TRADITIONAL MEDICINAL PLANTS FOR THE TREATMENT AND PREVENTION OF HUMAN PARASITIC DISEASES

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Contents:

Summary

Parasitic diseases are among the most prevalent infections worldwide. Humans have learned to use plants to treat parasitic diseases, and in the last century modern medicine has developed pure compounds from plants into pharmaceutical drugs. Nevertheless, use of traditional medicine continues, for social, cultural, medical and financial reasons, but remains under-researched. Ethnopharmacological research has brought to light

many plants with anti-parasitic properties, and often these plants contain several compounds which contribute together to this activity. Few clinical trials of herbal preparations have been carried out, but in some cases have demonstrated efficacy. Some plants also have insecticidal or molluscicidal properties, or interfere in some way with the vectors or intermediate hosts of parasitic diseases and can be used to control them or reduce transmission to humans.

1. Introduction

Unlike humans and other animals, plants do not have a specific immune system. They depend on a cocktail of chemicals to defend them from parasites and predators. Parasites attacking plants have similar biochemical pathways to those attacking humans, therefore many of the substances utilized by plants in their defense may be of use to humans in the treatment of their own parasitic diseases. Indeed human beings and other primates have, as a requirement for survival, learnt to use plants as medicines, and until the last two centuries, plants were the mainstay of all medical systems. Furthermore, many plants produce chemical defenses against arthropods and molluscs, which can be of use in the control of the vectors of parasitic diseases.

Human parasitic diseases can be classified into two principal groups: those caused by protozoa (single-celled organisms) and those caused by helminths (worms). Although helminths are probably the most widespread of human parasites, most are relatively benign, and treatable with relatively straightforward regimens of modern drugs. Of course traditional medicines are still used, and are valuable especially for those who do not have access to such drugs. However, the most lethal parasitic diseases, to which modern medicine has yet to find optimal treatments, are blood and tissue protozoa, namely malaria, the trypanosomiases and the leishmaniases. For this reason, this chapter will concentrate on these parasitic diseases.

2. Protozoa

2.1. Blood protozoa

2.1.1 Malaria

2.1.1.1 Importance of traditional medicine in treatment of malaria

In modern medical terms, malaria is defined as an infection caused by parasites of red blood cells, of the genus *Plasmodium*. There are four main species of Plasmodia which infect humans (via anopheline mosquitoes): *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. Of these, only *P. falciparum* causes severe and potentially fatal malaria. *P. vivax* and *P. ovale* cause self-limiting febrile illnesses, but both can become dormant in the liver and re-activate after a few months or even years. The most important species globally are *P. falciparum* and *P. vivax*.

The symptoms of malaria are similar to those of many other infections: fever, headache, nausea, vomiting, joint pains, and even sometimes cough or diarrhoea. Therefore it is

difficult to distinguish malaria from other infections (such as influenza) without doing a blood test to check for the presence and quantity of malaria parasites.

It is estimated that malaria causes 300 million episodes of illness every year, and over one million deaths, 90% of these in Sub-Saharan Africa. Although modern medicine has been successful at treating malaria, *P. falciparum* has evolved resistance to many of the first-line drugs, such as chloroquine and sulphadoxine-pyrimethamine. The most resistant parasites have evolved in the Burmese refugee camps on the Thai-Burma border. Although effective drugs exist to kill these resistant parasites, they are not readily available or affordable in many developing countries. The scientific malaria community is now arguing for the use of artemisinin combinations as first line treatment for malaria, to counteract growing drug resistance, but these will cost at least US $1 to 2 per course, which is more than can be afforded in many countries.

Malaria is not just a disease of poor countries; it is a disease of the poorest people in poor countries, which often strikes at the hardest times. Fifty-eight percent of malaria deaths occur in the poorest 20% of the population. In Brazil, 99% of malaria cases are transmitted in the Amazon region, where the population consists mainly of tribal people and poor immigrants from other areas. Furthermore, malaria often strikes in the season when conditions for the poor are the most difficult. In the highlands of Madagascar, the malaria season occurs just before the rice harvest, when local small farmers have no money left from the previous harvest, and food supplies are at their lowest. For patients from remote areas seeking modern health-care facilities, transport is difficult at the best of times; but in the rainy season, when malaria strikes, it can become almost impossible.

