BMJ Open

Efficacy of antimalarial herbal medicines used by communities in malaria affected regions globally: a protocol for systematic review and evidence and gap map

Moses Ocan ,[1,2] Nakalembe Loyce,[2,3] Kevin Ouma Ojiambo ,[2,4] Alison Annet Kinengyere,[2,5] Robert Apunyo,[2] Ekwaro A Obuku [2,6]

To cite: Ocan M, Loyce N, Ojiambo KO, *et al*. Efficacy of antimalarial herbal medicines used by communities in malaria affected regions globally: a protocol for systematic review and evidence and gap map. *BMJ Open* 2023;**13**:e069771. doi:10.1136/bmjopen-2022-069771

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069771).

Received 03 November 2022
Accepted 21 June 2023

For numbered affiliations see end of article.

Correspondence to
Dr Moses Ocan;
ocanmoses@gmail.com

ABSTRACT

Introduction With the rising resistance to artemisinin-based combination treatments, there is a need to hasten the discovery and development of newer antimalarial agents. Herbal medicines are key for the development of novel drugs. Currently, herbal medicine usage in communities for treatment of malaria symptoms is common as an alternative to conventional (modern) antimalarial agents. However, the efficacy and safety of most of the herbal medicines has not yet been established. Therefore, this systematic review and evidence gap map (EGM) is intended to collate and map the available evidence, identify the gaps and synthesise the efficacy of herbal antimalarial medicines used in malaria affected regions globally.

Methods and analysis The systematic review and EGM will be done following PRISMA and Campbell Collaboration guidelines respectively. This protocol has been registered in PROSPERO. Data sources will include PubMed, MEDLINE Ovid, EMBASE, Web of Science, Google Scholar and grey literature search. Data extraction will be done in duplicate using a data extraction tool tailored in Microsoft Office excel for herbal antimalarials discovery research questions following the PICOST framework. The Risk of Bias and overall quality of evidence will be assessed using Cochrane risk of bias tool (clinical trials), QUIN tool (in vitro studies), Newcastle-Ottawa tool (observational studies) and SYRCLE's risk of bias tool for animal studies (in vivo studies). Data analysis will be done using both structured narrative and quantitative synthesis. The primary review outcomes will be clinically important efficacy and adverse drug reactions. Laboratory parameters will include Inhibitory Concentration killing 50% of parasites, $IC_{50;}$ Ring Stage Assay, $RSA_{0–3\ hou;}$ Trophozoite Survival Assay, $TSA_{50.}$

Ethics and dissemination The review protocol was approved by the School of Biomedical Science Research Ethics Committee, Makerere University College of Health Sciences (SBS-2022-213).

PROSPERO registration number CRD42022367073.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The review will provide an evidence gap map on use of herbal antimalarial agents for malaria management in communities affected by malaria globally.
⇒ The review will provide an update on efficacy of herbal products against malaria parasites.
⇒ The study will combine both evidence synthesis and evidence gap map on herbal antimalarial products in malaria affected regions.
⇒ The review will focus only on herbal medicines whose efficacy has been compared against artemisinin agents as these are the current cornerstone in malaria treatment.
⇒ The review will focus on herbal antimalarial medicines in malaria affected regions only.

INTRODUCTION

Malaria remains a global public health problem affecting nearly half of the world's population. In the year 2020, global estimates indicated 241 million malaria cases and 627 000 malaria deaths.[1] Malaria was still deadly in 2021 as the 6th most important cause of death in Africa ahead of COVID-19 that was the 7th, up from the 22nd in 2020 driven by the delta variant. Sub-Saharan Africa carries the greatest burden, accounting for about 95% of all malaria cases and 96% of all deaths in 2020.[1]

Chemotherapy with effective antimalarial medicines remains the most predominant intervention for effective management of malaria globally.[2] Artemisinin-based combination treatments (ACTs) are the main stay and frontline treatments for uncomplicated *Plasmodium falciparum* malaria.[3] However, malaria treatment faces a number of challenges globally including; drug resistance, poor quality medicines, inaccessibility, unavailability and high cost.[4] Resistance to ACTs was originally reported in areas of the Greater Mekong Subregion such as Thailand and Cambodia.[5] Currently, artemisinin resistance

has also independently arisen in East Africa (Rwanda and Uganda).[5] This is a major threat for the global initiative on elimination and eradication of malaria[6] justifying concerted efforts to hasten the discovery and development of newer antimalarial molecules.

