European Journal of Integrative Medicine 28 (2019) 76–85

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Systematic Review

Plants with antimalarial properties: A systematic review of the current clinical evidence

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ARTICLE INFO

Keywords:
Malaria
Antimalarial plants
Botanicals
Herbal medicine
Systematic review

ABSTRACT

Introduction: Malaria is one of the most common major health problems in tropical low-and middle-income countries, with antimalarial drugs being highly effective but also threatened by increasing drug resistance. Clinically efficacious, well-tolerated antimalarial plants could be an important alternative treatment. This systematic review aims at identifying and critically appraising clinical trials testing plants with antimalarial properties for malaria treatment and/or prophylaxis.

Methods: Studies were identified through PubMed, Elsevier Scopus and Cochrane Central, and scanning article reference lists. Records were published in English between 01/01/2005 and 15/01/2018. A framework for analysis based on the CONSORT statement was used for data extraction. Risk of bias was assessed. A meta-analysis could not be conducted due to data heterogeneity.

Results: Nine studies met inclusion criteria. Extracts from *Argemone mexicana, Artemisia annua, Citrus aurantifolia, Nauclea pobeguinii*, *Nycthanthes arbor-tristis* and *Vernonia amygdalina* were examined. Methodological rigorosity varied. Adequate clinical response on day 14 with *A. mexicana* was 81% ($p = 0.027$) in one study and 89% (95% CI 84.1–93.2) on day 28 in another study. Similarly, 87.9% of participants taking *N. pobeguinii* had an adequate clinical response on day 14 ($p = 0.003$). The risk of bias and study quality varied. Two studies had a Jadad score of 3 and all others but one had a score of 1. All herbal preparations were safe with no moderate or severe adverse events being reported.

Conclusions: Studies have demonstrated that antimalarial plants show promise for malaria treatment and prophylaxis. *A. mexicana* and *N. pobeguinii* extracts were supported by the best evidence. More work should be undertaken to better understand relevant approaches.

1. Introduction

Malaria is one of the most common major health problems in tropical low and middle-income countries, including the regions of sub-Saharan Africa, Southeast Asia and South America [1,2]. Malaria is an entirely preventable and treatable mosquito-borne illness that is caused by *Plasmodium (P.)* parasites. The parasites are spread to people through the bites of infected 'malaria vectors', the female *Anopheles* mosquitoes [2]. There are five parasite species that cause malaria in humans, which are *P. falciparum, P. malariae, P. ovale* and *P. vivax* and *P. knowlesi. P. falciparum* is considered the deadliest species, leading to many fatal complications such as cerebral malaria [3]. Even though the prevalence of malaria has decreased in Africa since 2000, it is estimated that 3.2 billion people remain at risk of malaria; and of these, 1.2 billion are considered at high risk [2]. In 2013, there were an estimate of 98 million cases of malaria and an estimated 584,000 deaths [4].

The first line treatment to treat *P. falciparum* and chloroquine (CQ)-resistant *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria, are artemisinin combination therapies (ACT) [4]. Artemisinin must be combined with another drug or drugs in order to reduce resistance to it [5]. Artemisinin resistance has been extensively reported [6,7] and evidence to CQ resistance by *P. vivax* is starting to emerge [8]. When *P. vivax*, *P.*

Abbreviations: A. annua, *Artemisia annua* L. (annual wormwood) leaves and stems; ACT, Artemisinin combination therapies; *A. mexicana*, *Argemone mexicana* L. (Mexican poppy) whole plant; ACR, Adequate clinical response; AQ, Amodiaquine; AS, Artesunate; *C. aurantifolia*, *Citrus aurantifolia* Sw. (lime); CQ, Chloroquine; *N. arbor-tristis*, *Nyctanthes arbor-tristis*; *N. pobeguinii*, *Nauclea pobeguinii* Pob. Ex. Pell. (no English translation) stem bark; *P.*, Plasmodium; PICOS, Patients Interventions Comparators Outcomes Study design; RCT, Randomized clinical trial; RITAM, Research initiative on traditional anti-malarial methods; SP, Sulfadoxine-pyrimethamine; *V. amigdalina*, *Vernonia amygdalina* Del. (bitter leaf) leaves; WHO, World Health Organization

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https://doi.org/10.1016/j.eujim.2019.04.005
Received 10 October 2018; Received in revised form 7 March 2019; Accepted 17 April 2019
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ovale, *P. malariae* or *P. knowlesi* are CQ-sensitive, the first line treatment is still CQ. ACT treatment is highly effective for both falciparum (around 95%) and non-falciparum malaria [9–11], yet its effectiveness is much reduced by different reasons such as (1) poor accessibility in remote areas, (2) poor quality of antimalarial drugs in many endemic areas and (3) treatment-seeking behaviour for traditional[1] medicines [12,13].

Herbal[2] medicines are the source of the two main groups of modern antimalarial drugs: artemisinin from *Artemisia annua* L. (annual wormwood) leaves and stems; and quinine from *Cinchona spp.* (quina tree) bark [14,15]. Since the purification of quinine in the early 19th century and the discovery of artemisinin by Youyou Tu in 1972, there have not been any large-scale efforts to translate what has been found in herbal traditional texts, ethnobotanical surveys, and preclinical trials of botanicals, into potential clinical alternatives for the treatment of malaria [15–17].

The reverse pharmacology approach applied to malaria treatment, has proven the relevance, use and applicability of traditional knowledge [18,19]. This approach has demonstrated how a standardised phytomedicine can be developed faster and more cheaply than conventional antimalarial drugs [19]. The development of drugs can take up to 15 years and cost up to $800 m [20]. Moreover, the availability and affordability of these is very difficult for the poorest patients particularly where heavily subsidised schemes do not exist [19].

Despite the overall increase in quality-assured ACTs around the world, herbal medicines are widely used to treat malaria [2,21]. A meta-analysis showed that the overall percentage of respondents using herbal antimalarials was 20%, with ranges varying from 0% to 75% depending on the setting [22]. Over 1000 plants are being used globally as potential antimalarials in resource-poor settings as a result of lack of accessibility and affordability of ACTs and fragile health-care systems [23]. Clinically efficacious, well-tolerated antimalarial plants could be an important and sustainable source of treatment not only in resource-poor settings, but also to tackle the increasing levels of drug resistance [24,25]. Furthermore, herbal medicine is associated with fewer adverse effects than antimalarial drugs [26].