In these conditions, it is not surprising that under 20% of febrile episodes and deaths due to malaria come to the attention of any formal health system. Many of these patients use traditional medicines. At present, an average of 42% of febrile African children under five are treated with an antimalarial drug, and 80% of these with chloroquine, which has become largely ineffective. Even when antimalarial drugs are used, the dosage is incorrect in most cases.

Thus traditional medicine is already an important treatment option for many patients. History has proven traditional medicine to be the surest source of effective antimalarials. *Cinchona* spp (Rubiaceae) and *Artemisia annua* L. (Asteraceae) have provided the basis for two of the three main classes of antimalarials and, as recorded below, the antimalarial activity of lapachol from *Tabebuia* spp (Bignoniaceae) led to the development of atovaquone. There is evidence that many other plants contain useful antimalarial agents. Herbal remedies have several potential advantages, perhaps most importantly, that they are readily available and affordable. Patients, even in the remotest areas, could be empowered to prepare and administer effective herbal antimalarials, thus freeing them from dependency on unreliable supplies of modern medicine from the outside world.

Traditional medicine is not without its own limitations. Firstly, there is little clinical data on safety and efficacy. Secondly, the concentration of active ingredients in a given plant species varies considerably, depending on a number of factors. Thirdly, there is no consensus, even among traditional healers, on which plants, preparations and dosages

are the most effective. However these limitations are all remediable, through research. The Research Initiative on Traditional Antimalarial Methods (RITAM) was formed in 1999 by the Global Initiative For Traditional Systems (GIFTS) of Health at Oxford University, with the aims of promoting and facilitating such research. RITAM has produced systematic literature reviews and guidelines for further studies on herbal antimalarials. Unfortunately there is still little interest in traditional medicine from large funding organizations.

2.1.1.2 Important plant species and their active ingredients

2.1.1.2.1 Ethnobotanical studies

RITAM is constructing a database of ethnobotanical studies of herbal antimalarials. Ninety-four original ethnobotanical publications have been included to date, conducted in 33 tropical countries. Overall, 1277 plant species from 160 families have been reported for the treatment of malaria or fever. This data set is still incomplete, as there are many more studies which have yet to be included in the database.

Plant species were assigned an "Important Value for the treatment of Malaria" ("IVmal"), according to how widely they are used for the treatment of malaria. The number of species in each category of "IVmal", as well as definitions of "IVmal", are given in Table 1. Of the listed species, 849 were quoted by only a single study, which did not give enough information for an "IVmal" to be attributed, but by definition the IVmal cannot be greater than 3 if the plant is quoted in only a single study. There were 11 species used as antimalarials and/or antipyretics in all three tropical continents ("IVmal" = 8; see Table 2), and 47 used in two continents. The vast majority (1213) of the species were not recorded in the IUCN Red Data Book. However five species were listed as "endangered", 13 as "vulnerable", and three as "near threatened".

IVmal	No species	Definition
?	849	Insufficient data
1	95	reported once in a single ethnobotanical survey
2	30	reported twice in one community
3	6	reported at least three times in one community
4	42	reported in more than one community
5	91	reported in more than one survey, in the same country
6	106	reported in more than one country, in the same continent
7	47	reported in two continents
8	11	reported in three continents

Table 1. Number of species according to "IVmal".

Family	Species
Annonaceae	*Annona muricata* L
Anacardiaceae	*Mangifera indica* L.
Crassulaceae	*Kalanchoe* (= *Bryophyllum*) *pinnata* Lam
Cucurbitaceae	*Momordica charantia* L
Euphorbiaceae	*Jatropha curcas* L

Family	Species
	Ricinus communis L
Leguminosae	*Senna (=Cassia) occidentalis* (L) Link
	Senna (=Cassia) tora L
Malvaceae	*Sida rhombifolia* L
Menispermaceae	*Cissampelos pareira* L
Zingiberaceae	*Zingiber officinale* Roscoe

Table 2. Species used for fevers and/or malaria in three continents (IVmal = 8).