Traditional medicines (herbs) remain a corner stone for the discovery of novel drugs with more desirable medicinal and pharmacological properties.[7 8] Use of traditional medicine for treatment of malaria symptoms has previously been achieved with *Quinghao* isolated from a Chinese herbal medicine, *Artemisia annua* and quinine isolated from *Cinchona* species (Rubiaceae).[9 10] In various malaria affected regions globally, plants are traditionally used to alleviate symptoms of malaria such as fevers and treat malaria. This is due to inherited cultural practices and belief in traditional medicine, accessibility and relatively lower costs compared with the modern medicines, largely unknown and underappreciated toxicities and perceived efficacy.[11]

Why this review?

Communities have now resorted to use of natural plant products (herbs) that are assumed or claimed to have antimalarial efficacy. With the prevailing challenges facing the use of ACTs, use of herbal products and development of alternative conventional antimalarial medicines is key for malaria control and eradication efforts globally. However, the antimalarial efficacy of most herbal agents used by communities in malaria affected regions remains unknown. The continued use of herbal agents with unproven efficacy is potentially harmful to the population as it can lead to unwanted outcomes such as delay in getting effective treatment, morbidity and mortality. There is thus need, to establish the comparative antimalarial efficacy of herbal medicines and artemisinin agents used in malaria affected regions globally. This will help guide the current efforts to develop alternative antimalarial agents globally.

Several reviews have been conducted documenting information on different plants used for their antimalarial activities.[11–13] However, these reviews focused on studies that investigated in vitro and in vivo activities of these herbs without comparing their efficacies with the already existing modern antimalarial medicines. Our current review seeks to collate and map evidence comparing the antimalarial efficacy of herbal medicines with that of artemisinin agents in malaria affected regions globally.

How the intervention might work

Early detection and treatment remain the principal strategies for control of malaria globally. Treatment of malaria currently involves the use of ACT as recommended by WHO globally. However, this strategy is affected by the rising levels of resistance to artemisinin and the partner drugs and the relatively high cost. Artemisinin agents are the current cornerstone in treatment of malaria globally, however, they are faced with the threat of resistance development. Herbal medicines with antiplasmodial activity are used by communities in treatment of malaria in malaria affected regions globally. They are, therefore, used as alternatives to artemisinin agents in malaria affected regions globally especially in areas with reported partial resistance to artemisinin agents. Efficacious herbal medicines could potentially provide activity against both sensitive and slow artemisinin clearing parasites. Herbal antimalarial products may also help improve access to malaria treatment due to the cheaper cost, and convenient dosing. Thus, potentially contributing to the antimalarial drug development pipeline to help provide alternative to the current artemisinin agents.

METHODS

This will be a multimodal blended systematic review and evidence gap map (EGM). The EGM and systematic review will be done following the Campbell Collaboration[14] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, respectively.[15] There will be no language restriction.

This protocol was registered in PROPSERO (https://www.crd.york.ac.uk/prospero/) registration number CRD42022367073.[16]

Intervention-outcome framework for the EGM

The intervention domains will include medicinal plants and plant extracts. There will be two outcome domains clinical (symptom resolution; fever, body aches/fatigue, malaise, joint pains, nausea/vomiting, loss of appetite, adequate clinical and parasitological response) and laboratory (Inhibitory Concentration, $IC_{50;}$ Ring Stage Assay, $RSA_{0–3\ hours;}$ Trophozoite Survival Assay, $TSA_{50;}$ parasite clearance rate) (table 1).

Review question

What is the clinical, in vitro and in vivo efficacy of antimalarial herbal medicines used by communities in malaria affected regions globally?

Outcomes

Primary outcomes

- Clinical: *P. falciparum* parasite clearance (adequate clinical and parasitological response), symptom resolution (fever, nausea/vomiting, joint pains, fatigue/malaise, loss of appetite).
- In vitro studies: IC_{50}, $RSA_{0–3\ hours}$, TSA_{50}.
- In vivo (animal) studies: parasite suppression rate, Plasmodium *spp* clearance.

Secondary outcome

- Safety of antimalarial herbal medicines; in vivo studies (LD50, organ toxicity, teratogenicity, carcinogenicity, mutagenicity); clinical studies (reported side effects/adverse drug reactions).