Thus, factors such as drug resistance, treatment-seeking behaviour, lower costs and potentially fewer adverse effects indicate that herbal medicines can potentially serve as a good alternative to antimalarial drugs. If herbal medicines are going to be used, good quality research is needed to determine safety, quality, effectiveness, and dosage.

Even though *in vivo* studies using mice have found that a single dose of the dried whole plant *A. annua* (containing 24 mg/kg artemisinin) reduces parasitaemia more effectively than a comparable dose of purified artemisinin, extrapolating this to clinical practice might be questionable [27]. Nevertheless, preclinical studies provide useful information to build on and they may suggest the mechanism of action, to identify active constituents and safety and to clarify optimal dosage. A study concluded that a score set by the Research Initiative on Traditional Anti-malarial Methods (RITAM score) to combine information from reviews of published ethnobotanical studies and laboratory pharmacological studies of efficacy and safety was useful. The laboratory efficacy score correlated with clinical parasite clearance (rs = 0.7), and the ethnobotanical component correlated weakly with clinical symptom clearance although not with parasite clearance [28]. Even if the ethnobotanical score did not seem to be significantly correlated with the clinical score, the example of artemisinin discovery illustrates how useful traditional medicine knowledge can be. After reading traditional Chinese medicine texts, the team of researchers that noticed the usefulness of *A. annua* and later isolated artemisinin, realised that the traditional method of boiling the leaves might destroy the active components. In one old herbal text reporting the effectiveness of *A. annua* for malaria, it was reported that the leaves should be simply soaked in water. The team then concluded that artemisinin is most active when extracted using lower temperatures in the laboratory or when soaking the leaves in lukewarm water if prepared traditionally [29].

There is research showing the anti-plasmodial benefits of the synergistic interaction of different chemicals and/or phytochemicals of different plants [30]. These studies demonstrate how the crude plant extract is more efficient pharmacologically than the most active purified phytochemical from this extract [31]. This in combination with potential socioeconomic advantages, make the exploration of whole herbal treatment alternatives (*i.e.* giving an extract of the whole plant) worth pursuing [24].

In addition, for cases that cannot be managed with traditional herbal medicines, for severe malaria, or when pharmaceutical drugs are preferred, developing new antimalarial drugs is also an imperative. The evolution of drug resistance demands new antimalarial agents that could be found after an analysis of the pharmacological actions of other plant constituents [23]. In order to advance in this arena it is important to achieve a solid antimalarial research agenda among all stakeholders, including ethnobotanists, traditional healers and herbalists, scientists, entomologists, pharmacists and research institutions.

Willcox and Bodeker performed the latest non-systematic review on the use of traditional herbal medicines for malaria in 2004, including both clinical evidence and also ethnobotanical surveys. This review concluded that better evidence from randomised clinical trials (RCT) is needed assessing safety and efficacy before herbal remedies can be recommended on a large scale. Authors also identified that even among traditional healers there is no consensus on which plants, preparations, and dosages are the most effective [32].

Evidence can take many forms, including traditional use and case studies, but clinical evidence is considered most reliable and useful. So despite the plethora of preclinical evidence, definite conclusions can only be extracted from clinical evidence. Hence, the proposed review aims to expand the body of knowledge through using clinical trials exclusively and more current information in order to critically and systematically review the existing clinical evidence on plants with antimalarial properties.

This systematic review aims to expand the body of knowledge through critically appraising clinical trials in order to review the current evidence on plants with antimalarial properties.

2. Methods

2.1. Design and study selection

2.1.1. Information sources

Studies were identified through PubMed, Elsevier Scopus, Cochrane Central and scanning reference lists of articles. Records were restricted to English language and to articles published between 01/01/2005 and 15/01/2018. The following keywords and MeSH terms were used to search each source: malaria AND ("herbal medicine" OR plant OR botanical OR herb*) AND ("controlled trial" OR "clinical trial"). MeSH terms included were: malaria, herbal medicine and clinical trial.

2.1.2. Study selection

The screening of titles and abstracts, eligibility assessment and inclusion criteria was performed independently by the first reviewer. The second reviewer independently reviewed eligibility of abstracts and full texts. Disagreements between reviewers were discussed and resolved by consensus.

2.1.3. Eligibility criteria

The eligibility criteria were the following:

[1] 'Traditional' in this review refers to a form of medicine or treatment that has a historical basis in usage before the development of modern biomedicine.

[2] 'Herb(s)', 'herbal', or 'plant(s)' are used interchangeably in this review.

