

TRADITIONAL CHINESE MEDICINES FOR MALARIA THERAPY: A REVIEW

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Abstract. Malaria, one of the “big three” killer diseases, is a major public health problem as well as a major cause of mortality and morbidity in the world. The goals of the global malaria elimination program are to (i) reduce malaria case incidence by at least 90% by 2030, (ii) reduce malaria mortality rates by at least 90% by 2030, (iii) eliminate malaria in at least 35 countries by 2030, and (iv) prevent resurgence of malaria in all countries that are malaria-free. Currently, the malaria elimination strategy mainly depends on chemotherapy, with the available antimalarials divided into five categories according to the chemical structure and mechanism of drug actions, namely, aryl amino alcohol compounds, 8-aminoquinolines, antifolate compounds, artemisinins, and other agents. Artemisinin, a sesquiterpene lactone extracted from the Chinese medicinal herb *Artemisia annua*, has been recommended as the first-choice treatment for malaria by the World Health Organization. However, the rapid emergence of artemisinin tolerance in *Plasmodium falciparum* has hasten the development of novel antimalarials towards global malaria elimination. The effectiveness and safety of traditional Chinese medicines for treatment of parasitic diseases, including malaria, have been recognized. Here, we review other traditional Chinese medicines that show potential for malaria treatment. Crude extracts and pure compounds from ginger, garlic, the Asteraceae family, *Bupleuri radix* and *Daphne* spp have shown *in vitro* and *in vivo* antiplasmodial activities, and some have been tested for their antimalarial actions in malaria patients. Further randomized, controlled clinical trials to examine the efficacy and safety of traditional Chinese medicines for treatment of malaria and to unravel their underlying mechanisms appear justified.

Keywords: antimalarial, artemisinin, traditional Chinese medicine

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INTRODUCTION

Malaria is an acute, febrile, life-threatening, mosquito-borne parasitic disease caused by bites of *Plasmodium*-infected female *Anopheles* mosquitoes (Ashley *et al*, 2018). Although more than 200 *Plasmodium* spp have been identified, there are only five human species, namely, *P. falciparum*, *P. knowlesi*, *P. malariae*, *P. ovale*, and *P. vivax*, with *P. falciparum* being the deadliest and most prevalent on the African continent and *P. vivax* the most widespread and predominant outside sub-Saharan Africa (Sato, 2021). Malaria, together with human immunodeficiency virus/acquired immune deficiency syndrome (HIV)/AIDS and tuberculosis (TB), have been recognized as the “big three” killer diseases in the world (Parola, 2013), resulting in a major public health problem as well as a major cause of mortality and morbidity in tropical and sub-tropical regions of the world (Phillips *et al*, 2017). According to the 2021 World Malaria Report released by the World Health Organization (WHO), almost half of the world’s populations were estimated to be at risk of malaria infections in 2020, with approximately 241 million new cases of malaria and 627,000 deaths, 95 and 96 % respectively reported in sub-Saharan Africa (WHO, 2021b).

A global decline in malaria morbidity and mortality during the 20-year period between 2000 and 2019

led to the setting by WHO of ambitious targets for a global malaria elimination program, involving, by 2030, goals to (i) reduce malaria case incidence by at least 90 %, (ii) reduce malaria mortality rates by at least 90 %, (iii) eliminate malaria in at least 35 countries, and (iv) prevent a resurgence of malaria in all currently malaria-free countries (WHO, 2021a). However, the global COVID-19 pandemic (Hogan *et al*, 2020; Rogerson *et al*, 2020; Sherrard-Smith *et al*, 2020) and spread of insecticide resistance and antimalarial drug resistance have posed critical threats to achieving the established agenda for malaria elimination (Achan *et al*, 2018; Lindsay *et al*, 2021).

