Clinical review

Traditional herbal medicines for malaria

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Traditional medicines have been used to treat malaria for thousands of years and are the source of the two main groups (artemisinin and quinine derivatives) of modern antimalarial drugs. With the problems of increasing levels of drug resistance and difficulties in poor areas of being able to afford and access effective antimalarial drugs, traditional medicines could be an important and sustainable source of treatment.

The Research Initiative on Traditional Antimalarial Methods (RITAM) was founded in 1999 with the aim of furthering research on traditional medicines for malaria.[1] The initiative now has in excess of 200 members from over 30 countries. It has conducted systematic literature reviews and prepared guidelines aiming to standardise and improve the quality of ethnobotanical, pharmacological, and clinical studies on herbal antimalarials and on plant based methods of insect repellence and vector control. We review some of this work and outline what can be learnt from the developing countries on the management and control of malaria.

Summary points

- Over 1200 plant species from 160 families are used to treat malaria and fever
- On average, a fifth of patients use traditional herbal remedies for malaria in endemic countries
- Larger, more rigorous randomised controlled trials are needed with long term follow up
- So far only a few studies have reported on side effects from preparations
- In one trial, some patients stopped treatment due to minor side effects

Sources and selection criteria

We carried out searches of relevant articles published up to 2004 through Medline, Embase, CAB, Sociofile, and the central clinical trials database of the Cochrane Library, using the terms "traditional medicine" and "malaria", "malaria–therapy", "knowledge,–attitudes,–practice", "self–medication", and "drug–utilisation". We also searched the references of identified articles and handsearched journals on ethnobotany, herbal medicines, and tropical medicine, such as the *Journal of Ethnopharmacology*, *Fitoterapia*, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *Tropical Medicine*, and *International Health*. Authors were contacted for unpublished papers.

Table 1 Number of plant species according to importance value for treatment of malaria (IVmal)

IVmal	No of species	Definition of IVmal, according to frequency of reports
?	849	Insufficient data
1	95	Once in one ethnobotanical survey
2	30	Twice in one community
3	6	At least three times in one community
4	42	More than one community
5	91	More than one survey, in same country
6	106	More than one country, in same continent
7	47	Two continents
8	11	Three continents

We sought evidence for how often herbal medicines are used to treat malaria, and what factors affect this; which plants are most commonly used; and the clinical safety and efficacy of preparations from these plants (see bmj.com).

We entered each cited species into a database and assigned an IVmal (importance value for the treatment of malaria) according to how widely its use was reported. This system was first developed for use at a local level,[2] with values ranging from 1 to 4. We have extended this system to apply at an international level by creating additional values from 5 to 8 (table 1).

Use of herbal antimalarials

The proportion of patients using traditional herbal remedies for malaria varies widely. A meta-analysis carried out by us of 28 studies on treatment seeking behaviour showed that 307 of 315 458 respondents used such remedies. The overall percentage was 20%, but this value is misleading because the range varied widely from 0% to 75%. Many factors influence the use of traditional medicines to treat malaria (see box).[3]

Plant species

To date, 1277 plant species from 160 families used to treat malaria or fever have been listed on a database (figure). More studies are yet to be included in the

P+ *A more detailed description of the methods is on bmj.com*

database. Table 1 lists the number of species in each category of IVmal for 428 of the listed plants. Eight hundred and forty nine species were quoted only once in the studies consulted, therefore there is not enough information to generate a IVmal, but it must be 3 or less. Eleven species were used as antimalarials or antipyretics in all three tropical continents (table 2), and 47 species were similarly used in two continents. Most of the species (1213 plants) are not featured in the World Conservation Union's (IUCN) red list of threatened groups: of those that are, 5 were listed as "endangered," 13 were listed as "vulnerable," and 3 were listed as "near threatened."

Clinical safety and efficacy of herbal preparations

Eighteen case studies have reported on herbal antimalarials. Of cohort studies mentioning herbal treatments, 17 were for falciparum malaria, 12 for vivax malaria, and 5 for malaria of undefined species. Table 3 provides details of 10 controlled trials of herbal preparations for uncomplicated malaria.