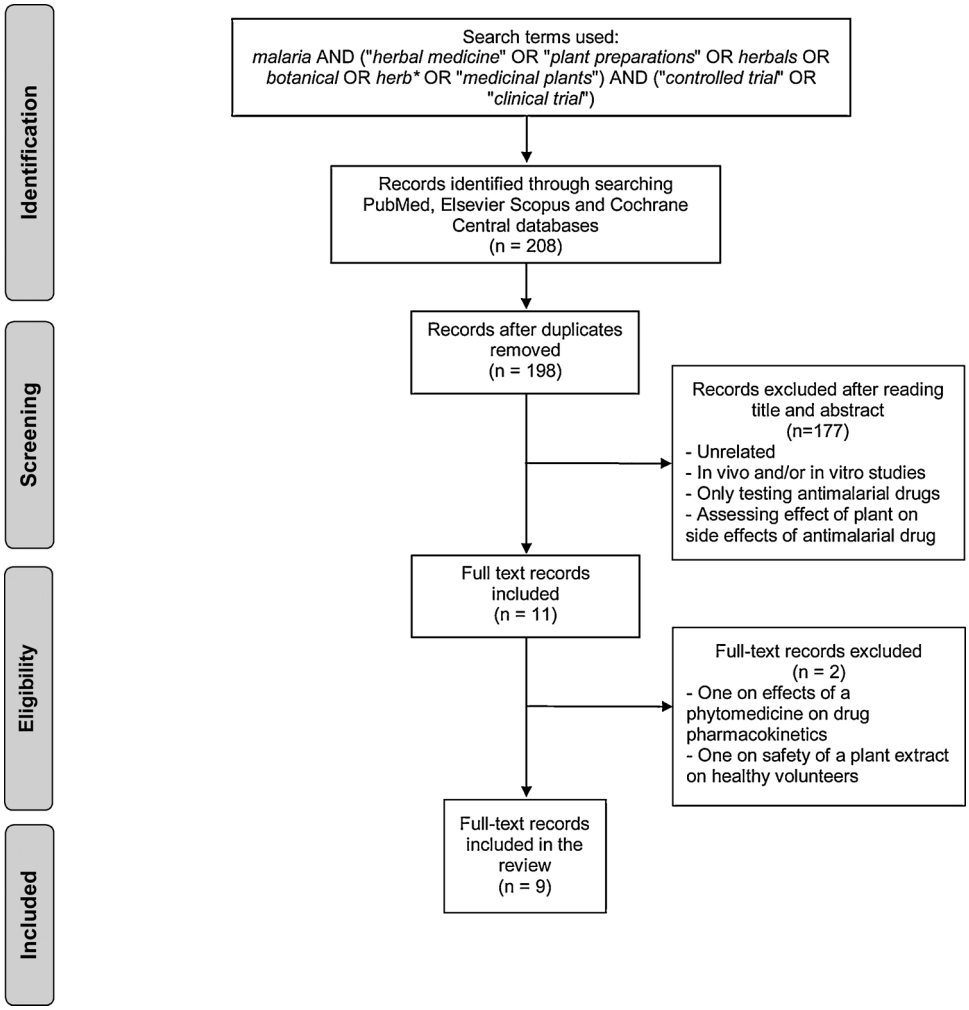


Fig. 1. Clinical study selection process.

(1)

(1) Randomised and non-randomised published clinical trials studying the administration and subsequent effect of whole plant extracts or standardised plant extracts to patients with malaria or as a prophylactic.
(2) Types of participants included adults and children with malaria or at risk of malaria. The limited amount of published clinical trials on the topic was anticipated; hence, there were no exclusion criteria in regards to age, sex or other characteristic.
(3) As to the intervention, plants or plant extracts could be used on their own in the treatment group or as an adjuvant to drugs. The review does not include interventions using antimalarial drugs that have been derived from plants.
(4) Primary outcome measures were parasitaemia or parasite clearance on days 1, 3, 14 and/or 28 [4]. Secondary outcome measures should be the monitoring of clinical symptoms (including fever), parasitaemia if this was not the primary outcome measure, and/or adverse events [4]. Studies assessing the prophylactic effect should have as an outcome the diagnosis of malaria.
(5) The dates considered in the search were 01/01/2005 until 15/01/2018 in all databases. Searches were performed from 2005 onwards because the latest non-systematic review on the use of traditional herbal medicines for malaria was published by Willcox and Bodeker in November 2004 [32].
(6) Only full-text published articles written in English were considered, as this is the only common language of both reviewers.

2.2. Data collection and extraction

A data extraction sheet was developed. This was based on the CONSORT 2010 statement for reporting randomised clinical trials, the CONSORT recommendations for herbal interventions and Bone and Mills Principles of Phytotherapy [33–35]. This was pilot-tested on one of the studies and the framework was refined accordingly. One reviewer extracted the data from all included studies and the outcomes from this process were discussed between the two reviewers. No authors were contacted for further information.

Using the PICOS approach [36] and Gagnier et al., 2006 [33] guidelines, information was extracted from each included trial on: (1) characteristics of study design and duration; (2) characteristics of trial participants; (3) type of intervention (including detailed information on the medicinal product and its characteristics); (4) comparison group (5) type of outcome measure and details about the evaluation process; (6) presentation of results and discussion; (7) limitations and funding of the study; (8) formulation, dosage and other relevant aspects to herbal practice; (9) safety and reported adverse events. After the extraction of detailed information using the framework for analysis developed by the first reviewer, another framework was developed to collect a summary of the analyses. This included an assessment of the quality appraisal and further comments.

Risk of bias in individual studies taking into account randomisation and blinding, was assessed using The Cochrane Collaboration's tool for assessing risk of bias and the Jadad scale [37,38]. The risk of bias across studies could not be performed due to the high variability of objectives

and outcomes within studies.

This review follows the overall structure and guidelines set by the PRISMA statement for reporting systematic reviews on health interventions [36]. A meta-analysis could not be conducted as the population in the individual studies was not uniform and not all studies used the same outcomes.

3. Results

3.1. Study selection

The search of PubMed and Elsevier Scopus provided a total of 198 records once duplicates were removed. No relevant studies were found on Cochrane Central. After screening the title and abstract of these, 11 were identified for more detailed inspection [Fig. 1]. The reference lists of these were reviewed for potential studies but no additional articles met inclusion criteria for this review. The full text of the 11 records was examined in detail. Of these, one was discarded, as the outcome was to assess the effect of a standardised phytomedicine on the pharmacokinetics of an antimalarial drug, which does not meet the inclusion criteria [39]. Another record was also discarded because it was a clinical phase I study assessing the short-term safety and tolerability of a standardised phytomedicine in healthy volunteers [40]. The outcome measures of this study did not meet inclusion criteria. After the screening and selection process, nine full-text records were included in the review.

3.2. Study characteristics

Table 1 presents the main characteristics of each study for which data were extracted. Five out of the nine studies were randomised controlled clinical trials.

3.3. Risk of bias within studies

Out of the five randomised clinical trials, two adequately concealed group allocation. One was double blinded, and two blinded only participants. Table 2 provides a summary of the risk of bias in the nine studies. Graz et al., 2010 [26] and Blanke et al., 2008 [42] appear to have the lowest risk of bias in both, the Cochrane tool and the Jadad scale.

3.4. Results of individual studies

The results of individual studies were extracted from the framework for analysis table, and were summarised in another table including a quality appraisal section. Table 3 illustrates a summary of the results of individual studies including adverse events.

