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MECHANISM OF ACTION OF QINGHAOSU (ARTEMISININE) AND RELATED COMPOUNDS

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ABSTRACT

Qinghaosu, a compound extracted from Chinese herb qinghao, shows a very potent antimalarial activity against chloroquine-resistant malaria. The mode of action of qinghaosu and its derivatives was investigated in this study. The drug did not show any effect on osmotic fragility, did not have Ca^{2+} ionophoretic activity, and did not inhibit merozoite invasion and multiplication in drug-pretreated normal red cells. Using the incorporation of [^{3}H]-leucine into protein as an index of protein synthesis, it was shown that qinghaosu, artemether and artesunate had inhibitory effect on protein synthesis in *P. falciparum* (K_1) within 1 h after the addition of the drugs at a concentration of 1×10^{-6}M. However, they did not show an inhibition in intact mouse reticulocytes at the same concentration. This may be due to selective drug uptake by the parasites or difference in protein synthesis machinery. Many antibiotics and antimalarial drugs have also been tested for their inhibitory effects on protein synthesis by *P. falciparum* (K_1) : only cycloheximide, actinomycin D and mefloquine showed inhibitory effects. The effect of qinghaosu and its derivatives on incorporation of [^{3}H]-hypoxanthine into DNA/RNA as an index of DNA/RNA synthesis was also studied. Inhibition in DNA/RNA synthesis was observed within 2 h after the addition of the drug (1×10^{-6}M). Doxorubicin and miconazole, two new oxidant drugs, also showed antimalarial activity against *P. falciparum* (K_1) and partially inhibited parasite protein synthesis.

The antimalarial activity of qinghaosu on *P. falciparum* (K_1) *in vitro* was increased as O_2 tension was increased, and was reduced by the addition of α-tocopherol, catalase and dithiothreitol but not by

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butylated hydroxytoluene and superoxide dismutase. From our studies, it can be suggested that qinghaosu and its derivatives may act as an oxidant drug through peroxide generation. In a study of combination of artesunate with known oxidant drugs (doxorubicin and miconazole), a synergistic effect against *P. falciparum* (K_1) was observed, suggesting that it is probably due to the potentiating activity of one oxidant drug on another. The observation is consistent with a potentiating mechanism through formation of peroxide by one drug (artesunate) and superoxide by another (doxorubicin or miconazole). However, artesunate (1×10^{-4}M) did not show alteration of reduced glutathione either in normal red cells or in *P. falciparum* (K_1)-infected red cells.

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