

Anti-plasmodial and Anti-malarial Potentials of Some Medicinal Plants in Africa: A Systematic Review

Ume A. O.^{1,2}, Afiukwa, C. A³, Eze G. O⁵, Ogbu C. A^{1,4}, Ajah O. F¹, Ede J. U¹, Onwe V. C¹, Afiukwa F. N⁶, Chukwu F.O⁷

¹ Department of Biology/Biotechnology, David Umahi Federal University of Health Sciences Uburu, Ebonyi State Nigeria.

² International Institute for Infectious Diseases, Biosecurity and Biosafety Research, David Umahi Federal University of Health Sciences Uburu, Ebonyi State Nigeria.

³ Department of Biotechnology, Alex-Ekwueme Federal University Ikwo, Ebonyi State Nigeria.

⁴ International Institute for Oncology Research, David Umahi Federal University of Health Sciences Uburu, Ebonyi State Nigeria.

⁵ Department of Scientific and Research Services, David Umahi Federal University Teaching Hospital, Uburu, Ebonyi State, Nigeria.

⁶ Department of Applied Microbiology, Faculty of Science, Ebonyi State University, Abakaliki, Nigeria.

⁷ Department of Biotechnology, Faculty of Science, Ebonyi State University, Abakaliki, Nigeria.

Abstract

Malaria remains a scourge in various sub-Sahara African countries, with 30% infants' mortality rate and 11% for adults. Resistance to artemisinin by *Plasmodium* has necessitated urgent search for alternative treatments. This study evaluated the anti-plasmodial and anti-malarial potentials of different African-medicinal plants. A review was conducted following PRISMA (2020) guidelines. Relevant articles were obtained from Google Scholar, PubMed as well as ResearchGate using keywords such as "*Plasmodium*," "anti-plasmodial activity," "anti-malarial activities," "herbal medicine," "African medicinal plants." Articles that reported *in-vivo*, *in-vitro* or both studies on African medicinal plants were screened and reviewed. Ultimately, 56 eligible articles were selected after removing duplicates. In total, 160 *in-vitro* and 100 *in-vivo* plant species were analyzed based on the plants' family, extraction solvent, level of biological activity using IC₅₀ values and percentage parasite suppression. The result of the *in-vitro* studies revealed that 51.3% of plant species had moderate anti-plasmodial activity, 30.0% had good activity, and 18.7% had very good activity. Potent species included *Alchornea cordifolia* (IC₅₀ = 0.2 – 0.5 µg/mL) as well as *Annickia kummeriae* (IC₅₀ = 0.12 µg/mL). For *in-vivo* studies, 52% of the plant species had moderate anti-plasmodial activity, 30% were good and 18% showed very good, with the highest suppression rates in *Maytenus senegalensis* (98.1%) and *Triphyophyllum peltatum* (99%). Based on the extraction solvent, methanol and ethanol were frequently used solvents that produced higher activity profile. However, significant discrepancy was observed in both *in-vivo* and *in-vitro* activities across the studies. This variation raises concerns about the dependability of the activity of the studied plant species and their potential as anti-malarial agents. Hence, the need to identify active compounds and validate their therapeutic efficacy through bioassay-guided fractionation and detailed mechanistic evaluations. This review points biotechnology researchers to exploring bioassay-guided fractionation, phytochemical screening, *in-silico* drug design, standardization, and molecular studies for creating effective plant-based anti-malarial therapies.

Keywords: *Plasmodium*, Anti-plasmodial activity, Anti-malarial activities, Herbal medicine, African medicinal plants

Corresponding author: E-mail: umeaugustineokpaga@gmail.com

Introduction

Protozoan parasite *Plasmodium* causes malaria, usually spread when an infected mosquito bite (Santos et al., 2021). Malaria remains a menace in many sub-Sahara African countries. According to WHO (2020), malaria continued to be the prime cause of illness and death of over 3.2 billion people globally. In 2015, the Federal Ministry of Health in Nigeria reports alarmed that malaria was all over the country accounting for 60% of hospital visits, 30% of infant deaths, and 11% of their mothers' death (WHO, 2020). This grave infection spread through the bite of an infected female *Anopheles* mosquito, which transmits the parasite to a healthy person (WHO, 2020). Santos et al. (2021) reported the increasing death rate from malaria affects over 90 countries, particularly in resource-limited regions of sub-Saharan Africa. In 2019, WHO, (2020) also estimated 229 million malaria cases globally, with 94% (215 million) occurring in Africa. Nigeria accounted for nearly a quarter of the global malaria burden, leading to close to 500,000 deaths each year (WHO, 2020).

Nagendrappa et al. (2017) noted that *Plasmodium falciparum*, *P. knowlesi*, *P. vivax*, *P. ovale*, and *P. malariae*. *P. falciparum* were the human malaria parasites known to be the most dangerous because they impose resistance to many malarial medications. Presently, several chemotherapeutic agents face prevalent resistance due to gene mutations in the *Plasmodium* (Talisuna et al., 2004). The fight against malaria in sub-Saharan Africa has been greatly affected by the resistance of *P. falciparum* to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) (Talisuna et al., 2004). Nagendrappa et al. (2017), reported unfortunate

resistance to doxycycline, primaquine, atovaquone, which are commonly used to treat malaria among pregnant women and children. Another cause for alarm includes the side effects associated with synthetic malaria drugs as well as high cost of drugs, necessitating, extensive search for more medicinal plants with anti-malarial and anti-plasmodial properties. This quest has led to the creation of new, more affordable antiprotozoal agents.

