Original Article

JHSMR Journal of Health Science and Medical Research

Antimalarial Potency of *Vernonia Amygdalina* Ethanolic Extracts in the Prevention and Treatment of *Plasmodium Berghei*–Infected Mice

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Received 20 January 2025 ● Revised 5 May 2025 ● Accepted 24 May 2025 ● Published online 16 September 2025

Abstract:

Objective: This study assessed the anti-malarial potency of *Vernonia amygdalina* ethanolic extracts (leaf and stem-bark) in the prevention and treatment of *Plasmodium berghei*-infected mice.

Material and Methods: Fresh leaves and stem bark of *Vernonia amygdalina* were collected in Kurmi LGA, Taraba State, based on ethnobotanical guidance, and authenticated at Ahmadu Bello University, Zaria (voucher number 02006). Non-pregnant mice (20–35 g) were acclimatized at the Modibbo Adama University Infectious Diseases Research Laboratory, Yola, for 14 days before curative (70 mice) and prophylactic (40 mice) tests. Plant extracts were administered orally, and parameters such as parasitemia, body weight, temperature, packed cell volume (PCV), and mean survival time (MST) were monitored.

Results: The leaf extract at 600 mg/kg demonstrated the highest parasitemia suppression (60.78%) with a significant increase in the MST of the infected mice. Similarly, the stem-bark extract at the same dose exhibited 60.62% parasitemia suppression, with the MST also significantly extended. In both cases, suppression rates and MST were dose-dependent, with higher doses providing better outcomes. The prophylactic test revealed that a dose of 200 mg/kg of leaf extract achieved 91.67% suppression of parasitemia, outperforming the stem-bark extract. The MST was significantly increased in all treated groups compared to the untreated controls.

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J Health Sci Med Res
doi: 10.31584/jhsmr.20251254
www.jhsmr.org

Conclusion: The study demonstrates that *Vernonia amygdalina* ethanolic extracts, particularly from the leaf, possess significant anti-malarial activity, supporting its potential use in malaria treatment. In addressing artemisinin resistance, *Vernonia amygdalina* extracts may exert their antiplasmodial effects through molecular mechanisms distinct from those targeted by artemisinin.

Keywords: anti-malarial, ethanolic extracts, parasitemia suppression, *plasmodium berghei*, *vernonia amygdalina*

Introduction

Malaria remains one of the most significant infectious diseases globally, caused by protozoan parasites of the genus *Plasmodium*. Human malaria is primarily transmitted through the bite of an infected female *Anopheles* mosquito during a blood meal. Four main species of *Plasmodium,* that is *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae,* are responsible for human malaria infections, with *P. falciparum* contributing to the majority of severe cases and deaths[1,2].

The World Health Organization (WHO) estimates that malaria infects approximately 247 million people annually, with nearly 619,000 deaths reported in 2021. Children under 5 years old are the most affected, particularly in Sub-Saharan Africa, which accounts for 95% of global malaria cases[3]. Nearly half of the world's population resides in malaria-endemic regions, encompassing over 90 countries. In these areas, over 2.4 billion people are at risk of malaria infection[4].

The burden of malaria extends beyond mortality and morbidity, imposing significant socioeconomic challenges[5]. Economically, malaria results in both direct costs, such as healthcare expenditures, and indirect costs, including loss of productivity due to illness and death. In endemic regions, the disease significantly hinders economic growth and development[5]. The United States Agency for International Development (USAID) highlights that malaria is endemic in more than 95% of Sub-Saharan African countries, excluding some high-altitude regions[6].

Despite progress in malaria control, the emergence of drug-resistant strains of *Plasmodium*, particularly to artemisinin-based combination therapies (ACTs), poses a critical public health challenge[7,8]. Resistance jeopardizes the efficacy of current treatments and emphasizes the urgent need to develop new, affordable, and effective antimalarial agents. Historically, many antimalarial drugs, such as artemether, chloroquine, and quinine, have been derived from natural products or inspired by plant-based compounds[9].

Traditional medicine continues to play a vital role in primary healthcare, particularly in low-resource settings. In Africa, up to 80% of the population relies on traditional medicine for treating various illnesses, including malaria[2]. The use of medicinal plants, referred to as herbal medicine or phytomedicine, involves utilising plant-derived materials such as seeds, roots, leaves, and bark for therapeutic purposes[10]. Research shows that over 50% of modern clinical drugs are either derived from or inspired by natural products, showing the importance of plant materials in drug discovery[9,11].

