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Plant derived antimalarial agents: New leads and challenges

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Abstract

New treatments for malaria are urgently needed due to the increasing problem of drug-resistance in malaria parasites. The long-established use of quinine and the more recent introduction of artemisinin and its derivatives as highly effective antimalarials demonstrates that plant species are an important resource for the discovery of new antimalarial agents. Furthermore, many plant species continue to be used in traditional medicines for the treatment of malaria and many people depend on such remedies as they cannot afford and/or do not have access to effective antimalarial drugs. In this paper the potential of plant species to yield new leads to antimalarial drugs will be illustrated with reference to cryptolepine, the main alkaloid present in the species, *Cryptolepis sanguinolenta*. In addition to this approach, there is currently increasing interest in the use and development of traditional herbal remedies for the treatment of malaria as these may have the potential to provide affordable antimalarial treatment for many who cannot afford the drugs needed to treat chloroquine-resistant *Plasmodium falciparum* infections. However, little is known with respect to the efficacy and safety of traditional antimalarials and clinical studies are urgently needed to establish their value. Some of the issues pertinent to this area will be briefly reviewed and it is hoped that this will stimulate further discussion and research on this important topic.

Introduction

It is estimated that malaria is directly responsible for the deaths of 1–2 million people each year (Bradley, 1995), and in addition, the disease contributes to an unknown number of other deaths as a result of malaria-related anaemia. The majority of malaria deaths are due to cerebral malaria and other complications following infection with *P. falciparum* that is transmitted by female mosquitoes of the genus *Anopheles*. Most of the deaths occur in Africa and in children under the age of 5 years (Winstanley, 2000). Undoubtedly, the situation has become steadily worse in the last 30 years, and a major factor responsible has been the increasing prevalence of *P. falciparum* resistant to chloroquine and to other antimalarial agents. Studies in a number of African countries have shown that the emergence of chloroquine-resistant malaria parasites is associated with a two-fold increase in malaria deaths but in one study in Mlomp, Senegal it was shown that malaria mortality in children under the age of 4 years increased 11-fold within 6 years of the emergence of chloroquine-resistance (Trape et al., 2002).

In 1972, Chinese scientists isolated artemisinin (Figure 1), an unusual endoperoxide sesquiterpene lactone as the active principle from *Artemisia annua* (Asteraceae) and it was quickly shown to be a rapidly acting antimalarial drug effective against chloroquine (and other drug) resistant parasites and as good as quinine (but less toxic) for the treatment of cerebral malaria (Klayman, 1985). As artemisinin is a non-polar compound, derivatives including ethers (artemether, arteether) and esters (sodium artesunate, sodium artelinate) were

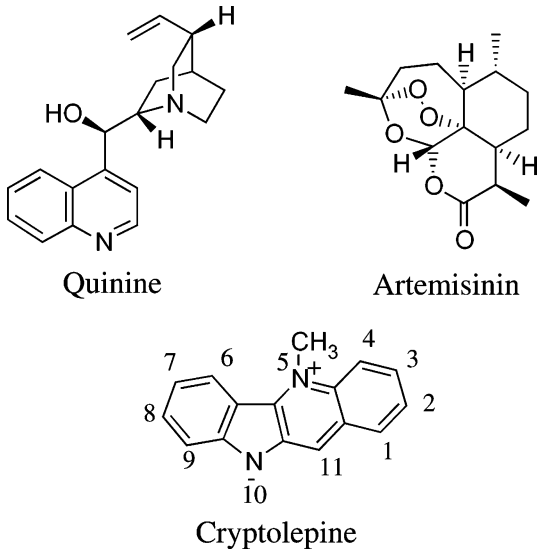


Figure 1. Structures of some antimalarial natural products.

prepared to improve its formulation characteristics and these are now increasingly used as an alternative to quinine (Wilairatana and Looareesuwan, 2002). The development of the artemisinin derivatives has been a major advance in the chemotherapy of malaria. However, although these agents are highly effective, of low toxicity and have even been shown to reduce malaria transmission on account of their effects on the gametocyte (mosquito infective) stages of the parasite (Price et al., 1996), the artemisinin derivatives do have limitations.