Plants and their derivatives have shown indispensable role in drug discovery in the pharmaceutical industry (Talisuna et al., 2004). In regions where malaria is predominant, particularly in Africa, countless people depend on herbal medicines for treatment (Suswardany et al., 2017). This dependance is basically because of high cost of conventional drugs, side effects, perceived effectiveness, trust in traditional treatments, and availability (Suswardany et al., 2017). Despite the significant research on traditional medicinal plants, there are few reviews on studies from Nigeria, mostly on the anti-plasmodial and anti-malarial potentials of plant extracts. Therefore, this review evaluated the findings from studies on medicinal plant extracts, focusing on their anti-plasmodial, and anti-malarial including the impact of different methods of extraction.

Materials and Methods

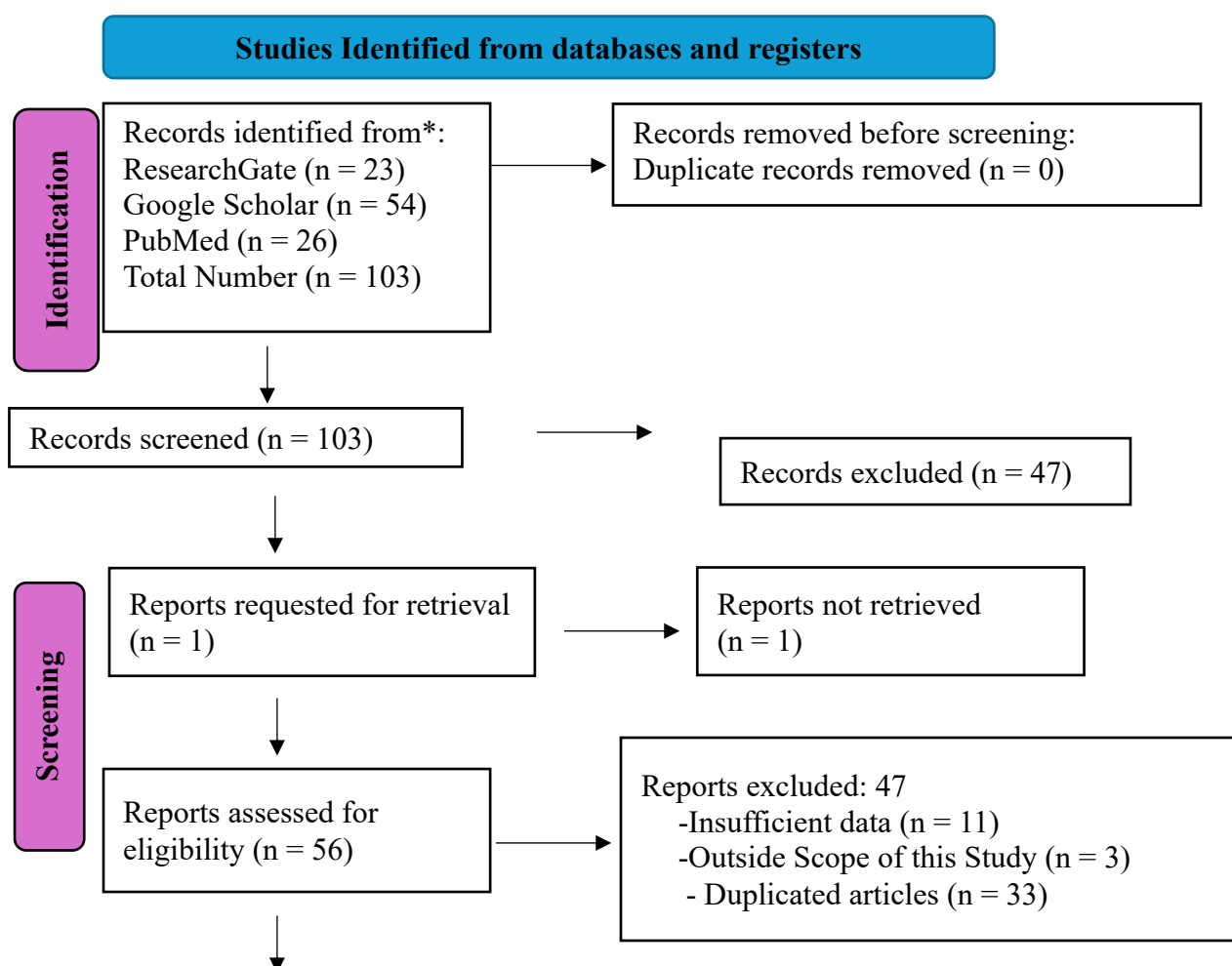
In-vitro studies conducted with different strains of *P. falciparum* are referred to as anti-plasmodial activity, while as *in-vivo* studies which determined the rate of parasite suppression using mice and other parasite models such as *P. berghei*, *P. yoelii*, and *P. chabaudi* were regarded as anti-malarial activities. Articles on the anti-

plasmodial and anti-malarial activities of the plant extracts for malaria treatment were selected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2020) guidelines as shown in Fig. 1. A clear search strategy was adopted across the databases using delimiters and combining search strings with keywords like "*Plasmodium*," "anti-plasmodial activity," "anti-malarial activities," "herbal medicine," "African medicinal plants," and confining results using filed-specific filters such as title, abstract, and keywords. At first, a total of 104 titles were identified, and then screened to obtain 103 articles. Out of which, 40 were excluded due to duplication from different search engines, resulting in 56 articles for review. Each species of plant was regarded as an independent dataset, permitting one article to produce many entries. Key data such as plant species name,

family, plant part, solvent, study type, *Plasmodium* strain, IC₅₀ values, parasite suppression percentage as well as activity classification were extracted using a standardized form. Data extraction was done in duplicate, and any discrepancies were resolved by consensus. Out of the eligible 56 articles, 35 (62.5%) of the studies were *in-vitro* (anti-plasmodial) as detailed in Table 2, while 16 (28.6%) were *in-vivo* (anti-malarial) as shown in Table 3, and 5 (8.9%) covered both *in-vitro* and *in-vivo* studies.