2.1.1.2.2 Pharmacological studies

Many of the plant species used as antimalarials in traditional medicine have been subjected to laboratory investigations in an attempt to provide evidence to support their clinical use. Often, these studies have been limited to determining the activities of crude extracts of the plants against malaria parasites *in vitro* and/or *in vivo* although in many cases the compounds responsible for the antiplasmodial effects have been isolated, identified and assessed for their antimalarial activities.

The bark of trees belonging to the genus *Cinchona,* native to South America, has been used to provide effective treatment for malaria for over three hundred years. Quinine, a quinoline alkaloid is the major antimalarial compound present in *Cinchona* although some other constituents including cinchonidine, cinchonine, and quinidine, also have antimalarial properties. Using the quinine molecule as a template, a number of synthetic quinoline antimalarials such as chloroquine have been developed. The quinoline antimalarials appear to act by binding to free haem released following the digestion of haemoglobin thus preventing its conversion to haemozoin (β-haematin). The drug-haem complex is believed to be toxic to the malaria parasite.

A decoction of the roots of the West African climbing shrub *Cryptolepis sanguinolenta* (Lindl.) Schltr. (Asclepiadaceae / Periplocaceae), is used in traditional medicine to treat malaria. A number of indoloquinoline alkaloids are present in this species of which cryptolepine is the major one. Cryptolepine has potent *in vitro* antiplasmodial activity against both chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum*, but it is also moderately cytotoxic. Cytotoxicity is associated with the ability of the alkaloid to intercalate into DNA and inhibit topoisomerase II, as well as DNA synthesis.

For well over a millenium, the Chinese herb Qing Hao (*Artemisia annua*) has been used traditionally in China for the treatment of fevers but it was only in the late 1960s that Chinese researchers discovered that ether extracts of *A. annua* cured malaria in mice. The active principle, artemisinin, isolated in 1972, is a remarkable compound by virtue of its unusual chemical structure and its potent and rapid antimalarial activity against multidrug-resistant malaria parasites. Artemisinin is a sesquiterpene lactone containing an endoperoxide group which bridges an oxygen-containing 7-membered ring. Looking at the structure it can be seen that the two oxygens of the peroxide group and the oxygen of the 7-membered ring are present in a 6-membered, 1,2,4-trioxane ring, so that artemisinin and its derivatives are often referred to as "trioxane" antimalarials. In contrast to the antimalarials of the quinine group, which, being alkaloids contain

nitrogen and are basic, artemisinin is a neutral, non-polar compound with a totally different type of structure, and it is therefore not surprising that it has a unique mode of action against malaria parasites. There is now considerable experimental evidence which suggests that the antiplasmodial effects of artemisinin and also those of its derivatives are due to a two step process. In the first, the interaction of artemisinin with haem, the residue remaining following the digestion of haemoglobin by the malaria parasite, gives rise to highly reactive free radicals. The second step involves the reaction of the artemisinin-derived free radicals with parasite molecules, thus disrupting normal metabolic processes and ending in parasite death.

Species of the Simaroubaceae have been used in traditional medicines for the treatment of protozoal diseases (malaria, amoebic dysentery) in Asia and Africa as well as in South and Central America. Their antimalarial activity is mainly due to the presence of quassinoids, a group of oxygenated terpenoids related to quassin, the first member of the group to be characterized, although quassin itself has no antimalarial activity. Alkaloids are also present in the Simaroubaceae but they are less active against malaria parasites than the quassinoids. Species investigated included *Brucea javanica* (L.) Merr. known as Yadanzi in China, *Eurycoma longifolia* Jack (Malaysia), *Ailanthus altissima* (Mill.) Swingle (India), *Simarouba amara* Aubl. (C. & S. America), *Simaba guianensis* Aubl.(S. America) and *Picramnia antidesma* Sw.(C. America) and this led to the isolation of 40 individual quassinoids. Ten of these were found to be 10-fold more active against multi-drug resistant *P. falciparum* (strain K1) than chloroquine diphosphate. Another factor that may be important is the presence in herbal teas of other compounds that may act additively or synergistically with quassinoids. At least some of the Simaroubaceae species used traditionally to treat malaria contain β-carboline alkaloids that have some activity against *P. falciparum*; although this is less than that of chloroquine, it is possible that some synergism could occur.