Currently, the malaria elimination strategy mainly depends on chemotherapy, which has the primary goal of achieving rapid, complete clearance of malaria parasites to prevent uncomplicated malaria cases from progressing to severe disease or death (Shrivastava *et al*, 2021). The currently available antimalarials can be divided into four categories according to chemical structure and mechanism of drug action, namely, aryl amino alcohol compounds (amodiaquine, chloroquine, halofantrine, lumefantrine, mefloquine, piperaquine, quinidine, and quinine), 8-aminoquinolines (primaquine and tafenoquine), antifolate compounds (chlorproguanil, proguanil, pyrimethamine, sulfadoxine, and trimethoprim), artemisinin and analogs (β -arteether, artemether, artemisinin,

artesunate, and dihydroartemisinin), and other chemical scaffolds (atovaquone, clindamycin, doxycycline, and tetracycline) (Na-Bangchang and Karbwang, 2019).

Artemisinin, also known as qinghaosu, is a sesquiterpene lactone containing an endoperoxide extracted from dried leaves or flower clusters of a sweet wormwood plant *Artemisia annua* (Qinghao), a Chinese herb used in traditional Chinese medicine (Li, 2012). The antipyretic action of the plant was first documented in “A Handbook of Prescriptions for Emergencies” by a Chinese physician Hong Ge in the 4th century AD (Hsu, 2006). In early 1970s, artemisinin, the active antimalarial ingredient of *A. annua*, was identified by Youyou Tu, who shared the 2015 Nobel Prize in Physiology or Medicine (Tu, 2016), and the discovery of artemisinin is considered a great contribution of traditional Chinese medicine to the world. Currently, artemisinin is the most common antimalarial used for malaria control and plays a critical role in the treatment of malaria throughout the world (Martino *et al*, 2019), and artemisinin-based combination therapy (ACT) is recommended by the WHO as the first-line treatment for uncomplicated *falciparum* malaria worldwide (Sinclair *et al*, 2009). The efficacy and safety of artemisinins against malaria have been extensively tested, and the description of artemisinin treatments for malaria

have been reviewed (Woodrow *et al*, 2005). However, the appearance of artemisinin-tolerant *P. falciparum* in western Cambodia in 2008 and its spread among countries in the Greater Mekong subregion has raised concern regarding ACT future usefulness (Jacob *et al*, 2021). Here, we discuss other traditional Chinese medicines that show potential for treating malaria, and which could replace artemisinin and analogs. We retrieved publications pertaining to traditional Chinese medicines for malaria therapy in PubMed and three Chinese electronic databases, namely, Wanfang Data (<https://www.wanfangdata.com.cn/>), CNKI (<https://www.cnki.net>) and VIP (<http://www.cqvip.com/>) up to October 1, 2022

Traditional Chinese medicinal products with antimalarial properties

Ginger

Ginger, rhizomes of *Zingiber officinale*, a herbal medicinal plant of the family Zingiberaceae, has been widely used as a spice, flavoring, food, and medicine (Anh *et al*, 2020). Previous studies have shown that ginger exhibits a variety of pharmacological actions, such as anti-inflammatory, antimicrobial, antiparasitic, antioxidant, anti-vomiting, and pesticidal activities (Ali *et al*, 2008). Ethyl acetate extract of *Z. officinale* demonstrates a 50 percent-inhibitory concentration (IC₅₀) of 10 µg/ml against both chloroquine-sensitive and -resistant strains of *P. falciparum*,

with a 50% cytotoxic concentration (TC₅₀) of 35 µg/ml against HeLa cells, an *in vitro* selective index of 3.5 (Kaushik *et al*, 2013). Administration of crude methanol extract of *Z. officinale* at doses of 250, 500 and 1,000 mg/kg body weight mice infected with the chloroquine-sensitive *P. berghei* ANKA strain results in 80.0±0.8, 76±1 and 67±1 percent parasitemia, and 19.9±0.8, 23±1 and 33±1 percent chemosuppression, and 6.3±0.2, 6.4±0.2 and 7.3±0.5 days of survival, respectively indicating that *Z. officinale* organic extract has a dose-dependent *in vivo* anti-plasmodial activity in a mouse malaria model (Biruksew *et al*, 2018). The aquatic solution of *C. xanthorrhiza* freeze-dried powder at a concentration of 1 mg/ml displays 100% inhibitory activity against *P. falciparum in vitro* (Murnigsih *et al*, 2005).

