Anti-malarial and cytokine-modulating effects of Andrographolide in a murine model of malaria infection

ABSTRACT

Malarial pathogenesis involves among others, uncontrolled or excessive cytokine production arising from dysregulated immune responses mounted by the host to eliminate the plasmodial parasite. The ubiquitous serine/threonine kinase, glycogen synthase kinase3β (GSK3β) is a crucial regulator of the balance between pro- and anti-inflammatory cytokine productions in the inflammatory response to pathogenic infections. Andrographolide, a bioactive compound in Andrographis paniculata, displays GSK3- inhibitory effects. A previous study elsewhere has shown that this compound has antimalarial activity but the molecular basis of its action is yet to be elucidated. Here we aimed to study the anti-malarial activity of andrographolide in a murine model of malarial infection to investigate whether its mechanism of action involves cytokine modulation and inhibition of GSK3β. Andrographolide showed strong and selective anti-plasmodial activity (IC50 = 13.70±0.71 μM; SI = 30.43) when tested against cultures of P. falciparum 3D7. Intraperitoneal administration of andrographolide (5 mg/kg body weight (bw)) into P. berghei NK65-infected ICR mice resulted in chemo-suppression of 60.17±2.12%, and significantly ($P<0.05$) improved median survival time of infected mice compared to nontreated control. In addition, andrographolide treatment significantly ($P<0.05$) decreased the level of serum pro-inflammatory cytokine, IFN-γ (1.4-fold) whilst the anti-inflammatory cytokines, IL-10 and IL-4 were increased 2.3- and 2.6-fold respectively. Western blot analyses revealed that andrographolide treatment of P. berghei NK65-infected mice resulted in an increased level of phosphorylated GSK3β (Ser9) in liver of infected mice. Andrographolide administration also decreased the levels of phosphorylated NF-κB p65 (Ser536) and phosphorylated Akt (Ser473) in liver of malaria- infected animals. Taken together, our findings demonstrate that the cytokine-modulating effect of andrographolide in experimental malarial infection involves at least in part inhibition of NF-κB activation as a consequence of GSK3β inhibition. Based on its cytokine-modulating effects, andrographolide is thus a plausible candidate for adjunctive therapy in malaria subject to clinical evaluations.