Table 1 Intervention-outcome domains for the evidence gap map

Intervention domains	Indicators	Description
► Medicinal plants	► Kind/type of plant (shrub, herb, tree)	► The type of plant, including geographical location
	► Parts of the plant used (leaves, back, roots, shoots)	► Plant material used, either entire plant or its parts (single or combined)
	► Name of the plant species	► Include both genus and species names
	► Age of the plant/part	► Either young or mature/old plant/or parts
► Plant extract	► Water extract	► Extraction time, extraction temperature, granulometry of the plant, proportion of plant and solvent used
	► Methanol extract	► Extraction time, extraction temperature, granulometry of the plant, proportion of plant and solvent used
	► Ether extract	► Extraction time, extraction temperature, granulometry of the plant, proportion of plant and solvent used
	► Chloroform extract	► Extraction time, extraction temperature, granulometry of the plant, proportion of plant and solvent used
	► Ethanolic extract	► Extraction time, extraction temperature, granulometry of the plant, proportion of plant and solvent used
	► Crude extract	► Proportions of the different extracts in the mixture
Outcomes domains	Indicators	Description
► Clinical outcomes	► Fever	► Relief from fever
	► Body aches/malaise	► Relief from body aches
	► Joint pains	► Relief from joint pains
	► Nausea/vomiting	► Relief from vomiting
	► Appetite	► Gaining of appetite
	► Adequate clinical and parasitological response[32]	► Resolution of clinical symptoms of malaria and plasmodium parasite clearance
► Laboratory outcomes	► IC_{50},	► Inhibitory concentration killing 50% of parasites
	► $RSA_{0–3\ hours}$	► Concentration killing early-stage parasites (0–3 hours)
	► TSA_{50}	► Concentration killing 50% of trophozoites

IC50: Inhibitory Concentration; RSA0-3hours: RingStageSurvivalAssay;TSA50:TrophozzoiteSurvivalAssay

Eligibility criteria

Inclusion criteria

- Peer-reviewed articles reporting clinical efficacy of herbal medicines in malaria treatment among children and adults in malaria affected regions globally.
- Peer-reviewed articles reporting on herbal medicinal plants used by communities for management of symptoms of malaria in malaria affected regions globally.
- Peer-reviewed articles reporting on the safety of herbal medicines used by communities in management of malaria symptoms.
- Peer-reviewed articles reporting on in vitro efficacy of antimalarial herbal medicines.
- Peer-reviewed articles reporting on in vivo efficacy of antimalarial herbal medicines.
- Peer-reviewed articles published from the years 2000 to date.
- Articles published in both English and non-English language.

Exclusion criteria

- Peer-reviewed articles whose full text cannot be retrieved. Efforts will be made to retrieve all included full text articles before prior to being excluded. The librarian (AAK) will use external sources like Web of Science, EMBASE, Sci-Hub, Lib-Hub and PDF Drive. In addition, AAK will contact other librarians for retrieval of full text articles. However, full-text articles which will still not be able to be accessed despite these efforts will be excluded from the review.
- Peer-reviewed articles from studies that did not receive ethical review and approval.

Identification of articles

Data sources

Article search will be performed by an experienced librarian (AAK) in PubMed, MEDLINE Ovid, EMBASE and Web of Science, and other grey literature sources. Medical subject headings terms and Boolean operators 'AND' and 'OR' will be used during article search. The

data sources will include scholarly databases, grey literature sources, contacting authors as well as screening reference sources of included studies. we shall search grey literature from organisation websites such as WHO, Medicines for malaria venture, institutional repositories and contact experts/researchers in malaria field. We will also search Google Scholar for additional studies that may be missed from the other sources. The search will be limited to 2000–2022.

We will also screen through reference lists of included studies for additional eligible studies that may not be identified by the search.

Search strategy

Full article search has not been done yet, however, scoping literature search was completed on 17 November 2022. The search terms below will be used in full article search to identify eligible articles, based on PICOST. Terms relating to the same element of PICOST will be combined using Boolean operator 'OR', while the different concepts/PICO categories will be combined using 'AND'.

Population

Laboratory

Plasmodium falciparum, Plasmodium species, wild-type plasmodium parasites, field plasmodium parasites, laboratory animals (Wister albino rats, Mice).

Clinical

Children, infants, adults.