Lapachol is a naphthaquinone found in the heartwood of South American species of the family Bignoniaceae that have been used traditionally in Brazil for the treatment of malaria and fevers. While lapachol itself was only weakly active *in vitro* against *P. falciparum*, the related derivative lapinone was shown to cure *P. vivax* malaria in man. The improved activity of lapinone compared to some other naphthoquinones has been attributed to higher potency and increased resistance to metabolic degradation, as it has been shown that terminal oxidation of the naphthoquinone hydrocarbon side chain leads to loss of activity. Unfortunately, although lapinone was highly potent when given by parenteral administration it had poor oral activity. The synthesis of naphthoquinone derivatives as potential antimalarial agents began in the 1940s and more recent work in the 1980s led to the development of atovaquone, now used clinically in combination with proguanil (as Malarone).

The powdered roots of *Dichroa febrifuga* Lour. (Saxifragaceae), known in China as Changshan, have been used traditionally for malaria treatment for many centuries. *D. febrifuga* contains quinazolone alkaloids and the compound febrifugine has been shown to have potent *in vitro* activities against both chloroquine-sensitive and chloroquine-resistant malaria parasites. In humans, oral or parenteral treatment with the plant extract have been reported to be effective for malaria treatment but nausea and vomiting

occurred in some patients. Interestingly, the original Chinese formulation also included anti-emetic plants such as ginger and liquorice.

2.1.1.2.3 Clinical safety and efficacy

Compared to conventional antimalarial drugs, there has been very little clinical research on herbal antimalarials. A systematic review has identified eighteen case reports (falciparum in 14 of these cases), 34 cohort studies (17 falciparum, 12 vivax, 5 undefined), and 10 controlled trials (4 falciparum, 6 vivax). There was often limited information about the method of preparation of the remedies, which would make them very difficult to replicate. In some cases, this is a deliberate intention of the authors, in order to protect intellectual property rights.

Few studies reported data on side effects of the herbal medicines. No cases of toxicity were reported. However, minor side effects can be important, if they are unpleasant enough to cause patients to stop taking the treatment. Some herbal antimalarials have a bitter taste, which can make them difficult to administer to children. Doses often need to be taken more frequently, and the volume to ingest is often larger than with conventional drugs.

Of the 17 cohort studies on falciparum malaria, six reported 100% parasite clearance on days 4-7, and a further three reported parasite clearance rates above 90%. However, follow-up data beyond day 7 are only available for two of these nine studies. One problem with cohort studies is that the population chosen may be semi-immune to malaria, and may clear parasites and symptoms even without effective treatment. Therefore high parasite clearance rates are not necessarily indicative of efficacy. In highly endemic areas (as in much of sub-saharan Africa) children are considered to have a good immune response to malaria above the age of 5. 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 (ACR) is a more useful measure of treatment efficacy. ACR is defined as absence of parasitaemia on day 14, or absence of fever (regardless of parasitaemia), without previously meeting the criteria for an "early treatment failure".

Some remedies may produce low rates of parasite clearance, but higher rates of ACR. For example, parasitaemia declined to very low levels, and patients were clinically cured after treatment with a decoction of *Terraplis interretis*. The Ugandan "AM" remedy cleared parasites in only 8% of patients, but parasitaemia declined to lower levels, and 55% of patients had an adequate clinical response.