Adequate clinical response (ACR) in all clinical trials unless otherwise specified, was defined as the absence of parasitaemia on day 14 irrespective of fever, or apyrexia irrespective of parasitaemia, without meeting any criteria of early or late treatment failure.

In the study by Willcox et al., 2007 [41], the dosage unit given of *Argemone mexicana L.* (Mexican Poppy) to each participant was not specified. Method of raw material authentication was not reported, and it is unknown whether it underwent qualitative testing. How the sample size was calculated was not reported. This was not a randomised study and it did not have a control group. There was no blinding. The ACR for groups A, B and C was 35, 73 and 65%, respectively ($p < 0.011$). The ACR was lower in children < 1 year (45%) and higher in > 5 years (81%) ($p < 0.027$). Very few had full parasite clearance, but 67% of ACRs had < 2000/μl (88% of ACRs in Group A; 59% in B; 73% in C). The study was properly justified and discussed its positive results in light with appropriate literature. Authors reported the overall risk of bias.

In the study by Graz et al., 2010 [26], the treatment preparation was the same as used in Willcox et al., 2007 [41] (decoction: 100 g of *A. mexicana* whole plant per 1 L of boiling water for 3 h). The unit dose in this study was specified. The authentication method of the raw material was not reported. It was a randomised study with a 2:1 herb/ACT ratio. There was a positive control and no blinding was performed. The study was an effectiveness assessment and this was reflected in the study setting. The second line treatment was not required for 89% (95% CI 84.1–93.2) of patients on *A. mexicana*, versus the 95% (95% CI 88.8–98.3) on ACT. The discussion and weaknesses of the study were thoroughly explained.

The study by Blanke et al., 2008 [42], was a double blind randomised trial with a positive control taking sulfadoxine-pyrimethamine (SP). The intervention treatment was standardised. To make it double blind, a placebo was given to both treatment groups. The sample size was small, and how this was calculated was not reported. The preparation method of the herbal intervention was not reported, but was instead given as a citation. The high rates of recrudescence using either 5 g or 9 g of *A. annua* per litre led to the decision to end recruitment. Limitations were not discussed in the paper.

In the study by Ogwang et al., 2012 [43] the dosage used was clearly specified. It was randomised using a 1:1 ratio. As this trial assessed the potential prophylactic effect of *A. annua*, the control arm received an herbal infusion with *Thea sinensis* L. (tea) leaves. Only participants were blinded. There was detailed information on the quantitative and qualitative testing of the herb and this was standardised to contain 0.4 − 0.8% artemisinin. *A. annua* infusion significantly reduced the risk of suffering more than one episode of malaria in 9 months by 55% ($p < 0.005$). When adjusted for bed net use, there was still significant protection by the infusion since participants taking *A. annua* and not using bed nets had a protective effect of 38.4% ($p < 0.03$). Authors did not report the limitations and only made reference to the generalisability issues of the study. This study also discussed the potential mode of action for the prophylactic effect of *A. annua*.

The study by Challand and Willcox, 2009 [44] is a clinical trial with a small sample size (n = 33). How this was calculated was not reported. This study did not have a positive group and only had one treatment group. Authors did not report the method of authentication of *Vernonia amygdalina* Del. (bitter leaf) leaves and did not specify whether it underwent qualitative testing. There were no details about the personnel administering the treatment. The outcome measures were clear. 67% of patients had ACR at day 14. 32% patients had complete parasite clearance at day 14 but of these, 71% had recrudescence by day 28. At day 28, 3 out of 20 patients had a parasitaemia > 1000/μL. Authors did not report the limitations of the study.

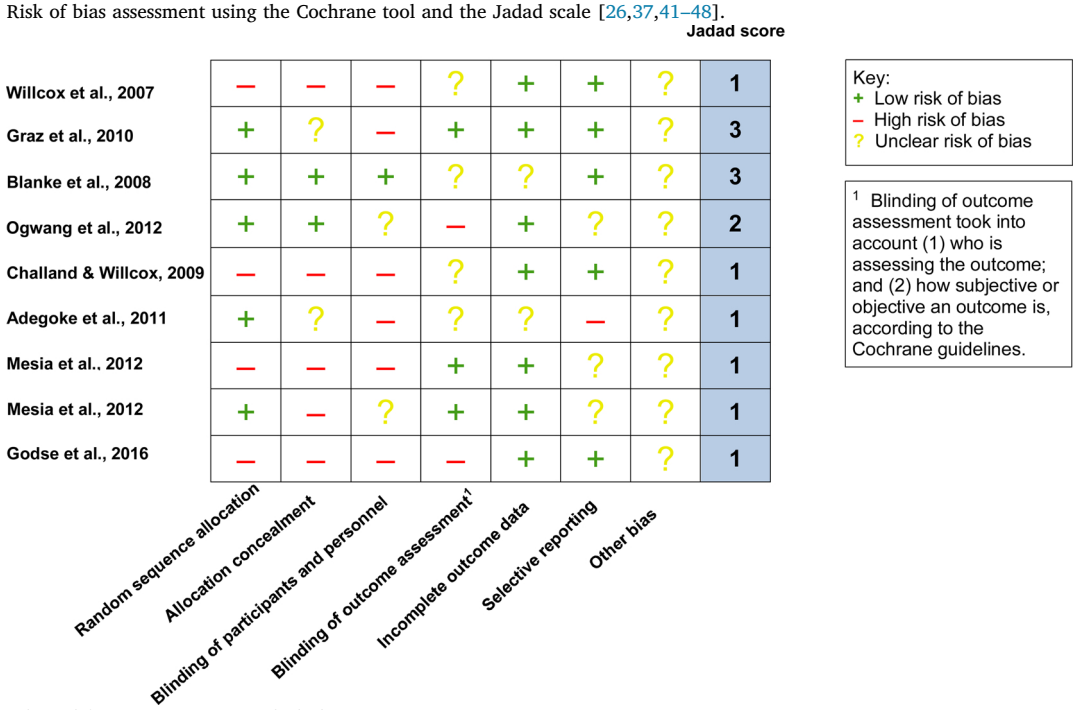
The study by Adegoke et al., 2011 [45] contained very little information on the rationale without justification of the *Citrus aurantifolia* Sw. (lime) juice use. Specific objectives were not stated. No information was given on the juice source, characteristics, authentication or qualitative testing. It was a randomised trial but no allocation ratio was given and no information on the randomisation process was reported. There was a positive group and the study was not blinded. This study did not present a clear diagram flow with participants. The mean (SD) time to > 75% reduction in parasite load was significantly lower in patients on ACT and *C. aurantifolia* juice versus those taking ACT alone: 30.5 ± 2.4 *vs.* 38.6 ± 3.3 h ($p < 0.007$). Limitations were not reported.