Often studies provided limited information on the methods used to prepare the remedies, making it difficult to replicate them. In some cases, this was deliberate, to protect intellectual property rights.[4]

Few studies (3 case studies, 13 cohort studies, 4 controlled trials) provided data on side effects. It seems that in the other studies, patients were not questioned about adverse effects or new symptoms since starting treatment. None of the studies reported serious adverse effects. Only three of the cohort studies and three of the controlled trials reported effects on biochemical variables (most commonly liver function tests), and two studies monitored electrocardiograms. No cases of toxicity were reported. Minor side effects can, however, be important. For example, almost half of the patients taking the Ugandan herbal remedy "AM" experienced one or more minor side effects.[4] These were sufficiently unpleasant in some cases to deter patients from continuing treatment (for example, diarrhoea, bitter taste). Some herbal antimalarials have a bitter taste, making it difficult to give them to children. Doses often need to be taken repeatedly, and the volume may be larger than with conventional drugs.[5]

Six of the cohort studies on falciparum malaria reported 100% parasite clearance on days 4-7 after treatment, and a further three reported clearance rates above 90%. Follow up data beyond this time are available for only two of these nine studies, however, and only five of them studied more than 40 patients. One problem with cohort studies is that the trial population may be semi-immune to malaria and thus may clear parasites and resolve symptoms without effective treatment. High clearance rates may therefore not indicate efficacy. In highly endemic areas (as in much of sub-Saharan Africa), children aged over 5 years are considered to have a good immune response to malaria. In areas with high transmission of malaria, achieving complete parasite clearance for any length of time may not be realistic. In these circumstances, WHO recommends that adequate clinical response is a more useful measure of treatment efficacy. Such a response is defined as the absence of parasitaemia on day 14 or absence of fever (regardless of parasitaemia), without previously meeting the criteria for an early treatment failure.[6]

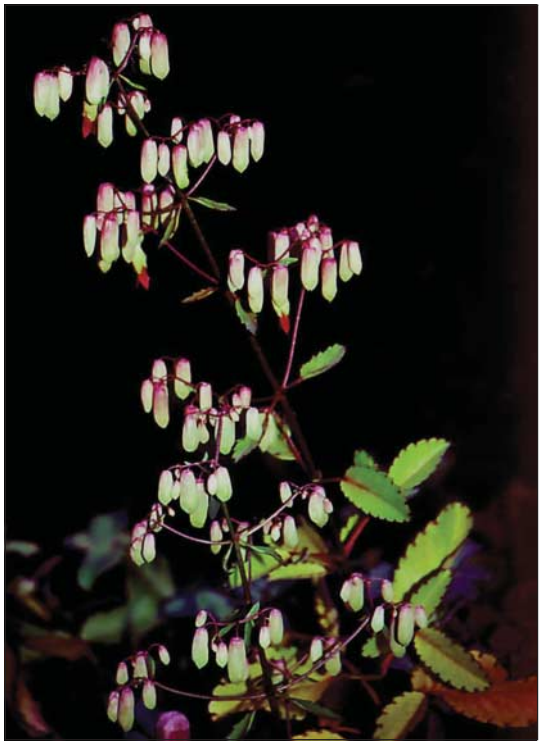
Some remedies may produce low rates of parasite clearance but higher rates of adequate clinical response. For example, in one study, parasitaemia declined to insignificant levels and patients were clini-

Table 2 Plant species used as antipyretics or antimalarials in three continents (importance value for treatment of malaria, 8)

Family	Species
Annonaceae	*Annona muricata*
Anacardiaceae	*Mangifera indica*
Crassulaceae	*Kalanchoe pinnata Lam*
Cucurbitaceae	*Momordica charantia*
Euphorbiaceae	*Jatropha curcas, Ricinus communis*
Fabaceae	*Senna occidentalis Link, Senna tora*
Malvaceae	*Sida rhombifolia*
Menispermaceae	*Cissampelos pareira*
Zingiberaceae	*Zingiber officinale Roscoe*

Influences on use of herbal antimalarials

- Study design
  Community compared with clinic (traditional or Western) setting
  Questions asked (open or closed, retrospective or prospective) and by whom (community member or healthcare staff)
- Definition of "malaria" or "fever"
- Factors involved in treatment seeking behaviours
  Perceived efficacy
  Availability of traditional and Western medicines
  Cost
  Location: urban or rural
  Age: adult or child



Leaf preparations of *Kalanchoe pinnata* are used to treat fever and malaria in Africa, Asia, and Latin America