Disease/condition

Malaria, fever, malaria fever, malaria symptomatic patients, *P. falciparum* infection, Plasmodium infection.

Intervention

Herbal medicine* OR herbal remed* OR medicinal plant* OR herbal formulation* OR plant medicine* OR herbal product* OR plant extract* OR medicinal herb* OR ethnomedicine* OR traditional herbal medicine OR alternative medicine OR ethnobotany OR phytomedicine OR shrub OR herb OR shoot OR leaves OR roots OR herbal extract.

Comparator

Clinical

Artemisinin based antimalarial agents.

Laboratory

Dihydroartemisinin, lumefantrine, piperaquine, amodiaquine, pyronaridine, chloroquine, quinine.

Outcome

Clinical

Fever, nausea, vomiting, joint pains, malaise, loss of appetite, symptom resolution, symptom clearance, adequate clinical and parasitological response.

Laboratory

IC_{50}, $RSA_{0–3\ hours}$, TSA_{50}, malaria parasite clearance, Plasmodium *spp* parasite clearance, *P. falciparum* clearance, malaria parasite suppression rate.

Setting

Globally.

Time

2000–2022, in line with the introduction of artemisinin in malaria treatment.

Evidence gap map

This will be a secondary product in addition to the systematic review. Our approach to the EGM will be informed by the Campbell Collaboration approach.[17] An EGM highlights where the evidence is and where more evidence is needed in terms of interventions and outcomes contained in the studies identified for this systematic review. They consolidate what is known and what is not known by mapping out existing and ongoing studies and providing a graphical representation of areas with strong, weak, or no evidence on the effect of interventions.

Briefly, we will apply the data already identified, screened and coded from this systematic review to develop the EGM. Using the EPPI mapper adds-on for EPPIR Web software for conducting systematic reviews we will produce an EGM in visual presentation of the evidence matrix. The intervention categories lie on the y-axis while outcome domains will run in the x-axis. Additional dimensions of the study or intervention characteristics, such as study design, geographical region and country income subgroup status or population subgroup, will be applied as filters.

Data management, screening and selection

For the initial management of references from search results, EndNote software will be used. The articles will be exported to EndNote V.20 and duplicates will be removed. The articles will then be screened in duplicate using predetermined eligibility criteria. The screening will be performed independently by the review team pair (KOO and NL) in EPPI-Reviewer V.4.13.0.0, using a screening tool developed a priori and piloted using 10% of the search yield, any disagreements between the reviewers will be resolved by consensus, and any further disagreements will be referred to the tie breaker (MO).

Data abstraction and coding

The data abstraction tool will be created and piloted using 10% of the eligible studies to ensure it captures all relevant data from included studies and the uploaded on EPPI-Reviewer V.4.13.0.0. The coding process will be carried out independently by two research team members (KOO and NL), whose results will be reconciled and disagreements resolved through discussion, and their results will later be validated for quality control and assurance by an independent senior reviewer (MO) to ensure completeness and correctness.

Table 2 PICOST model for the review question

Element of PICO	Description
Population (P)	Clinical: Malaria patients (children and adults) In vitro studies: Malaria parasites, *Plasmodium spp (eg, Plasmodium falciparum*). Wild or field strain parasites In vivo (animal) studies: Malaria parasites, *Plasmodium spp (eg, Plasmodium berghei*)
Intervention/ exposure	Clinical: Use of herbal medicines for management of symptoms of malaria among children and adult patients In vitro studies: Plant extracts used against *Plasmodium* parasites In vivo studies: Plant extracts used against *Plasmodium* parasite infections of laboratory animals
Comparator	► In vitro studies: None ► In vivo (animal) studies: Artemisinin antimalarial agents ► Clinical studies: Artemisinin-based antimalarial agents ► For in vitro studies, will use historical data of the IC50 values for Artemisinin agents to compare with the IC50 values obtained from herbal antiplasmodial assays
Outcomes	Prevalence of use of herbal medicines in treatment of malaria symptoms Clinical: symptom resolution (fever, nausea/vomiting, joint pains, fatigue/ malaise, loss of appetite), Adequate clinical and parasitological response Laboratory: IC_{50}, $RSA_{0-3\ hours}$, TSA_{50}, parasite suppression rate, Plasmodium *spp* clearance, *Plasmodium falciparum* clearance
Setting	Malaria affected countries globally (tropical countries) Designs: Cross-sectional studies, randomised controlled trials
Time	2000 to date (Introduction of Artemisinin in malaria treatment outside China)

Data items

The following categories of data will be abstracted, administrative information (author, year of publication, year of data collection, citation, country/region, funding source), methods (study design, population, sample size, laboratory procedures) and results (malaria symptom resolution, IC_{50}, $RSA_{0-3\ hours}$, TSA_{50}, malaria parasite suppression rate) as illustrated in the PICOST (table 2).