In the study by Mesia et al., 2012 [46], the objectives were not clearly stated. The study had a small sample size (n = 11). It was not randomised and there was no positive/control group, although this is justified, as it was a phase II trial. Who authenticated the raw material was not reported. The treatment intervention was standardised. All participants were fully cleared of parasitaemia and fever on days 3, 7, and 14 except for one patient, who had a recurrence of parasitaemia from day 7 until day 14. Neither p-values nor confidence intervals were reported as there was not a comparison group. Limitations and funding

Table 1
Summary of study characteristics [26,41–48].

Study	Trial design	Setting	# Participants	Age range	Inclusion criteria	Plant name & formulation	Control intervention	Follow-up	Outcomes
Willcox, et al., 2007	Prospective, dose escalating, quasi-experimental.	Rural village in Mali	80	Children and adults	*P. falciparum* parasitaemia > 2000/μl, with symptoms of malaria within the last 24 h and without any signs of severe disease.	*Argemone Mexicana* Decoction Group A n = 23 Group B n = 40 Group C n = 17	None	28 days	- Adequate clinical response on day 14. - Incidence of adverse events.
Graz et al., 2010	RCT	Rural village in Mali	298	Children and adults	Presumptive malaria diagnosed by traditional healer except: 1) severe malaria; 2) full dose of antimalarial on same day.	*Argemone Mexicana* Decoction n = 197	Artesunate-amodiaquine n=101	28 days	- Adequate clinical response on day 28. - Apyrexia on day 14. - Incidence and severity of adverse events.
Blanke et al., 2008	RCT Double-blind	Kigoma & Kasulu, Tanzania	19	> 18 years	*P. falciparum* malaria (2000/μL – 40000/μL)	*Artemisia annua* Infusion n = 13	Sulfadoxine-pyrimethamine n=10	28 days	- Parasitological cure rate on day 7, 14 and 28.- Clinical symptoms on days 14 and 28.
Ogwang, et al., 2012	RCT Single-blind	Flower farm in Uganda	132	Adults	Flower farm workers in Uganda with ≥2 malaria episodes in the year, no malaria prevention. Negative blood stains for malaria parasites.	*Artemisia annua* Infusion n = 67	*Thea sinensis* powder n = 65	9 or 12 months	- Monitoring for malaria episodes (defined as clinical symptoms and parasataemia).
Challand & Willcox, 2009	Prospective clinical trial	Primary health centers, Uganda	33	> 12 years	*P. falciparum* malaria (> 1000/μL), fever in past 48 hours, no signs of severe malaria/ pyrexial illnesses, no treatment for malaria in past 2 weeks.	*Vernonia amygdalina* Infusion n = 33	None	28 days	- Adequate clinical response at day 14 based on absence of parasitaemia only. – Incidence of adverse events.
Adegoke et al., 2011	RCT	Hospital in Nigeria	111	Children < 1–years	Children with both laboratory and clinical evidence of acute uncomplicated malaria.	*Citrus aurantifolia* Juice n = N/R	Artemisinin combination therapy n = N/R	3 days	- Rate of parasite clearance at 24, 48 and 72 hours.
Mesia et al., 2012	Phase IIA clinical trial	Inpatient medical center in Kinshasa, RDC	11	Adults	*P. falciparum* parasitaemia 500-200000/μl, with fever within the last 24 h and other symptoms of uncomplicated malaria.	*Nauclea pobeguinii* (PR 259 CT1) Ethanolic extract n = 11	None	14 days	- Adequate clinical response on day 14.- Parasite clearing time (PCT), fever clearance time, initial malaria symptoms resolution. - Incidence of adverse events.
Mesia et al., 2012	Phase IIB clinical trial (RCT) Single-blind	Inpatient medical center in Kinshasa, RDC	65	Adults	*P. falciparum* parasitaemia 500-200000/μl, with fever within the last 24 h and other symptoms of uncomplicated malaria.	*Nauclea pobeguinii* (PR 259 CT1) Ethanolic extract n = 33	Artesunate-amodiaquine n=32	14 days	- Adequate clinical response on day 14.- Parasite clearing time (PCT), fever clearance time, initial malaria symptoms.- Incidence of adverse events.
Godse et al., 2016	Observational clinical trial	Ayurvedic Hospital, India	20	15 55 years old	*P. falciparum and/or P. vivax* parasitaemia by microscopy and RDT, fever and chills.	*Nyctanthes arbor-tristis Paste n = 20*	None	30 days	- Adequate clinical response on days 7, 14 and 30.- Incidence of adverse events.

Table 2
Risk of bias assessment using the Cochrane tool and the Jadad scale [26,37,41–48].



Adopted from Higgins [37] and Clark [38].

sources were not reported.

Mesia et al., 2012 [47] did not state the specific objectives of their study. The study was randomised and single-blinded to patients. However, as one group was given capsules and the other tablets, how they achieved the blinding despite this was not reported. The individual who authenticated the raw material was not specified. The treatment intervention was standardised. The study showed a significant decreased parasitaemia in patients treated with *Nauclea pobeguinii* Pob. Ex. Pell. stem bark (PR 29 CT1) and artesunate-amodiaquine (ASAQ) with adequate clinical parasitological responses (APCR) at day 14 of 87.9 and 96.9%, respectively ($p < 0.003$). There was a positive group. Limitations and funding sources were not reported.

