

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

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 3 β (GSK3 β)-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 GSK3 β . 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 $\mu\text{g/mL}$, 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) GSK3 β (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 $\mu\text{g/mL}$ 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 GSK3 β 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 GSK3 β . 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 GSK3 β .