The first of these is the problem of recrudescence where drug treatment initially appears to clear all the parasites from the blood but, after a few weeks parasites re-appear and the disease recurs. Recrudescence is not due to drug resistance or re-infection of the patient but occurs because the drug has failed to kill *all* of the parasites and those that survive continue to multiply, so that after a few weeks the patient again experiences malaria symptoms. This problem may be related to the relatively short half lives of the commonly used artemisinin derivatives and the insensitivity of the early blood stage forms of the malaria parasite to these drugs (Wright and Warhurst, 2002). To overcome this problem longer courses of treatment may be given or, preferably, as recommended by the World Health Organisation, treatment with an artemisinin derivative should be followed by a dose of a second antimalarial to clear any remaining parasites (Wilairatana and Looareesuwan, 2002). The second and perhaps more important limitation is that compared to chloroquine, the artemisinin derivatives are expensive and out of the reach of many of those who suffer from malaria especially if treatment has to be followed by a second drug. The rise in malaria mortality and morbidity as a result of chloroquine-resistant malaria parasites coupled with poverty in Africa means that there continues to be an increasingly urgent need for effective and affordable antimalarial therapies. Even if the artemisinin derivatives could be made available to all those that need them, the possibility of the future development of malaria parasites resistant to these drugs must be borne in mind.

Plant-derived antimalarials have made and continue to make an immense contribution to malaria chemotherapy and it is the purpose of this review to consider the future potential of plants to provide new antimalarial treatments. Two different approaches to the development of new medicines for malaria will be considered: In the first an example of the potential of plants to yield novel compounds that can be investigated as leads to new drugs will be discussed, while the second will explore some of the issues with respect to the use of traditional herbal medicines for the treatment of malaria.

Leads to new antimalarial drugs

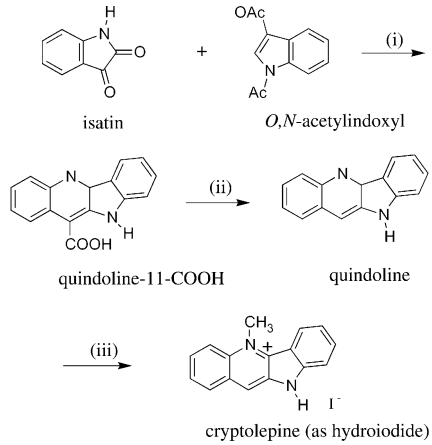
The importance of quinine (and of synthetic drugs derived from quinine such as chloroquine and mefloquine), and more recently of artemisinin and its semi-synthetic derivatives as plant-derived antimalarials (Figure 1), has encouraged the continuing search for new natural product-derived antimalarials. Many plant extracts, especially those from species with a reputation for use in traditional medicines have been evaluated in the laboratory for *in vitro* antiplasmodial activities and some have also been tested *in vivo*, usually in mice infected with *P. berghei* or *P. yoelii* (for reviews see del Rayo Camacho Corona et al., 2000; Schwikkard and van Heerden, 2002). In some cases, the constituent(s) responsible for their activities have been isolated and their structures elucidated but relatively few have been studied

further to assess their potential as lead compounds for the development of new antimalarial drugs. One example of a plant compound that is currently of interest as a potential lead compound is the alkaloid cryptolepine, a constituent of *C. sanguinolenta*.

Cryptolepine – a lead to new antimalarial agents?