Godse et al., 2016 [48] clearly state the objectives of the study. This is an observational study without a control group and a small sample size (n = 20). All patients were given *Nyctanthes arbor-tristis* Linn. leaf paste thrice a day. The raw material was not standardised, but fixed dosages were given to participants. The treatment intervention was standardised. Half of participants showed complete parasite clearance and apyrexia on day 7. Limitations were not reported.

4. Discussion

After searching in PubMed, Elsevier Scopus and Cochrane Central, 198 records were identified. Of these, 11 were selected for subsequent inspection based on title and abstract. Two were further discarded and a total of 9 studies met inclusion criteria. A meta-analysis could not be conducted due to the heterogeneity of data, such as the diversity of herbal preparations and variety within outcome measures. A systematic review appraising quality of studies and reviewing effectivity of plants and adverse side effects was performed. *A. mexicana* and *N. pobeguinii* extracts were supported by the best evidence. *A. mexicana* showed an ACR of 81% ($p = 0.027$) on day 14 in one study [41] and of 89% (95% CI 84.1–93.2) on day 28 in another study [26]. The trial using *N. pobeguinii* reported an ACR of 87.9% on day 14 ($p = 0.003$), which was similar to the ACR obtained when taking antimalarial drugs [47]. The risk of bias was varied, with the studies by Graz et al., 2010 evaluating *A. mexicana* decoction and by Blanke et al., 2008 evaluating *A. annua* infusion having the lowest risk of bias. All other studies had a score of 1 in the Jadad scale except the study by Ogwang et al., 2012 evaluating *A. annua* infusion which had a score of 2. All herbal preparations were safe to use and only self-limiting mild adverse events were reported on *A. mexicana* and *N. pobeguinii*.

The evidence for the applicability of herbs was mixed. Nine plant extracts were examined within the articles. These were two decoctions, three infusions, a juice, a leaf paste and two ethanolic extracts. All plant extractions were assessed for *P. falciparum* malaria except *N. arbor-tristis* that was assessed also on mixed with *P. vivax*. *A. mexicana* decoction was found to be effective for malaria treatment in both studies examined, despite the ACR being slightly lower than when using the first-line antimalarial drug. *A. annua* infusion was found to be ineffective for malaria treatment although significantly effective as a prophylactic. *V. amygdalina* was found to be moderately clinically effective for malaria treatment. The concurrent usage of *C. aurantifolia* juice led to a significant reduction in parasitaemia compared to the group only taking ACT. Whether this is because the juice increases the efficacy of ACT or not was not explored. *N. arbor-tristis* showed statistically significant efficacy, but the lack of control group and the small sample size make it difficult to draw any compelling conclusions. *N. pobeguinii* (PR 29 CT1) was found to be safe, clinically effective for malaria treatment and exhibited less side effects when compared to a first-line antimalarial drug.

Overall, the evidence suggests that even if not as clinically effective as ACTs or other antimalarial drugs, some plants if appropriately used (i.e. correct dosage and preparation) can significantly reduce ACR and decrease parasitaemia. The direct comparability of the studies was not possible due to the heterogeneity of the studies (RCTs, cohorts, phase II clinical trials), the different plants used and the widely varied risk of bias assessment. Most studies stated clear outcomes and measured these according to the World Health Organization (WHO) guidelines [4]. Most studies explicitly addressed what would be done with patients developing clinical deterioration.

The terminology used regarding efficacy and effectiveness could

Table 3
Summary of individual study results.

Study	Plant name	Formulation	Outcomes	Results	Adverse events
Willcox, et al., 2007	*Argemone mexicana*	Decoction	- Adequate clinical response on day 14. - Incidence of adverse events.	On day 14, adequate clinical response were 35%, 73% and 65% in groups A, B, C, respectively ($p = 0.011$). Overall adequate clinical response in participants aged > 5 years was 81%($p = 0.027$).	Cough and diarrhoea were the commonest adverse events and were reported in 17—25% of patients in each group.
Graz et al., 2010	*Argemone mexicana*	Decoction	- Adequate clinical response on day 28.- Incidence and severity of adverse events.	On day 28, second-line treatment was not required for 89% (95% CI 84.1–93.2) of participants on *Argemone mexicana*, versus 95% (95% CI 88.8–98.3) on ACT.	Both treatments were well tolerated, with fewer adverse events on botanical group (14.2%) than ACT group (18.8%). All adverse events were considered mild: cough, nausea, diarrhoea and/or vomiting.
Blanke et al., 2008	*Artemisia annua*	Infusion	- Parasitological cure rate on day 7, 14 and 28.- Clinical symptoms on days 14 and 28.	High rate of recrudescence in all patients in both groups. Most of the symptoms improved within 3 days after initiation of therapy in both groups (data not shown).	The *Artemisia annua* preparations were well tolerated.
Ogwang, et al., 2012	*Artemisia annua*	Infusion	- Monitoring for malaria episodes (defined as clinical symptoms and parasitaemia).	*Artemisia annua* infusion reduced the risk of suffering more than one episode of malaria in 9 months by 55% ($p = 0.005$) compared to placebo..	The *Artemisia annua* preparations were well tolerated.
Challand & Willcox, 2009	*Vernonia amygdalina*	Infusion	- Adequate clinical response on day 14 based on absence of parasitaemia only. –Incidence of adverse events.	On day 14 complete parasite clearance occurred in 32% on day 14. Of these, recrudescence occurred in 71% by day 28.	The *Vernonia amygdalina* preparations were well tolerated.
Adegoke et al., 2011	*Citrus aurantifolia*	Juice	- Rate of parasite clearance at 24, 48 and 72 hours.	The average time to achieve $> 75\%$reduction in parasite load was significantly lower in patients on ACT and *Citrus aurantifolia* juice ($p < 0.001$) than ACT alone.After 72 hours, more children on ACT and the juice (48.2%), had complete parasite clearance against those on ACT alone (23.6%) ($p = 0.007$).	N/A
Mesia et al., 2012	*Nauclea pobeguinii* (PR 259 CT1)	Ethanolic extract	- Adequate clinical response on day 14.- Parasite clearing time (PCT), fever clearance time, initial malaria symptoms.- Incidence of adverse events.	On day 14, complete parasite clearance and adequate clinical response occurred in 91% of participants.	73% ($n = 8$) complained of one or more minor side effects (fatigue, increased appetite, nausea, headache). They were transient and none of the participants stopped taking treatment because of adverse effects.
Mesia et al., 2012	*Nauclea pobeguinii* (PR 259 CT1)	Ethanolic extract	- Adequate clinical response on day 14.- Parasite clearing time (PCT), fever clearance time, initial malaria symptoms.- Incidence of adverse events.	On day 14, adequate clinical and parasitological response occurred in 87.9% of participants in the PR 259 CT1 group vs 96.9% in the antimalarial drugs (AS + AQ) group ($p = 0.003$).	Most common adverse events on both groups were: fatigue (46.9% in AS + AQ group vs. 24.2% in PR 259 CT1 group, $p < 0.0001$), headache (34.4% vs. 9.1%, $p < 0.0001$), and dizziness (31.1% vs. 12.1%, $p < 0.0001$).
Godse et al., 2016	*Nyctanthes arbor-tristis*	*Paste*	- Adequate clinical response on days 1, 3 and 7.- Incidence of adverse events.	On day 7, 50% of participants showed complete apyrexia and parasite clearance by day 7.	The *Nyctanthes arbor-tristis* paste preparations were well tolerated.