Statistical Analysis

Data gathered from the reviewed articles were summarized as, frequencies and percentages using IBM SPSS (version 23.0) to show the distribution of variables such as plant species, families, extraction methods, reported anti-plasmodial activity and anti-malarial activities.



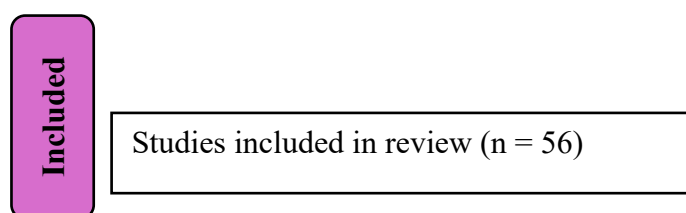


Figure 1. Study selection flowchart (PRISMA guidelines, 2020).

Inclusion and Exclusion Criteria for Selection of Relevant Articles

Search engines like Google Scholar, PubMed, and ResearchGate were used to identify relevant research articles conducted within the period of January 2000 to December 2024. The search process was refined using Boolean operators (AND, OR, NOT), truncation symbols, and field-specific filters to enable retrieval of relevant studies. Duplicate records retrieved from the multiple databases were systematically identified and removed using reference management software, followed by manual cross-checking to ensure complete elimination of repeated entries prior to screening. Only studies that met pre-defined eligibility criteria for experimental design

and outcome measurement were included (i.e., original research reporting anti-plasmodial or anti-malarial evaluation of medicinal plant extracts using validated laboratory models, where the experimental design and outcome measurement clearly described the biological system used (*P. falciparum* cultures or murine malaria models) and reported measurable parasitic response indicators (e.g., IC₅₀, LD₅₀, or percentage parasite suppression) as opposed to lack of experimental antimalarial evaluation, lack of quantifiable outcomes, or lack of laboratory-based assessment of plant-derived materials, or studies without sufficient methodological detail to allow interpretation of results). Plants anti-plasmodial and anti-malarial activities were based on the classification summarized in Table 1.

Table 1. Classification of anti-plasmodial and anti-malarial activities

Study type	Suppression Rate		
	Moderate	Good	Very-good
<i>In-vitro</i> (IC ₅₀)	1 10µg/mL ≤ IC ₅₀ < 20	5µg/mL ≤ IC ₅₀ < 10 µg/mL	IC ₅₀ < 5µg/ml
<i>In-vivo</i> (LD ₅₀)	≥ 50 % by 500mg/kg body weight/day	50 % by 250mg/kg body weight/day	≥ 50 % by 100 mg/kg body weight/day

Source: Santos et al. (2021)

Results

Distribution of Anti-plasmodial Activities Among Plant Families and Species

Table 2(a-f) summarized the antiplasmodial activities of 160 plant species from 28 different families as well as the potency values. The study showed that Fabaceae had 18 (11.3%), Asteraceae 15 (9.4%), Apocynaceae had 12 (7.3%), while Rubiaceae and Meliaceae had had 10 (6.3%), and 8 (5.0%) respectively. The remaining 97(60.6%) species were distributed

among other plant families. About 30 (18.7%) species such as *Alchornea cordifolia* (IC₅₀ = 0.2 – 0.5 µg/mL), *Annickia kummeriae* (IC₅₀ = 0.12 µg/mL), *Artemisia biennis* (IC₅₀ = 1.11 µg/mL), *Azadirachta indica* (IC₅₀ = 1.7 – 5.8 µg/mL), and *Brucea javanica* (IC₅₀ = 1.0 µg/mL) showed very strong anti-plasmodial activity especially against *Plasmodium falciparum*, while 82 (51.3%) including *Abrus precatorius* (IC₅₀ = 37 µg/mL), *Acacia tortilis* (IC₅₀ = 13.4 µg/mL), and *Ageratum conyzoides* (IC₅₀ = 11.5–12.1 µg/mL) recorded moderate anti-plasmodial effects.

Conversely, 48 (30.0%) species, such as *Abutilon grandiflorum* (IC₅₀ = 10 µg/mL), *Aerva lanata* (IC₅₀ = 8.6 µg/mL), *Ampelocissus africana* (IC₅₀

= 9.0 µg/mL), and *Adansonia digitata* (IC₅₀ = 8.2µg/mL) showed good anti-plasmodial activity.

Table 2a: *In-vitro* Anti-plasmodial Activity of Methanol Extracts of the Plants

Plant used	Activity Level	IC ₅₀ Range (µg/mL)	References
<i>Annickia kummeriae</i> , <i>Catha edulis</i> , <i>Artemisia biennis</i> , <i>Pennisetum purpureum</i>	Very good	0.12 – 3.05	(Essoh et al., 2023; Yamthe et al., 2015; Ngbolua et al., 2011; Clarkson et al., 2004)
<i>Aloe ferox</i> , <i>Ampelocissus africana</i> , <i>Aerva lanata</i>	Good	6.9 – 9.0	(Clarkson et al., 2004; Gessler et al., 1994)
<i>Abrus precatorius</i> , <i>Acacia spp.</i> , <i>Andrographis paniculata</i>	Moderate	12.3 – >200	(Essoh et al., 2023; Asokan et al., 2011; Hout et al., 2006; Koch et al., 2005)

Table 2b: *In-vitro* Anti-plasmodial Activity of Ethanol Extracts of the Plants

Plant used	Activity Level	IC ₅₀ Range (µg/mL)	References
<i>Zingiber officinale</i> , <i>Terminalia arjuna</i> , <i>Piper chaba</i> , <i>Artemisia turanica</i>	Very good	1.35 – 3.42	(Chaniad et al., 2023; Essoh et al., 2023; Sanon et al., 2016),
<i>Aframomum giganteum</i> , <i>Albizia coriaria</i>	Good	6.5 – 13.5	(Owuor et al., 2012; Lekana-Douki et al., 2011)
<i>Alstonia boonei</i> , <i>Hibiscus rosa-sinensis</i> , <i>Nigella sativa</i>	Moderate	16 – >100	(Chaniad et al., 2023; Abdissa et al., 2017; Ngbolua et al., 2011)