Moxibustion, a therapy that uses ignited materials (usually moxa) to heat selected areas of the skin surface, has been employed for clinical therapy of a wide range of disorders (Kim *et al*, 2011; Wang *et al*, 2014). Ginger-partitioned moxibustion, which has shown effective in promoting blood circulation and removing blood stasis and toxins (Li *et al*, 2021a), has been employed for management of breast fibroma (Li *et al*, 2021b), gastrointestinal disorders (Sun *et al*, 2021) allergic rhinitis (Wen *et al*, 2022), and chemotherapy-induced nausea and vomiting (Zhang *et al*, 2020a; Zhang *et*

al, 2020b). Administration of ginger-partitioned moxibustion given once every 3 days in five treatments achieved cure in 31 cases and improvements in 8 cases, with an overall effective rate of 92.9% among malaria patients in the Republic of Congo (Li, 2011). In addition, ginger is one of the most commonly used Chinese herbs for self-treatment of malaria in Ethiopia (Kovalev and Wells, 2020).

Garlic

Garlic (*Allium sativum*), an edible perennial plant of the family Amaryllis, is one of the most important bulb vegetables having a pungent flavor and has been widely used as a spice and flavoring agent globally, and also for treatment of diseases for thousands of years (Bayan *et al*, 2014). Previous studies showed that garlic exhibits a variety of pharmacological actions, such as antibacterial, antifungal, anti-protozoal, antiviral, antioxidant and anti-inflammatory, anticancer, anti-Alzheimer's disease, anti-metabolic, and anti-hypertensive activities (El-Saber Batiha *et al*, 2020). Administration of ajoene (4,5,9-trithiadodeca-1,6,11-triene 9-oxide), an extract of garlic, at a single dose of 50 mg/kg suppressed development of parasitemia in a *P. berghei* murine model with no obvious acute toxic effects noted, and combined with chloroquine (4.5 mg/kg) completely prevented the development of parasitemia (Perez *et al*, 1994). Oral administration of an ethanol solution

of allicin, a major active principle of garlic, to BALB/c mice infected with *P. yoelii* 17XL strain at a dose of 3 or 9 mg/kg on Days 0-2 post-infection resulted in a clear-cut reduction in parasitemia on Day 5 (27.1 and 32.6 % for the 3 mg/kg and 9 mg/kg dose group respectively), with a further decline of Day 7; there is a significant prolonged survival period of treated infected mice compared to untreated controls (p -value <0.05) (Feng *et al*, 2012). Injection of aqueous allicin solutions decreased *P. yoelii* infection in mice and treatment of *P. yoelii* sporozoites with aqueous allicin solution prior to injection into mice completely prevented malaria infection, while a 4-day treatment with allicin resulted in a significant reduction in parasitemia and extension of survival period in infected mice (Coppi *et al*, 2006). In addition, a combination of garlic and artemisinin derivatives achieved a higher antimalarial activity and longer survival period than garlic or artemisinin derivatives alone in murine malaria models (Palakkod Govindan *et al*, 2016; Vathsala and Murthy, 2020; Ounjaijean and Somsak, 2022).

There are clinical reports of the potential of garlic for malaria treatment. Among 447 Ethiopian children at under 5 years of age who had a recent episode of fever, 95 (22.2 %) were given medicinal plants as their first-choice treatment, and garlic decoction is the most commonly used herbal medicine; administration

of garlic decoction resulted in a cure rate of 51 % (18/35) in children and improvement in the remaining (Gurmu *et al*, 2018). Following topical treatment with a garlic-tobacco leaf mixture ointment 2 hours prior to and removal after a disease episode, clinical symptoms of *P. vivax* malaria ceased on the day of treatment, and a one-month follow-up showed no more episodes (Feng, 1972). In Nsukka Local Government Area, southeastern Nigeria, 1 % (2/213) of the study subjects used cold maceration with garlic for the treatment of malaria (Odoh *et al*, 2018). Thus, randomized, controlled clinical trials to test the efficacy and safety of garlic concoctions for malaria treatment appear warranted.