In the context of antimalarial research, in vivo models involving rodent-specific *Plasmodium* species, such as *P. berghei* and *P. yoelii*, are widely used to evaluate drug efficacy. These models, while not entirely replicating *P. falciparum* infection in humans, provide critical insights into drug activity, parasitemia reduction, and survival outcomes[12,13]. Given the increasing resistance to existing antimalarial drugs, there is a pressing need to explore

traditionally used medicinal plants, such as *V. amygdalina* and others, for their potential to yield novel antimalarial compounds[14].

Material and Methods

Description of study area

The fresh leaves and stem-bark of *V. amygdalina* were collected based on ethnobotanical descriptions with the assistance of taxonomists and local traditional healers in Kurmi LGA, Taraba State. Kurmi is geographically located between latitudes 6°30′ and 9°36′N and longitudes 9°10′ and 11°50′E, bordered by Donga and Takum LGAs to the west, Gashaka LGA to the east, Bali LGA to the north, Ussa LGA to the west, and Sardauna LGA to the south. The area experiences a wet and dry seasonal climate, with predominantly sandy-loam soils that range from grayish-brown to brown and are well-drained. Kurmi's high forest region is characterized by dense grasses and tall trees. Its inhabitants, primarily of Tigun, Ndola, and Ichen ethnicities, are mostly engaged in farming.

Experimental design

The collected plant materials were washed, air-dried, and packaged before identification and authentication at the Department of Plant Science, Ahmadu Bello University, Zaria, with a voucher number of 02006. Male and female (non-pregnant) mice weighing 20–35 g were sourced from the National Veterinary Research Institute, Vom, Plateau State, and acclimatized for 14 days at the Infectious Diseases Research Laboratory, Modibbo Adama University, Yola. During acclimatization, the mice were fed with standard rodent feed and tap water. A total of 70 mice were used for curative tests and 40 for prophylactic tests, with the mice divided into respective groups of 5 per cage. All plant extracts at doses of 200 mg, 400 mg, and 600 mg were administered orally using a cannula and syringe. The selection of these 3 doses was based on previous research findings. Observations included parasitemia, body weight, temperature, packed cell volume (PCV), and mean survival time (MST); all were conducted following the guidelines recommended by the Center for Drug Evaluation and Research[15].

Plant extraction and phytochemical analysis

For ethanol extraction, 100 g of powdered *V. amygdalina* plant material was macerated in 80% ethanol for 72 hours with intermittent agitation. The supernatant was filtered using Whatman grade 1 filter paper, concentrated with a rotary evaporator (BUCHI R-250, Switzerland) at 40 °C, and stored at –20 °C for use. Qualitative and quantitative phytochemical screening tests were performed in the Chemistry Laboratory of Ahmadu Bello University, Zaria, to detect secondary metabolites, including alkaloids, flavonoids, terpenoids, phenols, tannins, saponins, anthraquinones, and cardiac glycosides, following standard procedures[16].

Experimental procedures and data analysis

The *Plasmodium berghei* ANKA strain used in the study was sourced from the National Institute for Pharmaceutical Research and Development, Abuja, and maintained by serial passage in mice. The four-day suppressive test was used for both curative and chemoprophylactic groups, with mice treated with varying doses of *V. amygdalina* extracts and controls treated with chloroquine or left untreated. Parasitemia levels were evaluated microscopically using Giemsa-stained blood smears, with results expressed as mean±standard error of the mean (SEM). Statistical analysis was conducted using SPSS version 24, with one-way ANOVA used to compare the groups. Significant differences were noted based on mean values with distinct alphabetic annotations. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Health Sciences, Taraba State University, with the approval reference number of

RECFOHC/TSU/2023/008. The handling of the mice during the studies was in adherence with the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines.

Results

The phytochemical qualitative analysis revealed that both the leaf and stem-bark of *V. amygdalina* ethanolic extracts are rich in bioactive compounds. Alkaloids, phenols, saponins, tannins, and terpenoids were present in both parts of the plant (Table 1). Flavonoids, however, were detected only in the leaf, suggesting that certain phytochemicals may be part-specific.

Table 1 Phytochemical qualitative analysis of *V. amygdalina* (leaf and stem-bark) ethanolic extracts

Phytochemical	*V. amygdalina*	
	Leaf	Stem-bark
Alkaloids	+	+
Flavonoids	+	–
Phenols	+	+
Saponins	+	+
Tannins	+	+
Terpenoids	+	+

+ (Present), – (Absent)

The quantitative analysis showed significant variation (p-value<0.05) in the concentration of phytochemicals between the leaf and stem-bark extracts (Table 2). The leaf contains higher levels of alkaloids (6.51±0.03 mg), saponins (4.32±0.04 mg), and terpenoids (0.46±0.05 mg), while the stem-bark is richer in tannins (2.86±0.01 mg). Phenols and flavonoids were present in similar concentrations in both parts.