Risk of bias assessment

Two members of the research team (NL and KOO) shall independently evaluate the methodological quality of included studies. The risk of bias in observational (non-randomised) studies will be assessed using a modified Newcastle-Ottawa Scale tool.[18] The tool includes seven domains scored from 0 (high risk of bias) to 3 (low risk of bias), the mean of domains shall be considered to result in a score between 0 and 3, where a higher score represents a lower risk of bias. Randomised controlled trials, the Cochrane risk of bias tool will be used to assess risk of bias (selection bias, attrition bias, performance bias, reporting bias, detection bias and other biases, eg, conflict of interest).[19] For in vitro studies, the risk of bias will be assessed using QUIN tool.[20] The tool has 12-item criteria which will be scored, and the scores used to grade the in vitro study as high (<50%), medium (50%–70%) or low (>70%) risk of bias. For in vivo studies, risk of bias will be assessed following SYRCLE's risk of bias tool for animal studies.[21] The following risk of bias will be assessed in the in vivo studies, selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting). The in vivo studies will be scored and assigned a judgement of low, high or unclear risk of bias. Consensus on any disagreement in the quality assessment will be reached through discussion and consensus between the two independent reviewers (NL and KOO). Any further disagreement will be resolved through a tiebreaker (MO). For the EGM, the AMSTAR-2 tool will only be used for assessing risk of bias of the included systematic review articles.[22]

Publication bias

The included articles will be assessed for publication bias using the asymmetry of the funnel plots and/or Egger's test as appropriate.[23] These are rank-based data augmentation techniques that have been shown to be accurate for assessing publication bias due to missing data/studies. We will create funnel plots and use the symmetry of the plots to detect the likelihood of publication bias among the articles included in the review. In the absence of missing studies, the scatter plot resembles a symmetrical inverted funnel with a wide base and a narrow top.[24] The presence of large 'holes' or asymmetry in the plot indicates publication bias but could also be explained by other factors such as study heterogeneity. The performance of Egger's tests has been extensively studied for binary outcomes, but not for continuous ones. In this study we shall use Egger's test for binary outcomes.[23] For continuous outcomes, we shall assess publication bias using a modified funnel plot and a test considering meta-regression residuals as outcome instead of mean difference and inverse sample size as the exploratory variable unlike standard error.[25]

Assessment of strength and confidence of cumulative evidence

The overall strength of evidence will be assessed using a modified GRADE approach in which we assigned certainty of evidence ratings for the above-mentioned outcome variables using an approach developed by the

GRADE Working Group[26] and this will be done in duplicate, with any disagreements resolved by consensus.

Heterogeneity

The I^2 statistic will be used to assess the level of statistical heterogeneity in the articles. The I squared statistic will show the percentage (%) of heterogeneity attributable to between-study variation.[27] Heterogeneity will be categorised as, low (I^2=25%) (low), moderate (I^2=50) and high (I^2>75%).[28] Subgroup analysis will be done among articles categorised as low and moderate heterogeneity.

Criteria for determination of independent findings

Dependence may occur at the study or intrastudy levels. At the study level, the most complete and latest report, where available, will be selected in case of multiple reports of a single study. However, if different reports discuss different subgroups or outcomes, the data from all these reports will be treated as a single case, using integrative approach.[29] At the intrastudy level, only a single effect from each study will be included in each meta-analysis. Where studies report multiple effects for different outcome types, these will be synthesised separately. Where studies report multiple dependent effects for a particular outcome type, we shall use 'synthetic effects' to generate a sample-weighted average prior to incorporation in meta-analysis.