Asteraceae

Family Asteraceae is one of the largest angiosperm families, which contains more than 1,620 genera and 23,600 species of herbaceous plants, shrubs and trees all over the world (Carvalho *et al*, 2018). Asteraceae family members have been used as ornamentals, food and traditional medicine for centuries, and show potent antioxidant, anti-inflammatory, antimicrobial, diuretic and wound-healing properties (Rolnik and Olas, 2021). A recent systematic review of published articles retrieved from electronic databases, such as PubMed, Web of knowledge, ScienceDirect, and Saudi digital library and MSc/PhD theses, revealed medicinal plants of the Asteraceae family are the most abundant

of herbal plants used in laboratory tests for antimalarial activity against murine malaria models (Dkhil *et al*, 2021). Treatment with ethyl acetate extract of *Chrysanthemum morifolium* at a dose of 100 mg/ml inhibits *P. falciparum* intra-erythrocytic growth in culture (Wu *et al*, 1995). Intraperitoneal injection of *P. berghei*-infected mice with ethanol and chloroform extracts of *C. morifolium* at dose of 0.6 g/kg achieve on Day-1, -2, -3, -4, and -5 post-treatment parasitemia of 6.25, 12.05, 4.25, 2.11 and 1.56 %, respectively and treatment with 1.4 g/kg, parasitemia of 2.52, 5.64, 2.08, 2.17, and 0.68 %, respectively (Zhao *et al*, 1996d). Intraperitoneal injection of chloroform extract of *C. morifolium* at a dose of 1.4 g/kg inhibits development of *P. berghei* gametocytes into oocysts and sporozoites in *Anopheles stephensi* (Zhao *et al*, 1996b). Intraperitoneal injection of *C. morifolium* chloroform extract of at a high dose of 700 mg/kg rat results in inhibition of the development of exoerythrocytic-stage of *P. yoelii* (Zhao *et al*, 1996a; Zhao *et al*, 1996c). In addition, intraperitoneal injection of the alcohol extract from *C. morifolium* inhibited the development of *P. yoelii* erythrocytic-stage (Zhao *et al*, 1997a) and intraperitoneal injection inhibited development of the exoerythrocytic-stage (Zhao *et al*, 1997b).

Leaf extract of *C. indicum* prepared in dimethyl sulfoxide (DMSO) showed an IC₅₀ value of 20 µg/ml against both chloroquine-sensitive and -resistant strains of *P. falciparum* and a 50%

cytotoxic concentration (TC₅₀) of >100 µg/ml against HeLa cells, resulting in a selectivity index (TC₅₀/IC₅₀) of >5 (Kamaraj *et al*, 2012), indicating that it should be worthwhile to identify the active antiplasmodial component(s) of *C. indicum* leaf for consideration as possible candidate(s) for drug development. In Ethiopia, the Asteraceae family is the most commonly used traditional herbal medicine for treatment of malaria (Suleman *et al*, 2018).

Daphne spp

Daphne, a genus containing 70-95 species of deciduous and evergreen shrubs in the Family Thymelaeaceae, is noted for their scented flowers and often brightly colored berries (Moshiashvili *et al*, 2020). Daphnetin (7,8-dihydroxycoumarin), a coumarin derivative, is the major bioactive component isolated from the genus *Daphne*, such as *D. giraldii*, *D. marginate*, and *D. odora*, and has a wide range of pharmacological actions, *viz* anti-inflammatory, anti-oxidative, anti-cancer, depigmenting, analgesic, anti-arthritis, anti-pyretic, neuroprotective and antimalarial properties (Du *et al*, 2014; Wang *et al*, 2019; Javed *et al*, 2022). The antimalarial activity of daphnetin was firstly documented in 1992 (Yang *et al*, 1992), demonstrating 25-40 µmol/l 50 % inhibition of ³H-hypoxanthine incorporation by *P. falciparum* in culture; antiplasmodial activity is suppressed by addition of iron, and