The curative test with *V. amygdalina* leaf ethanolic extract demonstrates a dose-dependent reduction in parasitemia and an increase in suppression percentage, with 600 mg/kg showing the highest suppression (60.78%) among the test groups (Table 3). However, the ANOVA statistical test revealed that the standard drug (Group D) exhibited significantly higher suppression (81.72%) and extended survival (MST: 28.20±0.04 days) compared to the plant extracts. Negative control groups (E and F) recorded no suppression and poor survival rates.

The stem-bark ethanolic extract also showed dose-dependent antimalarial activity, with parasitemia suppression increasing from 52.78% (200 mg/kg) to 60.62% (600 mg/kg) (Table 4). Group D (standard drug) again showed the highest results with 82.47% suppression and MST of 27.90±0.01 days. Negative control groups showed the

Table 2 Phytochemical quantitative analysis of *V. amygdalina* (leaf and stem-bark) ethanolic extracts expressed as (mg/100 g)

Phytochemical	Leaf (mean±S.D.)	Stem-bark (mean±S.D.)	Mean difference	95% CI	Cohen's d
Tannins	1.37 ± 0.04^{a}	2.86 ± 0.01^{b}	−1.49	[−1.55, −1.43]	5.43
Alkaloids	6.51 ± 0.03^{a}	3.04 ± 0.03^{b}	3.47	[3.41, 3.53]	81.72
Saponins	4.32 ± 0.04^{a}	2.67 ± 0.02^{b}	1.65	[1.59, 1.71]	47.79
Flavonoids	2.87 ± 0.03^{a}	2.43 ± 0.04^{a}	0.44	[0.38, 0.50]	12.57
Terpenoids	0.46 ± 0.05^{a}	0.28 ± 0.02^{b}	0.18	[0.08, 0.28]	4.33
Phenols	3.24 ± 0.03^{a}	3.02 ± 0.04^{a}	0.22	[0.16, 0.28]	6.59

Superscripts a and b denote statistically significant differences (p-value<0.05), Mean difference=Leaf mean − Stem-bark mean, Cohen's *d* interpreted as: small (~0.2), medium (~0.5), large (>0.8); values here are inflated due to the small standard deviations and biological variability, All values based on *n*=3 (triplicate determinations)

highest parasitemia and lowest survival, indicating the importance of treatment. However, the ANOVA statistical test revealed that the standard drug (Group D) exhibited significantly higher suppression (82.47%) and extended survival (MST: 27.90±0.01 days) compared to the plant extracts.

In the prophylactic test, both the leaf and stem-bark ethanolic extracts demonstrated moderate preventive efficacy, with suppression percentages of 59.16% and 57.08%, respectively, and MST values of 18.00±0.17 and 17.68±0.10 days (Table V). However, the ANOVA statistical test revealed that the standard drug (Group C) exhibited significantly higher suppression (91.67%) and extended survival (MST: 29.40±0.001 days) compared to the plant extracts. These results confirm the preventive potential of *V. amygdalina* extracts, with room for improvement to match the efficacy of standard treatments. In addition, the ANOVA statistical test revealed that there was no significant difference between the efficacy of the plant doses when they were used for both treatment and prophylaxis.

Discussion

This study identified the presence of major phytochemical classes, including alkaloids, flavonoids, phenols, saponins, tannins, terpenoids, and steroids, in the ethanolic extracts of *V. amygdalina* (leaf and stem-bark) (Table 1, 2). These findings are consistent with other studies that also reported similar phytochemical profiles in

Table 3 Effect of *V. amygdalina* leaf ethanolic extract on % parasitemia and suppression in curative test groups

Group	Doses (mg/kg)	% Parasitemia	% Suppression	MST
Group A	200	22.10 ± 0.81^{b}	54.62^{a}	16.70 ± 0.34^{b}
Group B	400	20.70 ± 0.41^{b}	57.49^{ab}	19.28 ± 0.41^{b}
Group C	600	19.10 ± 0.39^{b}	60.78^{b}	20.00 ± 0.02^{b}
Group D	200	8.90 ± 2.32^{a}	81.72^{c}	28.20 ± 0.04^{c}
Group E	200	0.00	0.00	30.00 ± 0.00^{c}
Group F	0	48.70 ± 0.38^{c}	0.00	12.30 ± 0.22^{a}
Group G	0	0.00	0.00	30.00 ± 0.00^{c}

