermatitis. This is achieved by utilizing the exudate obtained from the bark of the tree (Ekawati et al., 2023). The stems of *T. macrocarpa* have been analyzed for phytochemicals, including alkaloids, flavonoids, terpenoids, and tannins. Amelia et al., (2021) identified and separated two newly found sarpagine-type indole alkaloids, alongside five previously identified alkaloids (12-methoxy-4-methylvoachalotine, 16-demethoxycarbonylvoacamine, isositrikine, affnisine, affinine). Compound 16-demethoxycarbonylvoacamine exhibited *in vit*ro antimalarial activity against the 3D7 strain of *Plasmodium falciparum*, with an IC_{50} value of 28.8 µM.

Tabernaemontana crassa

Appiah-Opong et al., (2022) examined eight Ghanaian traditional medicinal plants, namely *Cinnamomum zeylanicum*, *Morinda lucida* Benth, *Parkia clappertoniana* Key, *Tabernaemontana crassa* Benth, *Lippia multiflora* Moldenke, *Baphia nitida* Lodd, *Terminalia ivorensis* A.Chev, and *Treculia africana* Decne. Of all eight plants, the root extract of *Tabernaemontana crassa* showed the weakest antiplasmodial activity against the 3D7 strain, which is a strain of *Plasmodium falciparum* that is sensitive to chloroquine. The IC_{50} value for this activity was measured to be 62.33 µg/mL.

CONCLUSION

This literature review evaluated the indole alkaloid compounds found in species of the genus Tabernaemontana and their effectiveness in treating malaria. The antimalarial activity of Tabernaemontana genus members ranged from mild to strong. This antimalarial activity may be attributed to the presence of indole alkaloid molecules and multiple mechanisms. Generally, the toxicity profile of the indole alkaloid-rich extract showed no toxicity but was observable in some compounds.

Although the genus Tabernaemontana contains physiologically active chemical compounds, a significant number of species have not undergone chemical and biological assessments. Additional research is crucial to obtain a deeper understanding of the bioactive chemicals and active pharmacological actions of this genus, particularly in relation to its potential for malaria treatment.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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