Table 2c: *In-vitro* Anti-plasmodial Activity of Dichloromethane Extracts of the Plants

Plant used	Activity Level	IC ₅₀ Range (µg/mL)	References
<i>Alchornea cordifolia</i> , <i>Berberis holstii</i> , <i>Azadirachta indica</i>	Very good	0.17 – 2.5	(Mustofa et al., 2000; El-Tahir et al., 1999)
<i>Albizia coriaria</i> , <i>Artemisia afra</i> , <i>Aspilia africana</i>	Good	5 – 10	(Essoh et al., 2023; (Essoh et al., 2023)
<i>Bridelia micrantha</i> , <i>Burchellia bubaline</i>	Moderate	11 – 19	(Clarkson et al., 2004), (Abdissa et al., 2017)

Table 2d: *In-vitro* Anti-plasmodial Activity of Ethyl Acetate Extracts of the Plants

Plant used	Activity Level	IC ₅₀ Range (µg/mL)	References
<i>Abutilon grandiflorum</i> , <i>Cassia siamea</i>	Good	4 – 10	(Clarkson et al., 2004; Gessler et al., 1994)

<i>Cinnamomum camphora</i> , <i>Achillea millefolium</i>	Moderate	16 – 142	(Chaniad et al., 2023; Feiz et al., 2017)
<i>Brucea javanica</i> , <i>Annona reticulata</i> , <i>Alstonia congensis</i>	Very good	1.0 – 5.0	(Yamthe et al., 2015; Lumpu et al., 2013)

Table 2e: *In-vitro* Anti-plasmodial Activity of Aqueous Extracts of the Plants

Plant used	Activity Level	IC ₅₀ (µg/mL)	Range	References
<i>Carica papaya</i> , <i>Ageratum conyzoides</i>	Very good	2.15 – 3.44		(Owuor et al., 2012; Clarkson et al., 2004)
<i>Cassia occidentalis</i>	Good	<6		(Tona et al., 1999)
<i>Albizia coriaria</i> , <i>Aloe pulcherrima</i>	Moderate	15 – 18.6		(Essoh et al., 2023; Abdissa et al., 2017)

Table 2f: *In-vitro* Anti-plasmodial Activity of Chloroform, Hexane, Petroleum Ether, Alkaloids Extracts of the Plants

Plant used	Activity Level	IC ₅₀ (µg/mL)	Range	References
<i>Agathosma apiculata</i> , <i>Phyllanthus emblica</i>	Good	5 – 10		(Asokan et al., 2011; Clarkson et al., 2004)
<i>Lavandula spp.</i> , <i>Kleinhovia hospita</i>	Moderate	>14 – >200		(Chaniad et al., 2023; Essoh et al., 2023; Feiz et al., 2017)
<i>Cucurbita pepo</i> , <i>Sauropus androgynus</i> , <i>Piper nigrum</i>	Very good	2.0 – 4.5		(Chaniad et al., 2023), (Ezeani et al., 2022; Becker et al., 2011)

In-vivo Anti-malarial Activities of Plant Families and Species

The antimalarial activities of plants from different families and species were summarized in Table 3 (a-g). A total of 100 plant species from diverse botanical groups were assessed. Out of which, 15 (15%) species were from the *Fabaceae*, 8 (8%) from *Euphorbiaceae* species, 7 (7%) from *Asteraceae* species, 6 (6%) from *Rubiaceae* species, and 5 (5%) from *Apocynaceae* species, while the remaining 59% distributed among other plant families. In terms of *in-vivo* efficacy, very strong anti-malarial activity was the least represented, observed in about 18 (18%) species

comprising *Acacia nilotica* (*Fabaceae*), *Cassytha filiformis* (*Lauraceae*), *Clausena anisota* (*Rutaceae*), *Maytenus senegalensis* (*Celastraceae*), and *Triphyophyllum peltatum* (*Dioncophyllaceae*), 52 (52%) plant species from various families such as *Adansonia digitata* (*Malvaceae*), *A. indica* (*Meliaceae*), *V. amygdalina* (*Asteraceae*), *Nauclea latifolia* (*Rubiaceae*), and *Withania somnifera* (*Solanaceae*) had moderate anti-malarial effects. About 30 (30%) including *A. gummifera*, *Cassia singueana* (*Fabaceae*), *Carica papaya* (*Caricaceae*), *Tithonia diversifolia* (*Asteraceae*), and *Phyllanthus amarus* (*Phyllanthaceae*), showed good anti-malarial activity.

Table 3a: *In-vivo* Anti-malarial Efficacy of Methanol Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Acacia nilotica</i> , <i>Azadirachta indica</i> , <i>Icacina senegalensis</i>	Very good	62.6 – 87	(Alli et al., 2011; Gathirwa et al., 2008; Gathirwa et al., 2008; Okokon et al., 2006)
<i>Albizia gummifera</i> , <i>Cassia singueana</i> , <i>Premna chrysoclada</i> , <i>Trema orientalis</i>	Good	65.1 – 79.1	(Christian et al., 2017; Ukwé et al., 2010; Udobang et al., 2010; Gathirwa et al., 2008)
<i>Adansonia digitata</i> , <i>Balanites rotundifolia</i> , <i>schweinfurthii</i> , <i>Withania somnifera</i>	Moderate	53.1 – 90.2	(Alli et al., 2011), (Gathirwa et al., 2008), (Christian et al., 2017), [50]