Of the ten controlled trials, not all were randomized or double-blind. Four trials of "Ayush-64" (see below) in vivax malaria were reported to be double-blind, as both the herbal medicine and the drug were administered in identical capsules. When patients are randomized to receive either a traditional herbal decoction or modern tablets, they cannot be blinded; but the laboratory technicians performing the parasite counts can be and in one trial were blinded. Blinding is not reported for the other trials. Only one early trial was placebo-controlled, and this would now be considered unethical.

Of the trials for falciparum malaria, the most promising is that of *Cryptolepis sanguinolenta*, in which parasite clearance took only one day longer than with chloroquine, and in which fever clearance was 12 hours faster. Also of interest is a trial of *Artemisia annua* infusions compared to quinine. The parasite clearance was good at day 7, and significantly better than with chloroquine (in the context of high levels of resistance). However, a significant proportion of patients experienced a recrudescence, so that by day 28 only 37% of patients treated with *A. annua* were still free of parasites (compared to 86% in the quinine group). This emphasizes the need for follow-up lasting at least 28 days. However, clinical outcome measures are more important than parasite clearance in endemic areas, and were not reported in this trial. In the case of "Malarial", parasites were not cleared completely by the herbal medicine, but there was a good clinical response, which was sustained for the three weeks of follow-up. In a trial of *Cochlospermum tinctorium* A. Rich (Cochlospermaceae), patients were only followed for 5 days, and clinical criteria were not used, so it is not possible to comment about the long-term efficacy of this remedy.

Five of the trials were on vivax malaria, and four of these concerned the Ayurvedic remedy "Ayush-64". This is a mixture of four herbs: *Picrorrhiza kurroa* Royale ex Benth (Scrophulariaceae), *Alstonia scholaris* R. Br. (Apocyanaceae), *Swertia chirata* Ham (Gentianaceae), and *Caesalpinia bonducella* Fleming (Caesalpiniaceae). The initial parasite clearance observed was good, but many of the patients relapsed by day 28. In the fifth trial, oil-based *Artemisia annua* capsules cleared parasites and fever more rapidly than chloroquine, and the recrudescence rate by day 30 was only 8% in those given a 6-day course of capsules.

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Biographical Sketches

Merlin Willcox is a General Medical Practitioner based in Great Britain. He graduated from the University of Oxford in 1998 and is a Member of the Royal College of General Practitioners. He also holds the Diploma in Tropical Medicine and Hygiene from the Liverpool School of Tropical Medicine, and is a fellow of the Royal Society of Tropical Medicine and Hygiene. He has conducted clinical research on herbal antimalarials in Uganda, Madagascar and Mali. He was one of the founders of the Research Initiative on Traditional Antimalarial Methods (RITAM), an electronic network of researchers working in this area. Through RITAM, he has written systematic reviews of research on herbal antimalarials, and guidelines to improve and standardize the quality of such studies in the future. These were published in a book which he co-edited with Prof Gerard Bodeker and Prof Philippe Rasoanaivo, entitled "Traditional Medicinal Plants and Malaria" (2004, CRC Press).

Benjamin Gilbert, chemist, BSc, 1950 and PhD, 1954 at the University of Bristol, UK, the latter under the direction of Wilson Baker and W. David Ollis covering work on large ring compounds and then some synthetic work on a natural product. Post-doctoral study under Carl Djerassi, at Wayne State University, Detroit, Michigan, again with a natural insecticide, led in 1958 to a post as a Research Associate of Stanford University in Rio de Janeiro in collaboration with Walter Mors, a pioneer in the chemistry of

pharmacologically active Brazilian plants both medicinal and insecticidal. This in turn led to participation in a National Research Council effort to find new solutions for the control of endemic diseases which continued through the 1960s and 1970s and culminated in 1980 in a major Ministry of Health effort to create a Brazilian pharmaceutical industry based on raw materials produced within the country. Dr. Gilbert now remains in the central Ministry of Health R&D Institution, the Oswaldo Cruz Foundation in Rio de Janeiro, with the task of applying Brazilian biodiversity to national health problems both medicinally and in vector control.