Missing data

In case of missing data from the published articles, study authors will be contacted. When the author cannot be accessed or in case of no response from authors, we will report the characteristics of the study but will not include such a study in the meta-analysis. Where studies do not report group sample sizes to calculate the SE of the standardised mean difference (SMD), the following approximation will be used:

$$\mathrm{se(d)} = \sqrt{\frac{4}{N} + \frac{d^2}{2N}}$$

where se(d) is the SE of the SMD, d is the SMD and N is the total sample size.[30]

Data synthesis

SMDs from continuous outcome variables and ORs or prevalence ratios for dichotomous outcome variables will be synthesised separately. Effect sizes will be pooled statistically using inverse variance weighted random effects meta-analysis, using the metan command in Stata V.16. Pooled effects will be expressed in metric that is relevant, for example, a percentage change in odds, or a mean difference measured in natural units of outcome.

The synthesis will further be in form of summary of findings tables, simple graphs and forest plots as applicable using a STATA V.16. This will follow the format of the Cochrane consumers and communication review group.[31] We shall describe the included articles, group articles according to study design and type of intervention, organise and tabulate results to identify patterns and transform the results into a common descriptive format. These will be in form of outcome data tables, simple graphs and forest plots as applicable. These will feed into the summary of findings tables that inform the syntheses for sharing. We shall thus use both narrative and quantitative synthesis.

Sensitivity analysis

The sensitivity analysis will be done by removing studies from the meta- analysis one-by-one to see if the results of the meta-analysis are sensitive to any single study. We will also examine sensitivity of findings to risk of bias status (low risk, some concerns and high risk).

Ethics and dissemination

The review protocol was reviewed and approved by the School of Biomedical Science Research Ethics Committee, Makerere University College of Health Sciences (SBS-2022-213). The protocol was further cleared by Uganda National Council of Science and Technology, UNCST. Results will be disseminated through conference presentations and publication in peer-reviewed journal.

Patient and public involvement

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

The accessibility to quality and efficacious antimalarial medicines is fundamental towards successful malaria treatment. However, this may be compromised by the inaccessibility and high cost of these antimalarials in communities in addition to the rising rate of resistance. There is, therefore, need to accelerate research in discovery and development of novel efficacious and less toxic antimalarials.

Herbal extracts have proven to contain various phytochemicals which have pharmacological properties. Globally, researchers have carried out primary studies that have documented and provided knowledge on the antiplasmodial activities of numerous plants. This systematic review and EGM will, therefore, collate and map the available evidence, identify the gaps and synthesise the efficacy of herbal antimalarial medicines in malaria affected regions globally in comparison with the recommended artemisinin on market. This will help collate evidence on the most efficacious herbal extract that can be used to inform the antimalarial drug development process.

Author affiliations
[1]Pharmacology & Therapeutics, Makerere University College of Health Sciences, Kampala, Uganda
[2]Africa Centre for Systematic Reviews and Knowledge Translation, College of Health Sciences, Makerere University, Kampala, Uganda
[3]College of Health Sciences, Department of Pharmacology, Soroti University, Soroti, Uganda
[4]Clinical Epidemiology Unit, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

[5]Albert Cook Library, Makerere University College of Health Sciences, Kampala, Uganda
[6]Faculty of Epidemiology & Population Health, London School of Hygiene and Tropical Medicine, London, UK

Twitter Moses Ocan @MosesOcan, Kevin Ouma Ojiambo @Kevin_O_Ojiambo and Ekwaro A Obuku @ekwaroobuku

Contributors Conceptualisation of the study was done by (MO, NL and KOO). MO, NL and KOO drafted the protocol, critical review (MO, NL, KOO, AAK, RA and EAO) and approval of the final version (MO, NL, KOO, AAK, RA and EAO).

Funding The review is supported by funds from the Ministry of Science, Technology and Innovations grant number STI/SIVC/49/2022.

Disclaimer The funders do not have any role in the design, conduct, and interpretation of the findings of the study.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Moses Ocan http://orcid.org/0000-0002-8852-820X
Kevin Ouma Ojiambo http://orcid.org/0000-0003-4257-3926
Ekwaro A Obuku http://orcid.org/0000-0001-5311-2346