Table 3b: *In-vivo* Anti-malarial Efficacy of Ethanol Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Acacia nilotica</i> , <i>Azadirachta indica</i> , <i>Icacina senegalensis</i>	Very good	81.5 – 98.1	(Yamthe et al., 2015; Abdulrazak et al., 2015)
<i>Albizia gummifera</i> , <i>Cassia singueana</i> , <i>Premna chrysoclada</i> , <i>Trema orientalis</i>	Good	68 – 78.2	(Eluu et al., 2019; Christian et al., 2017), (Abdulrazak et al., 2015)
<i>Adansonia digitata</i> , <i>Balanites rotundifolia</i> , <i>Lannea schweinfurthii</i> , <i>Withania somnifera</i>	Moderate	60 – 75	(Eluu et al., 2019; Gathirwa et al., 2008)

Table 3c: *In-vivo* Anti-malarial Efficacy of Aqueous Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Adansonia digitata</i> , <i>Euphorbia cordifolia</i>	Very good	60.5 – 94.7	(Musila et al., 2013; Tona et al., 1999)
<i>Bombax buonopozense</i> , <i>Phyllanthus amarus</i> , <i>Telfairia occidentalis</i> , <i>Vernonia amygdalina</i>	Good	72 – 93	(Christian et al., 2017; Edagha et al., 2017; Gathirwa et al., 2008),
<i>Acacia nilotica</i> , <i>Ageratum conyzoides</i>	Moderate	79.5 – 89.9	(Alli et al., 2011; Ukwé et al., 2010)

Table 3d: *In-vivo* Anti-malarial Efficacy of Dichloromethane Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Triphyophyllum peltatum</i>	Very good	~99	(Edagha et al., 2017)
<i>Morinda morindoides</i>	Good	~74	(Okokon et al., 2006)
<i>Commiphora Africana</i>	Moderate	~64	(Eluu et al., 2019)

Table 3e: *In-vivo* Anti-malarial Efficacy of Chloroform Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Artemisia macivarae</i> , <i>Xylopia aethiopica</i>	Very good	60 – 80	(Becker et al., 2011; Ene et al., 2008)
<i>Trichilia megalantha</i>	Good	89 – 100	(Udobang et al., 2010)

<i>Cucumis metuliferus</i> , <i>Phyllanthus niruri</i>	Moderate	70 – 90	(Mzena et al., 2018; Edagha et al., 2017)
--	----------	---------	---

Table 3f: *In-vivo* Anti-malarial Efficacy of Ethyl Acetate Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Anthocleista djalensis</i> , <i>Croton macrostachyus</i> , <i>Lippia kituiensis</i>	Moderate	64.8 – 87.7	(Eluu et al., 2019; Ene et al., 2008; Okokon et al., 2006)

Table 3g: *In-vivo* Anti-malarial Hexane, Petroleum Ether, Hydroalcohol and Butanol Acetate Extracts of the Plants

Plant used	Activity Level	Suppression Rate (%)	References
<i>Cryptolepis sanguinolenta</i> , <i>Garcinia kola</i> , <i>Calpurnia aurea</i>	Very good	>80 – 93	(Christian et al., 2017; Tona et al., 1999; Gessler et al., 1994)
<i>Artemisia abyssinica</i> , <i>Mucuna pruriens</i>	Good	64.7 – 71.8	(Ene et al., 2008; Okokon et al., 2006)
<i>Dodonaea angustifolia</i> , <i>Peschiera fuchsiaefolia</i>	Moderate	43.4 – 55.8	(Mzena et al., 2018)

Discussion

Historically, medicinal plants have continued to play indispensable role in drug discovery as well as in disease management (Eluu et al., 2019). Majority of available antimalarial drugs are produced from plant sources or their bioactive compounds. The present review demonstrated that though many plant species showed strong anti-plasmodial ability (*in-vitro*), relatively limited number of plant extracts have been assessed *in-vivo*, particularly within Africa. This gap is indicative of the necessity for increased key and medical research across the continent, which was also highlighted by Udobang et al. (2010). Most studies included in this review were from Nigeria, followed by Kenya, South Africa, and the Democratic Republic of Congo, which is consistent with the idea that Nigeria is leading in antimalarial research, probably because it has the highest malaria burden (WHO, 2020). Malaria is highly endemic across sub-Saharan Africa, with most global cases occurring in the region (Santos et al., 2021). Therefore, research efforts are closely linked to disease burden and national health priorities, which points to the reasons for policy-driven research to develop novel antimalarial drugs across Africa. Plant extracts with IC₅₀ values below 20 µg/mL were deemed to have high antimalarial potential and were

considered appropriate for early-stage drug discovery (Essoh et al., 2023). Results from this study show that most plants that exhibit good anti-plasmodial activity *in-vitro* show only moderate activity *in-vivo*, and *in-vitro* potency was lost *in-vivo* in *Uvaria acuminata* (Gathirwa et al., 2008), while others show improved activity *in-vivo*, despite weaker *in-vitro* results, as reported for *Vernonia ambigua* (Ngbolua et al., 2011), and similarly for Muthaura et al. (2007). The commonly studied plant families include *Euphorbiaceae*, *Fabaceae*, *Rubiaceae*, and *Annonaceae*, while *Apocynaceae*, *Celastraceae*, and *Rutaceae* families are more likely to contain biologically active species.

The commonly explored plant families include *Euphorbiaceae*, *Fabaceae*, *Rubiaceae*, and *Annonaceae*, whereas families such as *Apocynaceae*, *Celastraceae*, and *Rutaceae* are more typically associated with biologically active species. *A. indica*, *N. latifolia*, *P. nitida*, and *Z. chalybeum* are among the most frequently studied plants, although *A. cordifolia*, *F. virosa*, *C. sanguinolenta*, and *Z. chalybeum* showed consistently strong anti-plasmodial and antimalarial effects across studies. The lack of clinical trials for these promising species represents a critical gap that urgently needs attention. The findings of this study largely aligned with several systematic reviews of the

anti-plasmodial and antimalarial potentials of therapeutic plants.

