changes in *P. cynomolgi* after artemisinin and chloroquine treatment were different which again points to different mechanisms of antimalarial action [66].

Disappearance of malaria symptoms and an increase in survival time was achieved in mice infected with *P. berghei* by combined use of artemisinin and primaquine as opposed to artemisinin or primaquine alone. The reoccurrence of malaria was also significantly delayed. Combination of artemisinin and primaquine resulted in a clear synergistic effect since the ED_{50} value for the combined use of artemisinin and primaquine was only $^1/_{10}$ that of artemisinin or primaquine alone; the acute toxicity of artemisinin or primaquine was not enhanced by combined use [67].

Artemisinin enhanced macrophage phagocytosis in mice. Both the in vivo phagocytic activity and the index of mouse abdominal macrophages were increased after intragastric administration of artemisinin. Phagocytic activity of macrophages for *Plasmodium* in an in vitro culture system was also increased in the presence of artemisinin. Acid phosphatase activity was elevated in abdominal macrophages from mice treated with artemisinin compared to those from control mice. The antimalarial activity of artemisinin appeared to be associated with its enhancing effect on macrophage phagocytic activity [68].

A pyronaridine-resistant line of *P. berghei* showed reduced sensitivity to six erythrocytic schizonticides including artemisinin, indicating the presence of cross resistance [69]. Resistance to artemisinin developed rapidly in a chloroquine-resistant line of *P. yoelii* passaged in mice but was not observed in chloroquine-sensitive *P. berghei* [70].

Treatment of mice infected with *P. falciparum* induced changes in membranes of the parasite together with alterations of ribosomal organization and endoplasmic reticulum. No changes were noted in digestive vacuoles or pigment, but nuclear membrane blebbing developed after 1 h and segregation of the nucleoplasm after 3 h. The morphological changes in ribosomes and endoplasmic reticulum in vivo correlated in time with the depression of protein synthesis observed in *P. falciparum* in vitro [71].

Artemisinin is a drug with low acute toxicity. In mice, an LD_{50} of about 4.2 g/kg after oral administration and 3.8 g/kg after i.m. injection of an oil suspension were obtained. In rats, the corresponding LD_{50} values were about 5.6 g/kg orally and 2.6 g/kg by i.m. injection. Restlessness, incoordination, tremors, diminished activity, lower respiration, and loss of the righting reflex appeared after administration of a toxic dose of artemisinin in dogs and in monkeys [64].

In monkeys, i.m. injections at a daily dose of 192 mg/kg artemisinin for 14 consecutive days caused severe ultrastructural changes in the myocardium which were visible on the third day after the last injection but apparently not after 35 days. This total dose caused the death of 75% of the animals within 3 days after 14 days of treatment. A dose of 24 mg/kg daily caused only mild myocardial lesions and diminution of circulating reticulocytes [72].

Intragastric administration of artemisinin at $^1/_{80}$ to $^1/_5$ the LD_{50} values (53–845 mg/kg) did not increase the number of micronuclei in mouse bone marrow polychromatic erythrocytes [73].

In clinical studies, artemisinin had good therapeutic effects on almost all patients treated and was without obvious side effects. All 2099 malaria patients infected with *P. vivax* or *P. falciparum* were clinically cured with artemisinin in different dosages.