REFERENCES

1 World Health Organization. World malaria report: briefing kit regional data and trend. 2021. Available: https://cdn.who.int/media/docs/default-source/malaria/world-malaria-reports/world-malaria-report-2021-regional-briefing-kit-eng.pdf?sfvrsn=338167b6_25&download=true
2 Wang M, Cui Y, Zhou G, *et al*. Validation of ELISA for quantitation of artemisinin-based antimalarial drugs. *Am J Trop Med Hyg* 2013;89:1122–8.
3 World Health Organization. *WHO guidelines for malaria*. World Health Organization, 2021.
4 Guyant P, Corbel V, Guérin PJ, *et al*. Past and new challenges for malaria control and elimination: the role of operational research for innovation in designing interventions. *Malar J* 2015;14:279.
5 Zhu L, van der Pluijm RW, Kucharski M, *et al*. Artemisinin resistance in the malaria parasite, Plasmodium Falciparum, originates from its initial transcriptional response. *Commun Biol* 2022;5:274.
6 World Health Organization. World malaria report 2021. Geneva,
7 Czygan F-C. The role of medicinal plants as an important part in modern medicine. *Adv Hortic Sci* 1990:56–60. Available: https://www.jstor.org/stable/42881533
8 Ak M. A brief review of traditional plants as sources of pharmacological interests. *Open J Plant Sci* 2019;4:001–8.
9 Bickii J, Tchouya GRF, Tchouankeu JC, *et al*. Antimalarial activity in crude extracts of some Cameroonian medicinal plants. *Afr J Trad Compl Alt Med* 2007;4:107–11.
10 Weniger B, Lagnika L, Vonthron-Sénécheau C, *et al*. Evaluation of ethnobotanically selected Benin medicinal plants for their in vitro Antiplasmodial activity. *J Ethnopharmacol* 2004;90:279–84.
11 Tajbakhsh E, Kwenti TE, Kheyri P, *et al*. Antiplasmodial, antimalarial activities and toxicity of African medicinal plants: a systematic review of literature. *Malar J* 2021;20:349.
12 Lemma MT, Ahmed AM, Elhady MT, *et al*. Medicinal plants for in vitro antiplasmodial activities: a systematic review of literature. *Parasitol Int* 2017;66:713–20.
13 Kaur H, Mukhtar HM, Singh A, *et al*. Antiplasmodial medicinal plants: a literature review on efficacy, selectivity and phytochemistry of crude plant extracts. *J Biol Act Prod Nat* 2018;8:272–94.
14 White H, Albers B, Gaarder M, *et al*. Guidance for producing a Campbell evidence and gap map. *Campbell Syst Rev* 2020;16:e1125.
15 PRISMA-P Group, Moher D, Shamseer L, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4.
16 Page MJ, Moher D, Bossuyt PM, *et al*. PRISMA 2020 explanation and elaboration: updated guidance and Exemplars for reporting systematic reviews. *BMJ* 2021;372:160.
17 Saran A, White H. Evidence and gap maps: a comparison of different approaches. *Campbell Syst Rev* 2018;14:1–38.
18 Wells G. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis*. 2004.
19 HigginsJP, Altman Dg Fau - GøtzschePC, Gøtzsche Pc Fau - JüniP. *The Cochrane collaboration's tool for assessing risk of bias in randomised trials*. 2011: 1756–833.
20 Sheth VH, Shah NP, Jain R, *et al*. Development and validation of a risk-of-bias tool for assessing in vitro studies conducted in dentistry: the QUIN. *J Prosthet Dent* 2022.
21 Hooijmans CR, Rovers MM, de Vries RBM, *et al*. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol* 2014;14:43.
22 Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
23 Egger M, Smith GD, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
24 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
25 Doleman B, Freeman SC, Lund JN, *et al*. Funnel plots may show asymmetry in the absence of publication bias with continuous outcomes dependent on baseline risk: presentation of a new publication bias test. *Res Synth Methods* 2020;11:522–34.
26 Schünemann HJ, Cuello C, Akl EA, *et al*. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in Nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol* 2019;111:S0895-4356(17)31031-4:105–14.:.
27 Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. (1464-3685 (electronic)). 2009.
28 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons, 2019.
29 López-López J-O, Page MJ, Lipsey MW, *et al*. Dealing with effect size multiplicity in systematic reviews and meta-analyses. *Wiley Online Library* 2018.
30 Waddington HJ. Broadening horizons in impact evaluation for water, sanitation and hygiene planning: recycling and reinterpreting evidence. *LSHTM* 2021.
31 Ryan R, Cochrane Consumers and Communication Review Group. *Cochrane Consumers and Communication Review Group: data synthesis and analysis*. 2013.
32 Organization WH. Methods for surveillance of Antimalarial drug efficacy. 2009.