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NATHAWUT SIBMOOH : ANTIMALARIAL ACTIVITY OF ARTEMISININ: AN IRON-DEPENDENT MECHANISM OF ACTION. THESIS ADVISORS : UDOM CHANTHARAKSRI, Ph.D., JUTAMAAD SATAYAVIVAD, Ph.D., SUPEENUN UNCHERN, Ph.D., PRAPON WILAIRAT, Ph.D., RACHANEE UDOMSANGPETCH , Ph.D. 148 P. ISBN 974-662-325-7

The oxidative stress in malaria was studied both *in vitro* and *in vivo*, as assessed by lipid peroxidation and membrane fluidity of the erythrocytes. The effect of artemisinin on oxidative stress was also investigated. Using spin labeling compounds, membrane fluidity of malaria-infected erythrocytes was determined and found to increase with the parasite counts. The thiobarbituric acid reactive substances (TBARs) were used as indicators of lipid peroxidation in the system. Artemisinin caused a further increase of TBARs in cultured medium of the infected erythrocytes and alteration in membrane fluidity, suggesting that the infected erythrocytes were prone to the effect of artemisinin.

The elevation of plasma TBARs and alteration of membrane fluidity were evident in malaria, especially in severe cases. The levels of plasma TBARs were related to the severity of disease. Treatment with artemisinin showed no effect on plasma TBARs, neither an alteration in membrane fluidity. Desferrioxamine, however, reduced oxidative damage during infection without compromising the therapeutic effect of artemisinin. This indicated that the intraerythrocytic activity of artemisinin was mediated through an induction of oxidative stress.

The interaction of artemisinin with iron was investigated *in vitro* in a simulated physiological environment, and the resulting products were tested for their antimalarial activity. It was found that artemisinin reacted with both ferrous and ferric ion, and at least two active products (one of them was dihydroartemisinin) were produced. These products might undergo rearrangement to artemisinin. At the first 5 minutes, ferrous ion was oxidized and dihydroartemisinin was immediately found. The reaction reached its plateau after 30 minutes. From the initial rate, the reaction of artemisinin with ferrous was optimal at pH7.25. It was concluded that the antimalarial activity of artemisinin was an iron-dependent reaction, resulting in at least two even more active products (one was dihydroartemisinin) than artemisinin.