



In vitro antiplasmodial activity, acute toxicity and phytochemical quantification of selected medicinal plants used for the management of uncomplicated malaria in eastern Uganda

Samuel Baker Obakiro ^{a b}  , Catherine Nabitandikwa ^{a b}, Kenedy Kiyimba ^{a b}, Moses Ocan ^c, Yahaya Gavamukulya ^{a d}, Moses Andima ^{a e}, Tonny Wotoyitide Lukwago ^{a b}, Richard Maseruka ^{a b}, Mercy Chebijira ^{a e}, Moses Opio ^{a b}, Joseph Francis Hokello ^{a f}, Dan Kibuule ^{a b}, Alice Nabatanzi ^g, Stephen Orena ^h, Paul Waako ^{a b}, Richard Oriko Owor ^{a e}

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Abstract

Ethnopharmacological relevance

The emergence of artemisinin resistance and limited antimalarial drug access in Uganda has increased reliance on herbal medicines as complementary and alternative therapies. Indigenous use of *Albizia coriaria*, *Zanthoxylum chalybeum*, *Entada abyssinica*, *Maytenus senegalensis*, and *Kigelia Africana* for malaria treatment is widespread but scientific evidence of their efficacy and safety was limited.

Aim of the study

This study aimed to validate the traditional antimalarial use of the five medicinal plants by evaluating their phytochemical composition, acute toxicity, and *in vitro* antiplasmodial activity against chloroquine-sensitive (3D7), chloroquine-resistant (Dd2) and clinical *P. falciparum* isolates.

Materials and methods

Phytochemical screening and quantification was conducted on 70% hydroethanolic extracts from dried plant samples using UV–Vis spectrophotometry. The acute oral toxicity testing was conducted in Wistar albino rats using OECD 423 limit dose test. The antiplasmodial efficacy was evaluated

using a 72-h SYBR Green assay on *Plasmodium falciparum* laboratory strains (3D7, Dd2) and clinical isolates.

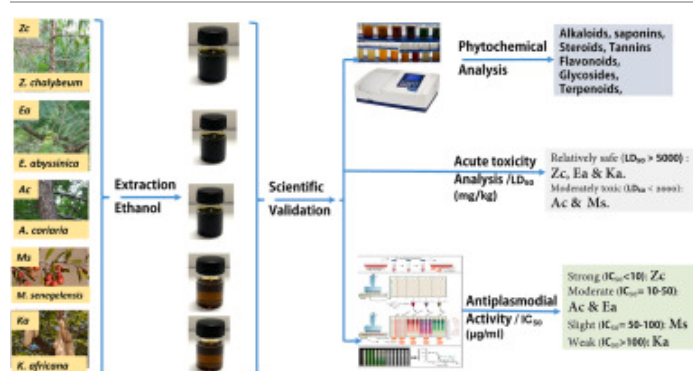
Results

Alkaloids, flavonoids, tannins, and terpenoids were present in all the plant samples in varying quantities. *Z. chalybeum* was the most potent extract (IC_{50} 0.81–1.28 $\mu\text{g/ml}$), followed by *A. coriaria* and *E. abyssinica* (IC_{50} 10–50 $\mu\text{g/ml}$). *M. senegalensis* showed weak activity while *K. africana* was largely inactive ($IC_{50} > 100 \mu\text{g/ml}$). *A. coriaria* and *M. senegalensis* showed moderate acute toxicity ($LD_{50} < 2000 \text{ mg/kg}$), while the other extracts showed no severe signs of acute toxicity in Wistar albino rats ($LD_{50} > 2000 \text{ mg/kg}$).

Conclusion

Zanthoxylum chalybeum, *Albizia coriaria* and *Entada abyssinica* demonstrated promising antiparasitic activity that supports their traditional use in management of malaria. However, more efficacy studies using *in vivo* models, sub-chronic and chronic toxicity studies particularly on *A. coriaria* and advanced phytochemical profiling are needed to delineate their therapeutic potential before being prioritized for development of standardized herbal remedies and novel antimalarial drugs.