Superscripts a, b and c denote statistically significant differences (p-value<0.05)

Table 4 Effect of *V. amygdalina* stem-bark ethanolic extract on % parasitemia and suppression in curative test

Group	Doses (mg/kg)	% Parasitemia	% Suppression	MST
Group A	200	22.90 ± 0.37^{b}	52.78^{a}	14.80 ± 0.12^{b}
Group B	400	21.00 ± 0.33^{b}	56.70^{a}	18.64 ± 0.24^{bc}
Group C	600	19.10 ± 0.59^{b}	60.62^{ab}	19.74 ± 0.29^{c}
Group D	200	8.50 ± 2.18^{a}	82.47^{c}	27.90 ± 0.01^{d}
Group E	200	0.00	0.00	28.28 ± 0.00^{d}
Group F	0	48.50 ± 0.40^{d}	0.00	10.00 ± 0.34^{a}
Group G	0	0.00	0.00	30.00 ± 0.00^{d}

Superscripts a, b, c and d denote statistically significant differences (p-value<0.05)

V. amygdalina. Alkaloids, terpenoids, and phenols, which were prominently detected, are well-documented for their anti-plasmodial activity, with mechanisms such as inhibiting haem polymerization, a critical process for parasite survival[14-16].

Alkaloids, flavonoids, terpenoids, and steroids are plant secondary metabolites known for their antiplasmodial activities through various mechanisms. Alkaloids achieve cure rates exceeding 98% in humans by inhibiting heme polymerization, disrupting the parasite's detoxification processes[17]. Flavonoids exert antiplasmodial effects by inhibiting the fatty acid biosynthesis (FAS II) pathway within the parasite's apicoplast, a pathway absent in human hosts[17]. Terpenoids, particularly sesquiterpenoids like artemisinin, contain an endoperoxide bridge that, upon cleavage, generates toxic free radicals detrimental to the malaria parasite[17]. Steroids have demonstrated potent activity against both 3D7 and W2 strains of *Plasmodium falciparum*, with IC_{50} values ranging from 11.2 to 22.0 μM[17]. The use of ethanol as a solvent in this study is in line with the suggestion from another study, which reported that organic solvents are more effective in extracting a broader spectrum of bioactive compounds compared to aqueous solvents[18,20].

The anti-malarial activity observed in the curative tests demonstrated significant parasitemia suppression, with levels exceeding 30% within 4 days (Table 3, 4). These results are consistent with other studies that reported similar efficacy in parasitemia suppression[14]. Additionally, it is reported that ethanol extracts exhibited superior activity compared to aqueous extracts, reinforcing the importance of using ethanol for the enhanced extraction of secondary metabolites. These secondary metabolites, such as flavonoids and alkaloids, play critical roles in parasite inhibition. For example, flavonoids are known to disrupt the influx of L-glutamine and myoinositol into infected erythrocytes, thereby limiting parasite growth[19]. Terpenoids and alkaloids inhibit haem polymerization by binding to haemin, leading to toxic unpolymerized haem accumulation within the parasite[13].

The prophylactic efficacy of *V. amygdalina* ethanolic extracts was also demonstrated, with parasitemia suppression exceeding 30% during the four-day prophylactic test (Table 5). This aligns with findings from other researchers who reported significant prophylactic effects of aqueous extracts of *V. amygdalina* against *Plasmodium berghei*[21,22]. Additionally, the significant prophylactic activity observed at doses of 600 mg/kg supports the related studies, which reported high prophylactic activity of similar plant extracts[23]. The role of phytochemicals in this activity is evident, as alkaloids, saponins, flavonoids, and phenols have all been implicated in enhancing immune defenses and directly inhibiting parasite growth[24].

Table 5 Effect of *V. amygdalina* (leaf and stem-bark) ethanolic extracts on % parasitemia suppression and MST in prophylactic test groups

Group	Doses (mg/kg)	% Parasitemia	% Suppression	MST
Group A	200	19.60 ± 0.27^{b}	59.16^{a}	18.00 ± 0.17^{b}
Group B	200	20.60 ± 0.73^{b}	57.08^{a}	17.68 ± 0.10^{b}
Group C	200	2.80 ± 2.43^{a}	91.67^{c}	29.40 ± 0.01^{c}
Group D	0	48.00 ± 0.44^{c}	0.00	11.74 ± 0.50^{a}

Superscripts a, b and c denote statistically significant differences (p-value<0.05).