Table 3 Trials of herbal medicines for uncomplicated malaria

Trial, setting	Study design	Species	Age of participants*	Treatment (No of participants)*	Parasite clearance*†	Symptoms*	Side effects
Boye 1989[12], Ghana	Open randomised controlled trial	*Plasmodium falciparum*	Not available	*Cryptolepis sanguinolenta* aqueous root extract (n=12); chloroquine (n=10)	Clearance time: 3.3 days; 2.2 days	Fever clearance time: 36 hours; 48 hours	Fewer in *C sanguinolenta* group
Mueller et al 2004[13], Democratic Republic of Congo	Open randomised controlled trial	*P falciparum*	≥18	*Artemisia annua* aqueous infusion 5 g/l (n=39); *A annua* aqueous infusion 9 g/l (n=33); quinine (n=43)	Day 7: 77%; 70%; 91%	Fever clearance on day 3: 91%; 81%; 92%	Fewer in *A annua* groups; tinnitus with quinine (27%)
Koita 1990[9], Guindo 1988[10], Mali	Open randomised controlled trial	*P falciparum*	5-45	"Malarial" (n=36); chloroquine (n=17)	Day 7: 58% <100; 92% <100	Fever clearance on day 7: 59%; 50%	Constipation (n=1); allergy (n=3)
Benoit-Vical 2003[14], Burkina Faso	Open randomised controlled trial	*P falciparum*	12-45	*Cochlospermum planchonii* root decoction (n=46); chloroquine (n=21)	Day 5: 52%; 57%	Not available; 100% fever clearance on day 5	Few, minor in both groups
Tsu 1947[11], China	Comparative study	*P falciparum* and *Plasmodium vivax*	Not available	*Dichroa febrifuga* root extract (n=12); placebo (n=8)	Day 7: 100%; 13%	Fever clearance on day 2: 92%; 13%	Abdominal pain, vomiting with *D febrifuga*
Yao-De et al 1992[15], China	Comparative study	*P vivax*	18-30	*Artemisia annua* capsules with oil (n=103); chloroquine (n=20)	Clearance time: 33 hours; 50 hours	Fever clearance time 18 hours; 24 hours	Not available for either treatment
CCRAS 1987[8], India	Double blind randomised controlled trial	*P vivax*	Not available	Ayush-64 (n=30); chloroquine and primaquine (n=28)	Not available	No significant difference between treatments	Not available for either treatment
			>12	Ayush-64 (n=58); chloroquine and primaquine (n=60)	Day 6: 95%; 100%	Improvements by day 6: 95%; 100%	Not available for either treatment
			>12	Ayush-64 (n=30); chloroquine and primaquine (n=30)	Day 6: 72%; 100%	Improvements by day 6: 72%; 100%	No effect on full blood count, liver function tests, or electrocardiogram; not available
Valecha et al 2000[5], India	Open randomised controlled trial	*P vivax*	18-60	Ayush-64 (n=54); chloroquine (n=50)	Day 28: 49%; 100%	Slow recovery; fast recovery	No effect on full blood count or biochemical variables, gastrointestinal effects (n=3); not available

CCRAS=Central Council for Research in Ayurveda and Sidhha.
*Entries between semicolons refer to different groups of patients receiving different treatments. Order of groups is same in each column.
†Percentage of patients clear of parasites by specified day.

cally cured after treatment with a decoction of *Terraplis interretis*.[7] In another study, the Ugandan herbal remedy "AM" cleared parasites in only 8% of patients, but parasitaemia declined to lower levels, and 55% of patients had an adequate clinical response.[4]

Not all of the 10 controlled trials were randomised or double blind (table 3). Four trials of the Ayurvedic remedy Ayush-64 to treat vivax malaria were reported to be double blind because both the herbal preparation and the comparator drug were provided in identical capsules.[5–8] Patients randomised to receive either herbal decoctions or chloroquine tablets cannot be blinded, but laboratory technicians who count the parasites can be, and in one trial they were blinded.[9–10] Blinding was not reported for the other trials. One early trial was placebo controlled,[11] which would now be considered unethical.

An aqueous root extract of *Cryptolepis sanguinolenta* shows promise in the treatment of falciparum malaria.[12] Parasite clearance was only one day longer with this remedy than with chloroquine, and the clearance of fever was faster by 12 hours. A larger trial is needed to confirm these results, however, as the number of patients was small. In another trial comparing the treatment of falciparum malaria with quinine or with infusions of *Artemisia annua,* the infusions resulted in good parasite clearance at day 7.[13] A high proportion of patients experienced a recrudescence, however, so that by day 28 only 37% of those treated with *Artemisia annua* were still free of parasites compared with 86% of patients treated with quinine. This emphasises the need for a follow up period of at least 28 days. Nevertheless, adequate clinical response, which is more important than parasite clearance in endemic areas,[6] was not reported in this trial. In the trial of the herbal remedy "Malarial" (Suma-Kala), parasites were not cleared completely, but there was a good clinical response, which was sustained for the three weeks of follow up.[9 10] In the trial of *Cochlospermum tinctorium*, patients were only followed for five days, and clinical outcomes were not used, so it is not possible to comment on long term efficacy.[14]