Graphical abstract



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Introduction

Malaria is a treatable and curable infectious disease which remains a public health concern to most health care systems especially in Sub-Saharan Africa (SSA) which bears over 90% of the disease burden (Oladipo et al., 2022). In 2022, there were 249 million malaria cases and 608,000 deaths (90% mortality from Africa) out of which more than half were from SSA. With the COVID-19 pushing the health systems to focus on the pandemic, there was a 2% increase in malaria cases in 2022. Of the four SSA nations that accounted for more than half of all malaria cases worldwide in 2022, Uganda (5%) was rated third by the World Health Organization (WHO, 2023). The endemicity

of malaria in Uganda varies with geographical region, with eastern and northern Uganda being hotspot areas (Ocen et al., 2023). Several strategies have been employed to combat the high burden of malaria in Uganda including vector control and chemoprevention. Additionally, a 4-dose malaria vaccine for new born children given at 6, 7, 8, and 18 months was rolled out in the Country. While these strategies have shown an improvement in the reduction of malaria cases, the resistance of the mosquitoes to insecticides, emergence and spread of drug resistant *P. falciparum* parasites have undermined the realization of a malaria free Uganda by 2020 (WHO, 2023). This highlights the urgent need for novel antimalarial agents against both sensitive and resistant *P. falciparum* (Chen, 2014; Clement et al., 2020; Irungu et al., 2023). The historical success of plant derived antimalarials such as quinine (Cinchona bark) and artemisinin derivatives (*Artemisia annua*), establishes medicinal plants as reservoirs of novel antimalarial molecules.

The indigenous use of herbal remedies in the management of malaria continues to gain momentum in Uganda due to their availability, affordability, perceived efficacy and safety (Gumisiriza et al., 2023; Tabuti et al., 2023; Tugume et al., 2016). In Tororo district, 76% of the study respondents reported to use herbal medicine as the first line option to treat malaria (Tabuti et al., 2023). Among the widely used plants by traditional medicine practitioners (TMPs) are *Z. chalybeum* (stem bark and rook bark), *A. coriaria* (stem bark), *E. abyssinica* (stem bark), *M. senegalensis* (leaves), and *K. Africana* (fruit). These species are typically prepared as monoherbal or polyherbal decoctions and orally administered usually 200–500mL three times daily for three to five days depending on the severity of malaria, age and weight of the patient with contraindication in pregnant women particularly in the second and third trimester (Angupale et al., 2023; Clement et al., 2020; Tabuti et al., 2023). The number of TMPs who reported using these plants were; *M. senegalensis* (30), *Z. chalybeum* (9), *A. coriaria* (2), *E. abyssinica* (not reported) and *K. Africana* (not reported) (Nabatanzi et al., 2020; Philip et al., 2017; Tabuti, 2008; Tabuti et al., 2023).

In our previous ethnobotanical study on medicinal plants for management of diabetes mellitus, these five plants were frequently mentioned as malaria remedies (Obakiro et al., 2023), indicating their broad therapeutic relevance. These herbal medicines, prepared as needed and usually stored for not more than two weeks and regarded generally safe though minor side effects such as bitter taste, nausea, vomiting and abdominal discomfort have been reported (Angupale et al., 2023). Beyond Eastern Uganda, their use for malaria has been documented in central Uganda, Western Uganda and Western Kenya (Angupale et al., 2023; Gumisiriza et al., 2023; Owuor et al., 2012). In addition to malaria, these plants are traditionally used in the management of HIV/AIDS (Owor et al., 2024), inflammatory diseases (Schultz et al., 2020), diabetes mellitus (Obakiro et al., 2023), and tuberculosis (Bunalema et al., 2014). Of particular concern is *Z. chalybeum*, a rare and increasingly threatened species in eastern Uganda, due to overharvesting, as a result of its versatile medicinal properties and thus needs urgent conservation strategies.

The World Health Organization recommends that all traditional and complementary medicines should undergo rigorous scientific validation to ensure their efficacy and safety before integration into modern health care systems (WHO, 2019). Despite the widespread use of herbal remedies in the management of malaria in Uganda, there is a paucity of scientific data regarding the comparative antiparasmodial efficacy, safety profiles, and phytochemical composition of several medicinal plants and the products themselves (Angupale et al., 2023). Although *Z. chalybeum* (Adia