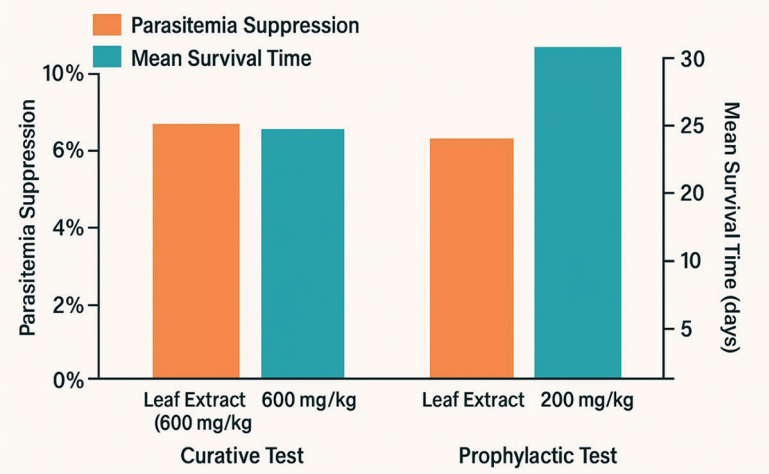

Figure 1 Graphical abstract showing the summarized key findings

The graphical summary of the key findings of the study (Figure 1) revealed the curative and prophylactic efficacy.

Comparatively, the parasitemia suppression and prophylactic activity observed in this study are in agreement with other studies emphasizing the anti-malarial potential of plant-derived compounds[25]. Also, another researcher highlighted the relevance of natural products in modern drug discovery, with over 50% of clinical drugs originating from plants[26]. Furthermore, the significant activity observed with ethanol extracts in this study is consistent with reports by a related study, which noted that the superior efficacy of ethanol in solubilizing both polar and non-polar bioactive compounds makes it suitable[18].

The physical improvement observed in infected mice treated with *V. amygdalina* extracts further validates the therapeutic potential of this plant. These findings agree with those of a related study that reported enhanced physical activity in treated rodent models, attributing it to the parasitemia suppression effect[14,25,26]. The combined action of phytochemicals such as alkaloids, flavonoids, and terpenoids not only targets the parasite but may also bolster the host's immune response, as reported in another study[24]. The efficacy of *V. amygdalina* in reducing parasitemia and preventing malaria shows its value as a potential source for developing novel anti-malarial agents.

In addressing artemisinin resistance, *Vernonia amygdalina* extracts may exert their antiplasmodial effects through molecular mechanisms distinct from those targeted by artemisinin. While artemisinin acts via the production of reactive oxygen species and alkylation of parasite proteins, these mechanisms are compromised due to mutations in the *kelch13* (K13) gene and an increased unfolded protein response in resistant *P. falciparum* strains[27,28]. *V. amygdalina* constituents, such as sesquiterpene lactones and flavonoids, are believed to target alternative metabolic and signaling pathways. For example, some flavonoids have been shown to inhibit plasmodial dihydrofolate reductase (DHFR) and mitochondrial electron transport, thereby disrupting folate metabolism and energy production in the parasite[29,30]. Furthermore, alkaloids and terpenoids present in *V. amygdalina* may impair parasite detoxification systems or interfere with heme polymerization, independent of artemisinin's peroxide bridge mechanism[31,32]. These multi-targeted actions could potentially suppress resistant strains that rely on specific survival adaptations to artemisinin,

thereby restoring or enhancing treatment efficacy. In this way, *V. amygdalina* may serve not only as a parasite clearance enhancer but also as a resistance-breaking adjunct by leveraging alternative molecular targets.

Conclusion

Based on the presented results, ethanolic extracts of *V. amygdalina* exhibited robust phytochemical richness and meaningful antimalarial activity, with leaves containing higher levels of alkaloids, saponins, and terpenoids and uniquely harboring flavonoids, while stem-bark was richer in tannins; both parts produced dose-dependent parasitemia suppression in curative assays (peaking around 60–61% at 600 mg/kg) and moderate prophylactic efficacy (~57–59% suppression), improving survival but remaining significantly less effective than the standard drug across models, and with no significant differences observed among plant doses within treatment or prophylaxis collectively supporting *V. amygdalina*, particularly the leaf fraction, as a biologically active antimalarial candidate that warrants further optimization (standardization, fractionation, and dosing studies) to approach the efficacy benchmarks of established therapies.

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