A decoction of the roots of the climbing shrub *C. sanguinolenta* is used in West Africa for the treatment of malaria (Boye and Ampofo, 1983). The plant contains a number of indoloquinoline alkaloids of which cryptolepine (Figure 1), is the major constituent and also the compound possessing the most potent antiplasmodial activity (Cimanga et al., 1997). Cryptolepine is present in relatively large amounts in the roots of *C. sanguinolenta* (>1% of the dried roots), and it has potent *in vitro* activities against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* (Wright et al., 2001). The synthesis of cryptolepine is straightforward and was in fact accomplished before the alkaloid was isolated from natural sources (Fichter and Boehringer, 1906), thus giving potential for the preparation of cryptolepine analogues for assessment as antimalarials. These features would suggest that cryptolepine may be a viable lead compound, but this alkaloid unfortunately has other less promising attributes. When tested in several cancer cell lines cryptolepine was found to be moderately toxic and subsequent investigations showed that this is due to the DNA intercalating and topoisomerase II inhibiting properties of the drug (Bonjean et al., 1998). In addition, cryptolepine has been shown to inhibit DNA synthesis (Bonjean et al., 1998) and is toxic to mice when given by I.P. injection (Wright et al., 2001). Although oral doses of cryptolepine did not appear to be toxic to mice infected with *P. berghei*, treatment with 50 mg kg^{-1} day^{-1} failed to cure the malaria infection although parasitaemia was reduced by 80% compared to control animals (Wright et al., 1996). These results indicated that cryptolepine is toxic and suggest that its oral bioavailability may be poor, properties that might preclude its consideration as a lead antimalarial agent. However, further experiments showed that, like chloroquine, cryptolepine inhibited the formation of β-haematin in a cell-free system (Wright et al., 2001). Quinoline antimalarials such as chloroquine are believed to act by binding to haem, the residue left behind following the digestion of haemoglobin by malaria parasites infecting red blood cells (Egan et al., 1994). Haem is toxic to the parasite but it is detoxified by conversion into malaria pigment (also known as haemozoin), and this has been shown to be identical to β-haematin (Bohle et al., 1997). This finding raised the possibility that the antimalarial mode of action of cryptolepine may be different from its cytotoxic mechanism of action, thus it was decided to prepare analogues of cryptolepine in an attempt to retain or enhance the antiplasmodial activity and reduce cytotoxicity. It was hoped that by substituting atoms or groups into the molecule that the intercalating ability of the molecule would be attenuated. Several routes are available for the synthesis of cryptolepine analogues but the one mainly employed in the author's laboratory was that based on the synthesis of quindoline (Holt and Petrow, 1947) in which isatin is condensed with *O*, *N*-diacetylindoxyl in the presence of alkali in oxygen-free conditions and the resulting quindoline-11-carboxylic acid is decarboxylated by heating in diphenylether to yield quindoline (Scheme 1). Cryptolepine is then prepared by methylating quindoline with iodomethane using sulpholane as a solvent. By using substituted *O*, *N*-diacetylindoxyl and/or isatin derivatives as starting materials a wide range of cryptolepine analogues may be easily prepared although some

Scheme 1[a]. Synthesis of cryptolepine.



[a] Reagents and conditions: (i) KOH, N_2, reflux 4 h; (ii) Ph_2O, 250 °C; (iii) CH_3I, tetramethylene sulphone, 50 °C, 12 h.

strongly electron withdrawing substituents such as nitro groups inhibit the first step in the synthesis.

As a result of testing a series of cryptolepine analogues against *P. falciparum* (multi-drug resistant strain K1) *in vitro* it was found that both the 2- and 7-bromocryptolepine derivatives were two-fold more potent than the parent and this prompted the synthesis of 2,7-dibromocryptolepine. The latter was found to be nearly 10-fold more active against *P. falciparum* than cryptolepine (IC_{50} values 0.049 and 0.44, respectively). Furthermore, tests on a series of analogues against chloroquine-sensitive (strain HB3) and chloroquine-resistant (strain K1) *P. falciparum* showed that there was no cross-resistance with chloroquine (Wright et al., 2001). A number of compounds were then tested in mice infected with *P. berghei* using Peters' 4-day suppressive test (Peters et al., 1975). The 2-bromo- and 7-bromo-analogues (at doses of 25 and 20 mg Kg day^{-1}, respectively) suppressed parasitaemia in the mice by 6 and 42%, respectively, compared to untreated infected controls, but 2,7-dibromocryptolepine (at a dose of 12.5 mg Kg day^{-1}) gave 89% suppression, thus correlating with the enhanced activity seen *in vitro*. Importantly, no toxic effects were seen in the mice but cryptolepine itself was toxic (Wright et al., 2001). Interestingly, not all dihalogenated analogues exhibited increased activities compared to the monosubstituted compounds; for example, 11-chlorocryptolepine was 2-fold more potent than cryptolepine against *P. falciparum in vitro* but 2-bromo, 11-chlorocryptolepine was 10-fold less active than the parent. Although, the 2-bromo-, 7-bromo-, and 2,7-dibromo-analogues were not toxic to the mice, they were not less cytotoxic than cryptolepine but they did appear to be less able to intercalate into DNA as shown by measurements of their effects on the melting point of calf-thymus DNA. Their ΔTm values were 4, 4 and 3 °C, respectively, while the ΔTm value for cryptolepine was 9 °C (Wright et al., 2001). The enhancement of both *in vitro* and *in vivo* antimalarial activities by 7-bromo- substitution has been confirmed by the synthesis of several analogues including 2-chloro, 7-bromo- and 2-bromo, 7-nitrocryptolepine and these compounds show potent *in vitro* antiplasmodial activities as well as >90% suppression of parasitaemia in the mouse 4-day suppressive test at doses of 25 mg Kg^{-1} day^{-1} (Onyeibor et al., 2005). Furthermore, the survival times of the mice compared to untreated controls were increased. Taken together, these data indicate that cryptolepine analogues are worthy of further study as lead antimalarial compounds although there are significant hurdles to be overcome, particularly the need for compounds that will produce a cure in mice infected with malaria and which can be shown to be orally active. The synthesis of new analogues and studies investigating the mode of action of cryptolepine and its analogues are continuing.