Tajbakhsh et al. (2021) reported that 80% of studies conducted on medicinal plants with anti-plasmodial activity involve *in-vitro* assays and less than 15% progressed to *in-vivo* validation, which corroborates our observations that most of the African-medicinal plants with promising anti-plasmodial potentials have not progressed beyond preliminary laboratory screening and that there is a significant translational gap between early discovery and therapeutic development. Similarly, Irungu et al. (2023) revealed that only a few medicinal plants from East Africa have been subjected to comprehensive pharmacological evaluation despite their promising anti-plasmodial activity.

They further noted that most of the studies showed either moderate or good anti-plasmodial activity, while only a few had strong activities of interest for drug development; in the present review, moderate activity was the most frequently reported category for evaluated plant species. Correspondingly, Kacholi et al. (2024) in their systematic review on medicinal plants in Tanzania, reported substantial methodological differences among studies, counting variability in extraction solvents, plant parts used, experimental models as well as strains of parasites, which led to the disparity in the reported anti-plasmodial activity. This brings into line the discrepancies identified in the current review, where species *A. digitata*, *S. occidentalis*, *A. coriaria*, and *M. lucida* showed different activity levels in different studies. The most studied plant families across these reviews are *Fabaceae*, *Euphorbiaceae*, *Rubiaceae*, and *Annonaceae*, and plant species that frequently show high activity include *A. indica*, *N. latifolia*, *P. nitida*, and *Z. chalybeum*. Of note, Tajbakhsh et al. (2021) also reported that *A. cordifolia*, *C. sanguinolenta*, and *Z. chalybeum* were among the most consistently active plants against *Plasmodium falciparum*, a finding that is supported by the present review and further confirmed by the addition of *F. virosa* to the list of plants that have shown strong and reproducible anti-plasmodial activity in multiple studies, yet there is very little evidence of these plants moving from preclinical evaluation into clinical evaluation, and another consistent observation from recent reviews is that, despite

the abundance of preclinically active medicinal plants, very few have advanced to human clinical trials, a bottleneck in the antimalarial drug discovery pipeline that must be addressed.

These studies have several limitations, including substantial heterogeneity in study design, such as extraction methods, solvents, plant parts analyzed, experimental protocols, variability in assay techniques (including differences in parasite strains of *P. falciparum* that are chloroquine-sensitive against resistant-strains, lack of standardization in reporting IC₅₀ values, dosage regimens, and control treatments, *in-vitro* assays, lack of *in-vivo* models and toxicity evaluations, and potential geographical variation in plant chemistry. This study highlights needs to advance anti-malarial drug development by identifying bioactive compounds consistently present in plants like *C. sanguinolenta* and *A. cordifolia*, conduct *in-vivo* studies to enhance thorough pharmacological evaluation, toxicity profiling, pharmacokinetics, and dose optimization.

This review highlights its importance in advancing antimalarial drug development by identifying consistently active plants such as *A. cordifolia* and *C. sanguinolenta*. It underscores the need for further *in vivo* studies and clinical trials to enable thorough pharmacological evaluation, including toxicity profiling, pharmacokinetics, and dose optimization. The study also emphasizes the importance of isolating and characterizing active compounds to develop standardized, clinically effective antimalarial agents. Overall, the review is highly relevant to biotechnology, as it identifies medicinal plants with strong anti-plasmodial potential that could serve as sources of novel drug candidates. Several recommendations are proposed to enhance the reliability and comparability of future studies through; standardized protocols for plant extraction, including solvent selection and preparation methods, should be established; uniform criteria for classifying anti-plasmodial activity (e.g., IC₅₀ thresholds) should be adopted across studies; researchers should use both chloroquine-sensitive and resistant strains of *Plasmodium falciparum* to make findings more relevant; *in-vitro* studies should be followed by systematic *in-vivo* validation including toxicity and safety assessments; detailed reporting of experimental

conditions and results should be encouraged to make results reproducible; and interdisciplinary collaboration between ethnobotanists, pharmacologists, and clinicians is needed to accelerate the translation of promising plant-based therapies into clinical use.

Conclusion

The study discovered that the plant's anti-plasmodial and anti-malaria qualities varied between studies. A critical assessment of these anti-malarial combinations became necessary due to differences in their efficacy *in-vitro* and *in-vivo*. Therefore, it remains pertinent to evaluate plant extracts' *in-vitro* and *in-vivo* efficacies before asserting their anti-malarial efficacy. To counteract the rise in anti-malarial drug resistance, this discovery is anticipated to influence the policy framework surrounding the production of anti-malarial drugs. Biotechnological approaches have over time proven useful identifying active compounds from plants as well as validating their therapeutic efficacy through bioassay-guided fractionation and detailed mechanistic evaluations. This review points researchers in the field of biotechnology and beyond to explore bioassay-guided fractionation, phytochemical screening, *in-silico* drug design, standardization, and molecular studies for creating effective plant-based anti-malarial therapies.

Conflict of Interest

The authors affirm that they have no conflicts of interest.