serve as a source of confusion when reviewing the results. However, the two concepts were not conflated according to their standardised definitions, and it is important for appraisers to understand the distinction. Research can be considered effective in the context of pragmatic trials seeking to understand how treatments work in the practise of medicine, while efficacious research concerns explanatory research including RCTs, clinical trials and laboratory studies [49].

The interaction between different chemical components and agents yields a more efficacious outcome and helps fight resistance [30,31]. Willcox et al., 2007 give an example of this in their study highlighting the case of berberine in *A. mexicana*. The amount of the phytochemical berberine found by HPLC was insufficient to explain the high in vitro activity displayed by this plant extract. Furthermore, berberine is poorly absorbed orally [41]. Hence, this suggests that other phytochemicals work synergistically or increase the bioavailability of berberine. Another example found in the studies reviewed is the mode of action of *A. annua* explored by Ogwang et al., 2012 [43].

The study by Blanke et al., 2008 concluded *A. annua* infusion to be ineffective. However, the 9 g/L dosage put forth in this study is not used in herbal practice [14]. A RCT published in 2004 also reported high recrudescence rate in the group *A. annua* infusion using 9 g/L [50].Yet, in practice, most medicinal infusions are made at a much higher strength (50 g of dried or 100 g of fresh herb per litre of water) [51]. Clinical studies in China have shown that a dose of 72–125 g of *A. annua* per day for three days was highly effective [14]. If future trials are planned, perhaps they might benefit from examining stronger dosages that more closely match what practitioners currently use.

Both *A. mexicana* and *V. amygdalina* proved to be effective and moderately effective, respectively. The authors' rationale for testing these herbs comes from a combination of traditional herbal practice gathered in ethnobotanical surveys and preclinical studies that show the plant extracts to have a very low IC50 [39,52–54]. Their usage of a dose escalating methodology and the reverse pharmacology approach[3] appears to be a rapid and successful way of testing the clinical efficacy of antimalarial plants [19].

Translating these results into clinical practice can be challenging. Standardisation of herbal products is a key issue put forth at present. Test product standardisation remains one of the most challenging aspects of clinical research on botanicals [55]. The proportion of phytochemicals in plants can vary in accordance with many factors such as the part of plant used, harvesting season, ripeness and soil components [35]. One of the main concerns held by medical personnel is being unable to ascertain the effectiveness of an herbal product without knowing whether it contains the optimal amount of the active constituent. Some argue that the quality of plant research in general would improve if standardisation and certified methods of analysis for active compounds were available [56].

Conclusions cannot be drawn from the nine studies regarding the relevance of standardisation. Five studies did not use standardised herbal extracts, while four did. Direct comparison between them is very difficult as their internal validity ranges from low to moderate and there is not a correlation between result outcomes and standardisation. However, for a higher external validity and generalisability, the plant extracts should be standardised to contain a certain amount of the active constituent(s) whilst keeping the other phytochemicals for synergy purposes. Research should also examine optimal dosage, preparation, harvesting time, and other relevant factors alongside these results related to standardisation. Many of the studies reviewed did state the specific time period during which the plants were harvested and where they were grown, as well as whether fresh or dried plant parts were used in preparations. This facilitates the process of comparison. Additionally, this makes it more applicable in rural areas as when the standardised products have difficulty reaching the most remote populations. From a policy perspective there should be clear country-wide guidelines and implementation strategies on these aspects so that traditional healers can prepare them accordingly.

In the review it is evident that the clinical trials still do not report as much information as the CONSORT statement requires. This flawed reporting style is also reflected in the results found by other systematic reviews, including one review of over 200 RCTs [57]. This appears to be a common issue in clinical studies for botanicals. According to Gagnier et al., sometimes trials fail to provide sufficient information relating the results to other research. In this review, three clinical trials thoroughly discuss their results in light of other relevant research. Furthermore, the quality of herbal interventions is much increased if authors justify the quality testing and raw material authentication undergone by the herbal product [58]. According to the CONSORT statement for herbal interventions [34], only one study reported full qualitative testing. Four reported most of the information requested on quantitative description. Seven well-described the characteristics of the herbal product. Only one reported the method of authentication of the herbal product. The dosage regime was very clear in eight studies and detailed practitioner descriptions were given in two studies.

There is evidence to justify the usefulness of traditional herbal medicines in the fight against malaria. There is strong evidence supporting the widespread seek-treatment behaviour in many communities for herbal antimalarial remedies [21,22]. Moreover, some of these preparations are proving to be effective. Policy makers in some African countries are translating these results into guidelines and practice. Examples of this are *Nauclea latifolia* Smith (pincushion tree) leaves (NIPRD AM1) in Nigeria, and *A. mexicana* (commercially known as Sumafoura) in Mali [59,60].

