Anti-malarial activities of two actinomycete isolates from sabah soil involved inhibition of glycogen synthase kinase 3ß

Abstract

Exploiting natural resources for bioactive compounds is an attractive drug discovery strategy in search for new anti-malarial drugs with novel modes of action. Initial screening efforts in our laboratory revealed two preparations of soil-derived actinomycetes (H11809 and FH025) with potent anti-malarial activities. Both crude extracts showed glycogen synthase kinase 3β (GSK3β)-inhibitory activities in a yeast-based kinase assay. We have previously shown that the GSK3 inhibitor, lithium chloride (LiCl), was able to suppress parasitaemia development in a rodent model of malarial infection. The present study aims to evaluate whether anti-malarial activities of H11809 and FH025 involve the inhibition of GSK3β. The acetone crude extracts of H11809 and FH025 each exerted strong inhibition on the growth of Plasmodium falciparum 3D7 in vitro with 50% inhibitory concentration (IC50) values of 0.57 ± 0.09 and 1.28 ± 0.11 µg/mL, respectively. The tested extracts exhibited Selectivity Index (SI) values exceeding 10 for the 3D7 strain. Both H11809 and FH025 showed dosage-dependent chemo-suppressive activities in vivo and improved animal survivability compared to non-treated infected mice. Western analysis revealed increased phosphorylation of serine (Ser 9) GSK3β (by 6.79 to 6.83-fold) in liver samples from infected mice treated with H11809 or FH025 compared to samples from non-infected or non-treated infected mice. A compound already identified in H11809 (data not shown), dibutyl phthalate (DBP) showed active anti-plasmodial activity against 3D7 (IC50 4.87 ± 1.26 µg/mL which is equivalent to 17.50 µM) and good chemo-suppressive activity in vivo (60.80% chemo-suppression at 300 mg/kg body weight [bw] dosage). DBP administration also resulted in increased phosphorylation of Ser 9 GSK3β compared to controls. Findings from the present study demonstrate that the potent anti-malarial activities of H11809 and FH025

were mediated via inhibition of host GSK3β. In addition, our study suggests that DBP is in part the bioactive component contributing to the antimalarial activity displayed by H11809 acting through the inhibition of GSK3β.