References

- Abdissa, D., Geleta, G., Bacha, K., & Abdissa, N. (2017). Phytochemical investigation of *Aloe pulcherrima* roots and evaluation for its antibacterial and anti-plasmodial activities. *PLoS One*, *12*, e0173882.
- Abdulrazak, N., Asiya, U. I., Usman, N. S., Unata, I. M., & Farida, A. (2015). Anti-plasmodial activity of ethanolic extract of root and stem bark of *Cassia sieberiana* DC on mice. *J. Intercult. Ethnopharmacol.*, *4*(2), 96–101.
- Alli, L. A., Adesokan, A. A., Salawu, O. A., Akanji, M. A., & Tijani, A. Y. (2011). Anti-plasmodial activity of aqueous root extract of *Acacia nilotica*. *Afr. J. Biochem. Res.*, *5*(7), 214–219.
- Asokan, B., Abdul, A. R., Naveen, K. K., & Dinkar, S. (2011). *In-vitro* antimalarial activity of medicinal plant extracts against *Plasmodium falciparum*. *Parasitol. Res.*, *108*(1), 15–22.
- Becker, J. V. W., van der Merwe, M. M., van Brummelen, A. C., Pillay, P., Crampton, B. G., & Mutlane, E. M. (2011). In-vitro anti-plasmodial activity of *Dicoma anomala* subsp. *gerrardii* (Asteraceae): Identification of its main active constituent, structure–activity relationship studies, and gene expression profiling. *Malar. J.*, *10*, 295.
- Chaniad, P., Techarang, T., Phuwajaroanpong, A., Plirat, W., Viriyavejakul, P., Septama, A. W., & Punsawad, C. (2023). Antimalarial efficacy and toxicological assessment of medicinal plant ingredients of Prabchompoothaweep remedy as a candidate for antimalarial drug development. *BMC Complement. Med. Ther.*, *23*(12).
- Christian, A. G., Thecla, E. C., Dick, E. A., Chile, A. E., Chimsorom, C. K., & Ckukwu, N. D. (2017). In-vivo anti-plasmodial activity of *Bombax buonopozense* root bark aqueous extract in mice infected by *Plasmodium berghei*. *J. Tradit. Clin. Med.*, *37*, 431–435.
- Clarkson, C., Maharaj, V. J., Crouch, N. R., Grace, O. M., Pillay, P., & Matsabisa, M. G. (2004). In-vitro anti-plasmodial activity of medicinal plants native to or naturalized in South Africa. *J. Ethnopharmacol.*, *92*, 177–191.
- Edagha, I. A., Peter, A. I., & Aquaisua, A. N. (2017). Histopathological effect of *Nauclea latifolia* ethanolic leaf extract and artemether/lumefantrine on the hippocampus of *P. berghei*-infected mice. *Int. J. Brain Cogn. Sci.*, *6*, 9–16.
- El-Tahir, A., Satti, G. M., & Khalid, S. A. (1999). Anti-plasmodial activity of selected Sudanese medicinal plants with emphasis on *Acacia nilotica*. *Phytother. Res.*, *13*(8), 474–478.

- Eluu, S. C., Oko, A. O., Osonwa, U. E., Eze, G. O., & Ngele, K. K. (2019). In-vivo antimalarial screening of ethanolic extract of *Cassythia filiformis* and its ameliorative effect on haematological and biochemical parameters altered in *Plasmodium berghei*-infected mice. *IDOSR J. Biol. Chem. Pharm.*, 3(1), 5–15.
- Ene, A. C., Ameh, D. A., Kwanashie, H. O., Agomo, P. U., & Atawodi, S. E. (2008). Preliminary in-vivo antimalarial screening of petroleum ether, chloroform, and methanol extracts of fifteen plants grown in Nigeria. *J. Pharmacol. Toxicol.*, 3(4), 254–260.
- Essoh, A. P., Cassiano, G. C., Mandim, F., Barros, L., Gomes, I., Medeiros, M. M., Moura, M., Cravo, P. V. L., & Romeiras, M. M. (2023). Antimalarial and cytotoxic activity of native plants used in Cabo Verde traditional medicine. *Plants*, 12(4), 963.
- Ezeani, C., Ezenyi, I., Erhunse, N., Sahal, D., Akunne, T., & Okoli, C. (2022). Assessment of antimalarial medicinal plants used in Nigerian ethnomedicine reveals antimalarial potential of *Cucurbita pepo* leaf extract. *Heliyon*, 8(8), e09916.
- Feiz, H. M. H., Mahbodfar, H. R., Zamani, Z., & Ramazani, A. (2017). Antimalarial evaluation of selected medicinal plant extracts used in Iranian traditional medicine. *Iran. J. Basic Med. Sci.*, 20(4), 415–422.
- Gathirwa, J. W., Rukunga, G. M., Njagi, E. N., Omar, S. A., Mwitari, P. G., & Guantai, A. N. (2008). The in-vitro anti-plasmodial and in-vivo antimalarial efficacy of combinations of some medicinal plants used traditionally for treatment of malaria by the Meru community in Kenya. *J. Ethnopharmacol.*, 115(2), 223–231.
- Gessler, M. C., Nkunya, M. H. H., Mwasumbi, L. B., Heinrich, M., & Tanner, M. (1994). Screening Tanzanian medicinal plants for antimalarial activity. *Acta Trop.*, 56(1), 65–77.
- Hout, S., Chea, A., Bun, S. S., Elias, R., Gasquet, M., & Timon-David, P. (2006). Screening of selected indigenous plants of Cambodia for anti-plasmodial activity. *J. Ethnopharmacol.*, 107(1), 12–18.
- Irungu, B. N., Rukunga, G. M., Mungai, G. M., & Muthaura, C. N. (2023). Medicinal plants traditionally used for the treatment of malaria in East Africa: A review of their anti-plasmodial activity and pharmacological potential. *J. Ethnopharmacol.*, 308, 116239.
- Kacholi, D. S., Munissi, J. J. E., & Nondo, R. S. O. (2024). Medicinal plants used for malaria treatment in Tanzania: A systematic review of ethnobotany, pharmacology, and anti-plasmodial activity. *Plants*, 13(2), 215.
- Koch, A., Tamez, P., Pezzuto, J., & Soejarto, D. (2005). Evaluation of plants used for antimalarial treatment by the Maasai of Kenya. *J. Ethnopharmacol.*, 101(1–3), 95–99.
- Lekana-Douki, J. B., Liabagui, S. L. O., Bongui, J. B., et al. (2011). In-vitro anti-plasmodial activity of crude extracts of *Tetrapleura tetraptera* and *Copaifera religiosa*. *BMC Res. Notes*, 4(1), 1–5.
- Lumpu, S. L., Kikueta, C. M., Tshodi, M. E., et al. (2013). Antiprotozoal screening and cytotoxicity of extracts and fractions from the leaves, stem-barks and root barks of *Alstonia congensis*. *J. Ethnopharmacol.*, 148(2), 724–727.
- Musila, M. F., Dossaji, S. F., Nguta, J. M., Lukhoba, C. W., & Munyao, J. M. (2013). In vivo antimalarial activity, toxicity and phytochemical screening of selected antimalarial plants. *J. Ethnopharmacol.*, 146(2), 557–561.
- Mustofa, V. A., Benoit-Vical, F., Pelissier, Y., Kone-Bamba, D., & Mallié, M. (2000). Anti-plasmodial activity of plant extracts used in West African traditional medicine. *J. Ethnopharmacol.*, 73(1–2), 145–151.
- Muthaura, C. N., Rukunga, G. M., Chhabra, S. C., Omar, S. A., Guantai, A. N., & Gathirwa, J. W. (2007). Antimalarial activity of some plants traditionally used in treatment of malaria in Kwale district of Kenya. *J. Ethnopharmacol.*, 112(3), 545–551.
- Mzena, T., Swai, H., & Chacha, M. (2018). Antimalarial activity of *Cucumis metuliferus* and *Lippia kituiensis* against *Plasmodium berghei* infection in mice. *Res. Reprod. Trop. Med.*, 9, 81–88.