administration to *P. yoelii*-infected mice significantly prolongs survival. More recent studies by Wang *et al* (2000) reported daphnetin at 1, 2, 4, 8, and 10 $\mu\text{mol/l}$ having *in vitro* inhibitory activity against *P. falciparum* schizonts in a dose-dependent manner, comparable to chloroquine treatment; oral administration of *P. yoelii*-infected mice a dose of 1, 10, 50, and 100 mg/kg at four hours post-infection once daily for four consecutive days results in 15, 31, 74, and 72 percent reduction in parasitemia, respectively and prolongs the survival period from 8 ± 3 days in controls to 9 ± 4 , 9 ± 3 , 25 ± 8 , and 22 ± 10 days, respectively, while intraperitoneal injection at dose of 1, 10, 50, and 100 mg/kg at four hours post-infection once daily for four consecutive days results in 15, 73, 88, and 91 percent reduction in parasitemia and prolongs survival from 9 ± 5 days in controls to 11 ± 8 , 24 ± 10 , 25 ± 11 , and 27 ± 8 days, respectively. Following oral administration of daphnetin at doses of 10, 50 and 100 mg/kg at 0.5 hour post-infection for four consecutive days, no *P. yoelii* infection is detected in mice on Day 7 post-treatment, but there is 9 ± 7 , 11 ± 8 and 9 ± 11 percent parasitemia, respectively compared to 13 ± 12 percent parasitemia in controls on Day 8 post-treatment, indicating that treatment with daphnetin alone has no activity against *P. yoelii* exo-erythrocytic-stage; however, combination of daphnetin with primaquine at a dose of 50 and 5 mg/kg respectively achieves an inhibitory activity against *P. yoelii*

exo-erythrocytic-stage comparable to treatment with primaquine alone at a dose of 10 mg/kg (Liu *et al*, 2001). Mu *et al* (2002) confirmed that daphnetin at a dose of 1, 4, 8, and 12 $\mu\text{mol/l}$ results in 45.2, 67.7, 80.0, and 88.5 percent reduction in parasitemia of intra-erythrocytic *P. falciparum* growth in culture, and this activity is antagonized by the presence of Fe^{2+} . Subsequently, Mu *et al* (2003) reported exposure *in vitro* of *P. falciparum* to 4 $\mu\text{mol/l}$ daphnetin for 24 hours results in a significant reduction of parasite superoxide dismutase activity (14 ± 2 versus 34 ± 3 U/mg protein in controls, p -value < 0.01), which is reversed by 4 $\mu\text{mol/l}$ iron chelator deferoxamine B, and that daphnetin treatment causes a reduction in rate of DNA synthesis at 1 hour post-treatment (hpt) (19 ± 3 versus $20\pm 4\%$ control), 6 hpt (27 ± 5 versus $28\pm 2\%$ control), 15 hpt (42 ± 2 versus $50\pm 2\%$ control), 21 hpt (54 ± 5 versus $86\pm 6\%$ control), and 26 hpt (65 ± 3 versus 100% control). Similar antimalarial activity of daphnetin was observed in subsequent *in vitro* and *in vivo* assays (Wang *et al*, 2004a), and daphnetin-artemether combination produces a higher antimalarial activity against *P. berghei*-infected mice compared to that of daphnetin or artemether alone (Guo *et al*, 2004). Pure (crystallized) and crude daphnetin preparation showed median inhibitory effective dose (ED_{50} value) of 18.36 mg/kg (95% confidence interval (CI): 5.96-56.54 mg/kg) and 11.46 mg/kg (95% CI: 8.63-15.22 mg/kg) respectively against *P. berghei*

schizonts (Wang *et al*, 2004b), and two daphnetin derivatives, DA79 and DA78, demonstrated a potent *in vitro* activity against *P. falciparum* growth in culture (Huang *et al*, 2006; Huang *et al*, 2008); in addition, daphnetin treatment of *P. falciparum in vitro* results in suppression of parasite cytochrome C oxidase and ribonucleotide reductase activity. These results are supportive of further development of daphnetin as a novel antimalarial.