In low-resource settings where patients cannot access biomedical drugs, acceptable alternatives are necessary. Evidence-based herbal medicine provides a particularly attractive alternative given its fit with the existing structures in these countries and the capacity of locals to grow, harvest and prepare their own plant remedies for treatment and prophylactic purposes. Indeed, herbal medicine is traditionally associated with lower costs, fewer significant side effects than conventional drugs and relative safety in application when prescribed correctly [61]. The very few adverse effects reported in the studies are consistent with this perspective, thus increasing the potential benefits available through these interventions and improving their candidacy as topics for further exploratory study. However, it is important to consider that only frequent side effects are likely to be encountered in small studies. More work should be done to build the evidence base of herbal medicine and to translate these results into practice, particularly in settings where alternative treatments are not readily available.

4.1. Limitations

This review has several limitations. A meta-analysis could not be performed because of the heterogeneity of data. The quality of the studies varied. Randomisation was adequate in one trial. Comparability across studies was not possible due to the different methodological nature of the studies and different herbs and dosage ranges used. Four out of nine studies used a standardised herbal extract. Four reported most of the information requested on quantitative description and only one reported the method of authentication of the herbal product.

The risk of bias assessment is a complementary tool that despite being necessary has also its limitations, as it is both focused on randomisation and blinding. This review used two different tools for cross-verification purposes. In addition, there is low comparability between

[3] Ashok Vaidya developed the reverse pharmacology approach in Ayurvedic herbal medicine [[64]]. The first step is to select a remedy through a retrospective treatment-outcome study using traditional medicine knowledge. The second step would be to set up a dose-escalating clinical trial that shows the safest and most efficacious dose. The third step would be to set up a RCT using a comparator. Isolation of compounds is usually performed at the end of the pathway for quality assurance purposes [[19]].

studies as sample and interventions are not similar. The risk of bias also varied greatly between studies. The results of this review should be understood within this context, as not all studies were capable of direct comparability.

Despite using the framework for analysis to extract the data, some information may have been inadvertently omitted. This could have created individual study bias within the results. Furthermore, the potential for reporting bias exists as the approach taken towards this review may have been driven by an overly optimistic viewpoint stemming from reviewers' backgrounds in herbal medicine.

Unpublished studies were not considered in this review. This might lead to publication bias, which could have resulted in missing some plants that have been studied but were found to have negative results or other outcomes that would have served as a barrier to publication. The limitation to English-only studies could have also resulted in the omission of relevant articles published in other languages, particularly as much of this research appears to be conducted in non-Anglophone countries.

5. Conclusions and recommendations

Malaria is a transnational issue of great importance to global health. Despite the high effectiveness of currently available antimalarials, humans across the globe are still dying of malaria or affected significantly by the condition and its sequelae due to multifactorial treatment barriers and increasing resistance. Between 0 and 75% of people use herbal medicine for malaria, depending on the context [22]. Researching the clinical efficacy and effectiveness of traditionally used herbal medicines can be of great use in terms of building the evidence base and supporting better treatment and prevention outcomes, particularly in places where a high proportion of the population already has the existing infrastructure to benefit from improvements in herbal remedies and the access to conventional antimalarials is limited.

This review has identified nine studies meeting inclusion criteria. Plants tested in seven of them include participants testing positive for *P. falciparum* malaria, one mixed with *P. vivax* and one the trial studying prophylaxis. Overall, the strength is low as per the GRADE approach to assessing clinical evidence [62], as most studies were not randomised trials and not all had a comparison group. Nevertheless, the results of the individual studies are positive in six studies, moderately positive in one and negative in another. *A. mexicana* and *N. pobeguinii* extracts were supported by the best evidence with *A. mexicana* showing an ACR of 81% ($p = 0.027$) in one study and 89% (95% CI 84.1–93.2) in another study. *N. pobeguinii* had an ACR of 87.9% ($p < 0.003$), which very close to that of antimalarial drugs. All outcome measures reflected each study's objectives. All plant extracts studied in the clinical trials of this review, were well tolerated and are safe to use, as none of them showed any moderate, severe or long-standing adverse events.

From a global health standpoint, traditional practices in non-Western societies are often considered relevant and important to engage in research in order to avoid imposing non-local perspectives on local citizens [63]. It is then left to wonder why this approach has been largely ignored in terms of utilising traditional medicine in the global fight against malaria. Promoting evidence-based medical standards for herbal medicine would support the existing resources in many countries facing the heaviest burden of malaria, where herbal medicine is often already integrated with the lives of many local residents. This would also be a sustainable, cost-effective and empowering methodology, as citizens of these countries would be able to take charge over their own medicine production and utilization through herbal medicine. Thus, future global health research would benefit greatly from increased inclusion of traditional medical viewpoints and practices in studies [63].

If herbal medicine for the treatment or prophylaxis of malaria is going to be translated into policy, appropriate and high-quality research is necessary. This research should reflect traditional practices and can be supported by results of preclinical trials. The dose escalating method and reverse pharmacology approach are recommended as plausible alternatives in order to enact this. Furthermore, if previous studies have been proven ineffective at specific dosages, the dosage should be increased where it is safe to do so (*i.e. A. annua* infusion for malaria treatment) and tested at that concentration in future trials. This would improve resource allocation in terms of study design and would also promote the creation of studies that are more closely in line with current theory and practice.

Randomisation, blinding and the use of a comparison group are also recommendations for future studies of herbal interventions. More transparent reporting is required to increase the quality of future trials, particularly concerning the quantitative information of a herbal product requested by CONSORT, qualitative testing, and authentication of the raw material. Justification of dosage would also be a very important component to include in future work, as it would allow readers to better understand the projected efficacy of interventions.

The quality of future studies and implementation of relevant results will depend on the joint efforts of key actors including scientists, ethnobotanists, traditional healers, medical professionals, herbalists and policy-makers. It is important to balance and properly weight these perspectives in order to create the most effective strategies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current review are available from the corresponding author on reasonable request.

Conflict of interests

The authors declare that they have no conflict of interests.

Funding

Not applicable.

Authors' contributions

All research was done by authors. AA was involved in the conception and design of the study. AA was the first reviewer and JG was the second reviewer. AA and JG contributed to the acquisition, analysis and interpretation of the data. AA was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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