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Effects of combined treatment with *Tithonia diversifolia* and Chloroquine on Chloroquine-resistant malaria in mice

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The development of Chloroquine as an antimalarial drug and the subsequent evolution of drug-resistant *Plasmodium* strains had major impacts on global public health in the 20th century. *In vivo* curative anti-plasmodial activity of ethanol extract and fraction of *T. diversifolia* leaves alone and in combination with Chloroquine were evaluated using albino mice infected with Chloroquine resistant *P. yoelii* (*P. yoelii*^R) intraperitoneally. Possible effects on the hematological indices and mechanisms of anti-plasmodial action were monitored using standard protocols. Oral administration of the ethanol extract of *Tithonia diversifolia* leaves to mice caused no death at doses ranging from 10-5000 mg/kg. The presence of the phytochemical content of the extract in the order: Reducing sugar>alkaloids>steroids>phenol>terpenoids>tannins>soluble carbohydrate were obtained. The result of the percentage parasitemia of mice infected with *P. yoelii*^R treated with 5 mg/kg b. w of artemeter, different doses of crude extract and C70:M30 fraction co-administered with 10 mg/kg b. w of Chloroquine from day 7 to day 28 revealed significant ($p<0.05$) reduction compared with infected mice administered 0.2 ml of distilled water. The mice infected with *P. yoelii*^R treated with 5 mg/kg b. w of artemeter, 200 mg/kg b. w of crude extract and C70:M30 fraction co-administered with 10 mg/kg b. w of Chloroquine showed significant ($p<0.05$) reduction in hemozoin level compared with the infected mice administered 0.2 ml of distilled water. The mice infected with *P. yoelii*^R treated with 5 mg/kg b. w of artemeter, crude extract and C70:M30 fraction showed dose dependent significant ($p<0.05$) increase in the PCV and RBC compared with the infected control mice. The plasma calcium ion (Ca^{2+}) and free fatty acid concentration revealed significant ($P<0.05$) decrease in the *P. yoelii*^R infected mice treated with varying doses of the extract in combination with Chloroquine compared with the parasitized untreated mice. The respective antimalarial drugs and the extract increase the percentage inhibition of phospholipase A₂. The effect of the crude extract, active fraction and antimalarial drugs causes inhibition of hypotonicity-induced hemolysis. This indicates that *T. diversifolia* leaf extract dose-dependently restores the efficacy of Chloroquine against *P. yoelii*^R malaria in mice due to rapid rate of recovery from plasmodial infections with the co-administration.

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