CHAPTER I
INTRODUCTION

Febrile illness is most common found in malaria pathogenesis. Malaria has been associated with a unique pattern of cyclical fever coincided with schizont rupture. Different *Plasmodium* species showed different pattern of fever depending on the length of their erythrocytic-stage cycle. The duration of the cyclical fever for *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium ovale* is 48 h, but for *Plasmodium malariae* is 72 h. In malaria, febrile illness is induced via a poorly defined immunologic mechanism activated by malaria toxins and hemoglobin metabolites released from the ruptured, infected red blood cells (iRBCs). It has been argued that malarial febrile illness is an evolutionary adaptation that benefits both the parasite and its host. Cultivation at febrile temperatures has been shown to inhibit *in vitro* growth of *P. falciparum* cultures. It is possible that during acute malaria infection, elevated host temperature induces a cascade of molecular events that maintain the total parasite burden at a threshold level by limiting its replication rate, allowing host defense mechanisms to activate and mature. Although inhibition of exponential parasite growth caused by febrile temperature may appear to aid only the host, it may also provide sufficient time for the parasite to further transmit infection, making it a potential parasite survival strategy. In spite of the possible beneficial effects of malaria induced febrile illness, some recent study suggests that fever may, in fact, augment the pathogenesis of malaria by enhancing cytoadherence of parasite iRBCs to CD36 and intercellular adhesion molecule 1 (ICAM-1) molecules that serve as host there are receptors on endothelial cells. The authors (Udomsangpetch *et al.,* 2002) found an increased level of the variant antigen erythrocyte membrane protein 1 (EMP-1), a parasite ligand that mediates binding to host receptors on endothelial cells, on the surfaces of ring and trophozoite infected red blood cells (iRBCs) when heated to 40°C. It leads to the enhanced cytoadherence which could be due to the increase in the trafficking of EMP-1 to the surfaces of iRBCs. In mammalian cells, an increase in temperature can lead to a number of changes within the cell, including protein denaturation, transient cell cycle arrest, and changes in membrane fluidity. Heat shock

proteins (HSPs), the primary mediators of the heat shock response, act as molecular chaperones by preventing aggregation and promoting folding of cellular proteins. In humans, HSPs appear to be possible regulators of key apoptotic pathways, and targeting HSPs that interact with the cellular apoptotic machinery is emerging as a novel approach for pharmacologic intervention in cancer. To understand the molecular changes that occur and biochemical pathways altered in *P. falciparum* parasites in response to febrile temperatures, this work compared the parasite development under drug and drugless condition including the heat shock protein expression profiles of parasites cultivated at 37°C and 41°C. The use of sensitive 3D7 and resistant K1 strain for analysis methods allowed the detection of parasite development, drugs sensitivity and *P. falciparum* heat shocks proteins 70 (*PfHsp70s*). Moreover, we also investigated whether the febrile temperature could induced *in vitro* killing of sensitive strain of *P. falciparum* parasites compared to that of K1. We believe that the identification of heat-inducible parasite factors and biochemical pathways that contribute to the regulation of parasite density and potentially influence their virulence in a non-immune host could lead to new anti-malarial drug and vaccine targets.