- Nagendrappa, P. B., Annamalai, P., Naik, M., Mahajan, V., Mathur, A., & Susanta, G. (2017). A prospective comparative field study to evaluate the efficacy of a traditional plant-based malaria prophylaxis. *J. Intercult. Ethnopharmacol.*, 6(1), 36–41.
- Ngbolua, K. N., Rakotoarimanana, H., Rafatro, H., Ratsimamanga, U. S., Mudogo, V., & Mpiana, P. T. (2011). Comparative antimalarial and cytotoxic activities of two *Vernonia* species: *Vernonia amygdalina* from the Democratic Republic of Congo and *Vernonia cinerea* subsp. *vialis* endemic to Madagascar. *Int. J. Biol. Chem. Sci.*, 5(2), 345–353.
- Okokon, J. E., Ita, B. N., & Udokpoh, A. E. (2006). The in vivo antimalarial activities of *Uvaria chamae* and *Hippocratea africana*. *Ann. Trop. Med. Parasitol.*, 100(6), 585–590.
- Owuor, B. O., Ochanda, J. O., Kokwaro, J. O., Cheruiyot, A. C., Yeda, R. A., & Okudo, C. A. (2012). In-vitro anti-plasmodial activity of selected Luo and Kuria medicinal plants. *J. Ethnopharmacol.*, 144(3), 779–781.
- Sanon, S., Ollivier, E., Azas, N., Mahiou, V., Gasquet, M., & Ouattara, C. (2016). Ethnobotanical survey and *in-vitro* anti-plasmodial activity of plants used in traditional medicine in Burkina Faso. *J. Ethnopharmacol.*, 86, 143–147.
- Santos, B. M., Dias, B. K. M., Nakabashi, M., & Garcia, C. R. S. (2021). The knockout for G protein-coupled receptor-like PfSR25 increases the susceptibility of malaria parasites to the antimalarials lumefantrine and piperazine but not to Medicine for Malaria Venture compounds. *Front. Microbiol.*, 12, 638869.
- Suswardany, D. L., Sibbritt, D. W., Supardi, S., Pardosi, J. F., Chang, S., & Adams, J. A. (2017). Cross-sectional analysis of traditional medicine use for malaria alongside free antimalarial drugs treatment amongst adults in high-risk malaria endemic provinces of Indonesia. *PLoS One*, 12, e0173522.
- Tajbakhsh, S., Soleimani, N., & Ramezani, M. (2021). Evaluation of anti-plasmodial activity of medicinal plants used in traditional medicine: A systematic review. *Malar. J.*, 20, 343.
- Talisuna, A. O., Bloland, P., & Di Alessandro, U. (2004). History, dynamics, and public health importance of malaria parasite resistance. *Clin. Microbiol. Rev.*, 17(1), 235–254.
- Tona, L., Ngimbi, N. P., Tsakala, M., Mesia, K., Cimanga, K., Apers, S., De Bruyne, T., Pieters, L., Totté, J., & Vlietinck, A. J. (1999). Antimalarial activity of 20 crude extracts from nine African medicinal plants used in Kinshasa, Congo. *J. Ethnopharmacol.*, 68, 193–203.
- Udobang, J. A., Nwafor, P. A., & Okokon, J. E. (2010). Analgesic and antimalarial activities of crude leaf extract and fractions of *Acalypha wilkensis*. *J. Ethnopharmacol.*, 127, 373–378.
- Ukwe, V. C., Epueke, E. A., Ekwunife, O. I., Okoye, T. C., Akudor, G. C., & Ubaka, C. M. (2010). Antimalarial activity of aqueous extract and fractions of leaves of *Ageratum conyzoides* in mice infected with *Plasmodium berghei*. *Int. J. Pharm. Sci.*, 2, 33–38.
- World Health Organization. (2020). World malaria report 2020: 20 years of global progress and challenges. World Health Organization.
- Yamthe, L. R. T., Fokou, P. V. T., Mbouna, C. D. J., Keumoe, R., Ndjakou, B. L., & Djouonzo, P. T. (2015). Extracts from *Annona muricata* L. and *Annona reticulata* L. (Annonaceae) potently and selectively inhibit *Plasmodium falciparum*. *Medicines (Basel)*, 2, 55–66.