Traditional antimalarials

Since, as mentioned above, antimalarial drugs (other than chloroquine), are unavailable or unaffordable to many who live in malarious areas, the use of traditional medicines for malaria treatment is an attractive and often the only option. The plants required are locally available (although supplies may become more difficult as time goes on due to overcollection, deforestation and development), and traditional medicines are more affordable as well as being culturally acceptable. They are widely used for the treatment of malaria and fever but little is known concerning their clinical efficacy and safety since few clinical studies have been carried out. Indeed, given the increasing mortality due to malaria it may be pertinent to question the effectiveness of traditional antimalarials: if these remedies are effective why are there so many deaths from malaria? Clinical trials are urgently needed to answer this question. With a view to address the above, the Research initiative on traditional antimalarials (RITAM) has been established by the organisation Global Initiative for Traditional Systems of Health (GIFTS of Health) initiated by Dr G. Bodeker, Oxford, UK. RITAM is a global network of people who are interested in validating local herbal medicines used for the prevention and/or the treatment of malaria and also local methods for insect repellance and vector control. It is hoped that these might provide effective treatments for those for whom manufactured drugs are not available as well as effective and affordable methods for vector control. RITAM members have recently compiled a book on traditional antimalarials including a review of clinical trials that have

been carried out to date (Willcox et al., 2004). For further information about RITAM readers are welcome to contact Dr Merlin Willcox, e-mail: merlinwillcox@doctors.net.uk.

Clinical trials with traditional antimalarials

The design and execution of clinical trials for traditional antimalarials presents a considerable challenge and a few of the reasons why this is the case will be outlined below. Firstly, malaria is a complex disease and a thorough understanding is essential in order to design studies that will produce meaningful data. Perhaps the most important question with respect to a traditional antimalarial is 'Will this medicine prevent, (or at least reduce), the risk of severe disease and death from malaria?'. This apparently straightforward question is particularly difficult to answer given that deaths from malaria may occur in less than one in 200 untreated patients (Trape et al., 2002). Thus, large numbers of patients would be needed to show a significant reduction in death or severe disease. The situation is further complicated by the immune status of the patient. Most of the deaths due to malaria occur in children under the age of 5 years who have little or no immunity to the disease. Children in Africa suffer repeated episodes of malaria, and if they survive gradually develop partial immunity to the disease so that children over 5 years and adults are much less likely to die from malaria or suffer severe disease. However, during their first pregnancy especially, women and their unborn children are at great risk from malaria because the immune response is suppressed in pregnancy and parasitised red cells accumulate in the placenta (Warrell and Gilles, 2002). Also, non-immune older children and adults that move from non-malarious to malarious areas are at risk of severe disease/death. Even if it is demonstrated that a traditional medicine is effective in older, partially-immune patients, it may not necessarily be effective in young children, (or others) with little or no immunity to the effects of malaria infection. The immune status of the patient must therefore be considered when carrying out studies with antimalarials as partially-immune patients may well recover from the disease without the need for drug therapy and properly matched untreated controls would be needed to show any beneficial effects of the medicine under test. In addition, there are many other practical and ethical difficulties that need to be considered.

As noted above, the extracts of many plant species used in traditional antimalarials have been evaluated in the laboratory for their *in vitro* antiplasmodial activities and some have been tested for *in vivo* antimalarial activities; for reviews see (del Rayo Camacho Corona et al., 2000; Schwikkard and van Heerden, 2002). Often the results show only modest activity against the parasites *in vitro* or against malaria in mice. This would suggest that the species are likely to have only a limited effect in man and that cure of the disease is unlikely. However, this may not necessarily mean that medicines made from these species are of no value. Partially effective treatments might be beneficial in that the course of the disease is shortened perhaps reducing anaemia and lowering the risk of death or serious illness from other anaemia-related diseases. Other possible benefits could be the alleviation of symptoms such as pain and fever and immunomodulation leading to increased immunity. For example, species of *Alstonia* are widely used traditionally for the treatment of malaria but there is little convincing evidence that these species have antiplasmodial or antimalarial properties (Wright et al., 1993), although the alkaloids from *Alstonia scholaris* have been reported to have pronounced febrifugal effects in fowls with malaria (Mukerji, 1946). *Strychnos myrtoides* is a plant used in Madagascar as an adjuvant with chloroquine for the treatment of malaria. Although the major alkaloid constituents are devoid of activity against malaria parasites, they have been shown to potentiate the action of chloroquine against chloroquine-resistant parasites (Rasoanaivo et al., 1994). The antimalarial action of the Chinese herb *Dichroa febrifuga* is thought to involve the immune response as it stimulates activated macrophages to produce nitric oxide (Murata, et al., 1998).