et al., 2016; Bbosa et al., 2014; Correa-Barbosa et al., 2023; Muthaura et al., 2015a) and *A. coriaria* (Karupppannan et al., 2013; Omara et al., 2023; Schultz et al., 2021) have previously reported antiplasmodial activity, these studies used different parasite strains and/or solvents of extraction from different geographical regions, lacked comparative analysis across multiple plasmodium strains (especially clinical isolates) and often did not include phytochemical quantification. This creates a critical gap in understanding the comparative efficacy and safety of these species under standardized laboratory conditions. This study aimed to address these gaps through a simultaneous comparative evaluation of five medicinal plant species traditionally used for malaria treatment in Eastern Uganda. The study assessed the *in vitro* antiplasmodial activity against chloroquine-sensitive (3D7), chloroquine-resistant (Dd2), and clinical field isolates of *P. falciparum*. Thereafter performed acute toxicity testing in animal models (Wistar rats) and conducted quantitative phytochemical analysis using UV spectrophotometry thereby providing novel insights into their relative efficacy, safety and bioactive phytochemical profiles. The present study advances the scientific validation of traditional knowledge and contributes novel insights into the therapeutic potential and safety of key medicinal plants used in malaria management in East Africa.

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Section snippets

Plant sample collection and identification

The medicinal plants investigated were selected based on their widespread use in management of malaria in Eastern Uganda, a malaria-endemic region and their high frequency of citation as first line remedies for malaria in several ethnobotanical surveys conducted in eastern Uganda (Malinga et al., 2020; Tabuti, 2008; Tabuti et al., 2023). These plants are; *Albizia coriaria* Oliv. (Fabaceae) *Zanthoxylum chalybeum* Engl. (Rutaceae), *Entada abyssinica* DC. (Fabaceae), *Maytenus senegalensis* (Lam.) ...

Phytochemical screening

All the tested phytochemicals were present in the extracts except for emodols and anthracenosides which were absent in *E. abyssinica* and *K. Africana* (Table 1). The most abundant phytochemicals in the extracts were alkaloids, flavonoids, saponins, tannins, terpenoids, steroids and glycosides. *Albizia coriaria* Oliv. (Fabaceae) *Zanthoxylum chalybeum* Engl. (Rutaceae), *Entada abyssinica* DC. (Fabaceae), *Maytenus senegalensis* (Lam.) Exell (Celastraceae) and *Kigelia Africana* (Lam.) Benth (Bignoniaceae) ...

Quantification of phytochemicals from the different samples

...

Discussion

Phytochemical screening revealed the presence of key classes of secondary metabolites including alkaloids, flavonoids, tannins, terpenoids, saponins, glycosides, and steroids. These compounds are known to possess various biological activities, especially antiplasmodial effects. Quantitative analysis revealed that *A. coriaria* had the highest levels of flavonoids and steroids, *E. abyssinica* had the highest tannins, and *K. africana* was rich in triterpenoids. Conversely, *Z. chalybeum* had limited

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Limitations and future perspectives

Treatment of uncomplicated malaria in Uganda often employs polyherbal preparations, a complexity not captured in this study's mono herbal experimental design which did not account for potential pharmacodynamic synergistic, additive and antagonistic effects that may occur in complex herbal formulations. Therefore future research should systematically investigate the pharmacodynamic interactions both synergistic and antagonistic among these species to scientifically validate and optimize ...

Conclusion

The hydroethanolic extract of *Z. chalybeum* (root bark), exhibited promising *in vitro* antiplasmodial activity and a favourable acute toxicity profile supporting its traditional use and identifying it as a prime candidate for further investigation. However, to translate these findings into a potential therapeutic agent, bioassay guided fractionation, analytical techniques and advanced metabolite profiling using LC-MS/MS are needed to isolate and characterize the bioactive principles in these ...

CRedit authorship contribution statement

Samuel Baker Obakiro: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Catherine Nabitandikwa:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Kenedy Kiyimba:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Moses Ocan:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Yahaya** ...

Ethics approval

The study protocol was reviewed and approved by Cure Children's Hospital Uganda Research and Ethics Committee (CCHUREC/11/020) and registered with the Uganda National Council of Science and Technology (HS1222ES). ...

Consent for publication

Not applicable. ...

Availability of data and materials

The raw data supporting the findings of this study can be obtained from the corresponding author upon request. ...

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Declaration of competing interest

The authors confirm that there is no conflict of interest related the publication of this paper. ...

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