Bupleuri radix

Bupleuri radix, also known as Chaihu, a large genus of annual or perennial herbs or woody shrubs belonging to Family Apiaceae, is one of the most commonly used herbs in Chinese herbal medicine, and crude extracts and pure compounds from *B. radix* showed a wide range of pharmacological actions, such as anti-inflammatory, anti-cancer, antipyretic, antimicrobial, antiviral, hepatoprotective, neuroprotective, and immunomodulatory activities (Yang *et al*, 2017). As a traditional Chinese medicinal herb in use for more than 2,000 years in China and other Asian countries, *B. radix* has been applied as an antipyretic agent (Yuan *et al*, 2017) and in the past decades prescribed in decoction formulations for malaria therapy (Li, 1954; Ruo and Sui, 1956; Chen, 1959). Among 44 malaria cases (39 cases with *P. vivax* and 5 cases with *P. malariae*), administration of Chaihu decoctions results in fever abatement among 36 cases within 3 days and the

remaining 8 cases within 4 to 6 days post-treatment, although 25% malaria recurrence were detected during a follow-up period of 26 to 75 days post-treatment, but no adverse events were reported (Li, 1960). Oral administration of “Xiaochaihu” decoction 4 to 5 hours prior to clinical symptom for two consecutive days produced complete cure in 13 cases of *P. vivax* and one case of *P. malariae* malaria, and no recurrence was found during the 16-year follow-up (Liu, 1976). In a pregnant woman at the second trimester, malaria parasites are not detected in blood following four doses of Xiaochaihu decoction, with a healthy female child delivered 4 months post-treatment and no recurrence observed during the two-year follow-up period (Yong, 1994). In addition, a randomized, controlled clinical trial demonstrated that among severe malaria patients in artesunate-Xiaochaihu combination treatment group compared to only artesunate treatment group there are significant reductions in mean duration of fever abatement (26 ± 9 versus 49 ± 16 hours, p -value <0.05), mean duration of malaria-associated symptoms (5 ± 1 versus 8 ± 2 days, p -value <0.05) and mean duration of hospital stay (8 ± 2 versus 11 ± 3 days, p -value <0.05), and a significantly higher overall response rate (96 versus 88 %, p -value <0.05) (Gao *et al*, 2019).

Concluding remarks

An ideal antimalarial is required to meet the following criteria: (i) high

efficiency: a cure rate >95% 28 days post-treatment in areas endemic for multi-drug resistant *P. falciparum*, (ii) rapid action: mean duration to clear 95% of parasitemia <20 hours, (iii) short course of disease: 1-3 days, (iv) low toxicity: prevalence of treatment-associated adverse reactions <10%, (v) transmission interruption: suppression of *P. falciparum* gametocytes development in bone marrow and loss of infectivity in blood at the end of treatment (within 1 to 3 days), and (vi) low cost (Achieng *et al*, 2017).

Traditional Chinese medicines have shown potential for clinical therapy of a wide range of disorders (Cai *et al*, 2011; Alissa, 2014; Matos *et al*, 2021), and the use of traditional Chinese medicines for treatment of malaria dates back to more than 1,600 years (Graziose *et al*, 2010). However only artemisinin and its analogues are in clinical use. Considering that a large number of medicinal herbs have been tested for antimalarial activity, we highlighted five commonly used traditional Chinese medicines, lead compounds of which have with highest potential to be developed into antimalarials, namely, ginger, garlic, Asteraceae, *Daphne* and *B. radix*. Further studies are undergoing to unravel the mechanisms of action of these lead compounds. In addition, other compounds present in *Artemisia annua* with antimalarial and other medicinal properties are being examined (Septembre-Malaterre *et al*, 2020).

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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