Antiplasmodial properties of kaempferol-3-*O*-rhamnoside isolated from the leaves of *Schima wallichii* against chloroquine-resistant *Plasmodium falciparum*

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Abstract. Previous intervention studies have shown that the most effective agents used in the treatment of malaria were isolated from natural sources. Plants consumed by non-human primates serve as potential drug sources for human disease management due to the similarities in anatomy, physiology and disease characteristics. The present study investigated the antiplasmodial properties of the primate-consumed plant, *Schima wallichii* (*S. wallichii*) Korth. (family *Theaceae*), which has already been reported to have several biological activities. The ethanol extract of *S. wallichii* was fractionated based on polarity using *n*-hexane, ethyl acetate and water. The antiplasmodial activity was tested *in vitro* against chloroquine-resistant *Plasmodium falciparum* (*P. falciparum*) at 100 μg/ml for 72 h. The major compound of the most active ethyl acetate fraction was subsequently isolated using column chromatography and identified by nuclear magnetic resonance. The characterized compound was also tested against chloroquine-resistant *P. falciparum* in culture to evaluate its antiplasmodial activity. The ethanol extract of *S. wallichii* at 100 μg/ml exhibited a significant parasite shrinkage after 24 h of treatment. The ethyl acetate fraction at 100 μg/ml was the most active fraction against chloroquine-resistant *P. falciparum*. Based on the structural characterization, the major compound isolated from the ethyl acetate fraction was kaempferol-3-*O*-rhamnoside, which showed promising antiplasmodial activity against chloroquine-resistant *P. falciparum* with an IC_{50} of 106 μM after 24 h of treatment. The present study has provided a basis for the further investigation of kaempferol-3-*O*-rhamnoside as an active compound for potential antimalarial therapeutics.

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Introduction

Malaria is an infectious disease endemic throughout tropical countries. Malaria is also prevalent in subtropical areas, where the disease is contagious affecting both indigenous population and travelers (1). Malaria is caused by *Plasmodium* parasites that are transmitted through the bite of *Anopheles* mosquitoes and have a life cycle in mosquito and human hosts (1). Of all parasite types, *Plasmodium falciparum* (*P. falciparum*) is the most dangerous *Plasmodium*, causing human malaria with a mortality of 1-2 million people annually. According to surveys conducted between 1900 and 2008 in 2,366 locations in Indonesia, four species of *Plasmodium* may infect humans, *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. *P. falciparum* is the most common parasite that is contagious in Indonesia, with prevalence rates of 33% in Papua, 29% in Lesser Sundas and 21% in Sumatra (2). Findings of studies performed in other parts of Indonesia, including the Thousand Island district (3), Nias Island (4), Sumba Island (5) and Aceh (6), have shown that *P. falciparum* was the most frequent parasite that caused malaria.

Eradication of malaria remains challenging due to drug resistance of *Plasmodium*. Hyde (1) reported that the first synthetic antimalarial drug, found in the 1930s, was chloroquine, which was highly effective, safe and cost-effective. Since 1957, however, resistance to administration of chloroquine was observed in Thailand and by 1988 this resistance had spread to sub-Saharan Africa and other areas of the world. Several factors affect antimalarial resistance, including the overuse of drugs for prophylaxis, incomplete therapeutic treatments of active infections, genetic and metabolic adaptive abilities of the parasites and a massive parasite proliferation (1). The incidence of malaria infections, which is ~250 million cases and 80,000 mortalities annually, has revealed the emerging requirement for identifying new classes of medicine (7).