Five of the 10 controlled trials only studied vivax malaria, four of which concerned the herbal remedy "Ayush-64."[5 8] Initial parasite clearance with Ayush-64 was good, but many patients relapsed by day 28. Another trial showed that oil based capsules of *Artemisia annua* cleared parasites and fever more rapidly than did chloroquine, and by day 30 only 8% of those given a course of capsules for six days showed recrudescence.[15]

Future research

Although traditional medicine is widely used to treat malaria, and is often more available and affordable than Western medicine, it is not without limitations. Firstly, there are few clinical data on safety and efficacy. Secondly, there is no consensus, even among traditional healers, on which plants, preparations, and dosages are the most effective. Thirdly, the concentration of active ingredients in a plant species varies considerably, depending on several factors.

None the less, these limitations are all remediable, through research. The Research Initiative on Traditional Antimalarial Methods has written systematic reviews, some of which have been summarised here, and guidelines aiming to standardise and improve the quality of future research.[3] These reviews and guidelines are far from complete. They should be seen

Additional educational resources

Willcox ML, Bodeker G, Rasoanaivo P. *Traditional medicinal plants and malaria*. Boca Raton: CRC, 2004—book contains detailed systematic reviews and guidelines for further studies in malaria control

The Research Initiative on Traditional Antimalarial Methods (www.who.int/tdr/publications/publications/ritam.htm)—features a report of the inaugural meeting of RITAM

World Health Organization Essential Drugs and Medicine Policy (www.who.int/medicines/organization/trm/orgtrmmain.shtml)—details WHO Traditional Medicine Strategy 2002-5

as a springboard for further research rather than a definitive product.

The IVmal system is one way of prioritising plant species for future research. Plants that are used to treat malaria in several different areas are more likely to be effective.[2] There are some drawbacks though. Plants may be prepared in many ways; so it might be more useful to discuss the IVmal of a particular remedy rather than of a plant species. The IVmal is also limited by the geographical distribution of plants and by the extent of ethnobotanical studies. In many areas no ethnobotanical study has been undertaken, and research in these areas is a priority. Traditional medicines are being forgotten with the death of healers who have no successors to their knowledge.

Clinical observations on traditional remedies are feasible and useful. Some herbal remedies may be safe and effective for the treatment of malaria, as shown by the studies reviewed here. Nevertheless, better evidence from randomised clinical trials is needed before herbal remedies can be recommended on a large scale. As such trials are expensive and time consuming, it is important to prioritise remedies for clinical investigation according to existing data from sociological, ethnobotanical, pharmacological, and preliminary clinical observational studies. In remote settings with poor resources where modern antimalarials are not steadily available, research can provide an evidence base for traditional medicine, to inform local treatment choices.

Preventing children's deaths is the key objective of any malaria control programme. Once a remedy has been shown to be safe and effective for uncomplicated malaria in adults, studies on mortality in children would be the necessary next step. It has already been shown that mortality can be reduced in the under 5s by training mothers to recognise malaria and to give early treatment.[16]

The evidence summarised in this article, together with the guidelines proposed, should not only assist researchers already working in this specialty but also inspire other researchers and funding bodies to give serious consideration to the potential of traditional remedies for malaria.

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Corrections and clarifications

UK legislation on analgesic packs: before and after study of long term effect on poisonings
A word was inadvertently deleted from table 1 during the authors' final revision of this Primary Care paper by Keith Hawton and colleagues, and this deletion may have confused readers (6 November, pp 1076-9). The first two column headings suggested that the numbers cited were totals for each of the four year groups, whereas in fact they were annual rates. The headings should therefore read: "Annual mortality before legislation" and "Annual mortality after legislation."

Early contact with patients is beneficial
The title and content of this summary for This Week in the BMJ, reporting on the Learning in Practice article by Tim Dornan and Chris Bundy ("What can experience add to early medical education? Consensus survey") in the same issue (9 October, pp 834-7) may have misled readers about the message of the article. A better title would have been "Students favour early clinical contact with patients." The summary should have made clear that the medical students interviewed in the study had not had early experience with patients and that the staff were being interviewed about how they felt early experience might affect the course. There was no evidence that early contact could generate, for example, motivation and confidence as it was a speculative qualitative study.