Interestingly, in 1938 D.B. Wilson suggested that when treating malaria, only minimal therapy should be used, sufficient to prevent death but insufficient to clear all the parasites from the blood so that the development of immunity is not impaired (Trape et al., 2002). This suggestion has resulted in much debate over the years and in the context of traditional antimalarials raises the possibility that partially effective remedies might

be better in the long term than curative treatment since they might allow better development of immunity. However, it must be emphasised that the above is speculative and further clinical studies are needed in order to resolve this and other issues related to the use of traditional antimalarials.

Only a few clinical studies with traditional antimalarials have been carried out and these have recently been reviewed (Willcox et al., 2004). Currently, there is considerable interest in using locally grown *A. annua* (the source of artemisinin) for the treatment of malaria but to date only two clinical studies have been reported. These will be briefly discussed below as they illustrate some of the difficulties and limitations typical of many of the trials carried out with herbal antimalarials. In 1992 in China, 144 malaria patients were treated with tablets containing an ethanolic extract of *A. annua* or with capsules in which the extract was formulated in oil (Yao-De et al., 1992, reviewed in Yu and Zhong, 2002). The treatments were found to be effective in reducing parasitaemia and fever at doses equivalent to 80.8 g raw herb for the tablets and 73.6 g for the capsules, given over 3 days. More recently, a herbal tea prepared from *A. annua* was evaluated in malaria patients in the Democratic Republic of Congo with the result that clearance of parasitaemia and a reduction of symptoms was reported in 92% of 48 patients after 4 days treatment (Mueller et al., 2000). In both of the above studies, patients were over the age of 10 years and therefore they were likely to be partially-immune to malaria. In the Chinese study, follow up of patients for 30 days showed that recrudescence was common (about 30% although this was reduced to 8% in patients treated with the capsule formulation for 6 days), but there was no follow up in the other study. The amount of artemisinin present in the herbal tea used in the Congolese study was determined by analysis and this was found to be much less than the usual clinically used dose. However, it is possible that the smaller dose present in the herbal tea may be adequate especially if the subjects had partial immunity to malaria, although a difference in the efficacy of artemisinin between non-immune and partially-immune malaria patients has not been shown. It is also possible that other compounds in the tea such as flavonoids acted synergistically with the artemisinin or enhanced its bioavailability. Experimental evidence from *in vitro* studies suggests that some flavonoids may enhance the action of artemisinin against *P. falciparum* (Elford et al., 1987). If however, parasites are exposed to subtherapeutic doses of artemisinin there is the possibility that the development of parasites resistant to artemisinin may be encouraged. To date there have been no clinical reports of artemisinin resistance but resistant parasites have been produced in the laboratory (Chawira et al., 1986). Although it has been argued that the development of malaria parasites resistant to artemisinin is unlikely because of the rapid action and short half-life of the drug, the ability of microorganisms to develop resistance should not be underestimated.

It is clear from the above that the effectiveness of *A. annua* used as a herbal tea or in the form of a crude extract to treat malaria in non-immune patients has not yet been demonstrated and it may be unwise to promote the use of such preparations at least in young children until further studies have been carried out.

Conclusion

The investigation of plants used in traditional medicines for the treatment of malaria may well lead to the development of new antimalarial drugs. Cryptolepine is a promising lead compound and several analogues have a potent suppressive effect on parasitaemia in mice infected with *P. berghei* with no apparent toxicity to the mice. However, analogues that are able to cure malaria in mice are yet to be found. As an alternative approach to drug development, the further investigation of traditional antimalarials is an attractive option, but showing that these remedies are effective especially in preventing severe disease or death from malaria in young children presents a considerable challenge. The bark of a South American *Cinchona* tree provided quinine and a herb from China furnished artemisinin, but bearing in mind that malaria is primarily an African problem, it is to be hoped that in the future we can look forward to antimalarials *from* Africa *for* Africa.

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