

**Screening for eukaryotic signal transduction and *Mycobacterium isocitrate lyase* inhibitor from actinomycetes and fungi of dipterocarp rain forests at Imbak Valley, Sabah, Malaysia**

**Abstract**

A diversity of actinomycetes and fungi was isolated from various sites during the Imbak Valley Scientific Expedition 2000. A total of 144 soil samples were collected under trees that have been identified to species or genus level. Imbak Valley is a lowland dipterocarp forest, which is interestingly dominated by *Dryobalanops beccarii*. Isolation of *Streptomyces* and non-*Streptomyces* actinomycetes on HV medium and other specific isolation media for non-*Streptomyces* yielded 203 isolates from 89 soil samples. Morphological characterisation of the isolated actinomycetes was carried out based on aerial mycelium colour, substrate mycelium colour and diffusible pigment production on oatmeal medium. Nine strains of fungi were isolated from the six soil samples plated on PDA medium. All actinomycetes isolates were grown under aerobic condition in liquid culture and extracted with acetone, and used for screening against proteins involved eukaryotic signal transduction. Yeast MAPK kinase and MAP kinase phosphatase were some of the targeted proteins used in this research. MKK1P386 and MKK1P386-MSG5 mutant yeasts were used to screen for these inhibitors, as these yeast kinase and phosphatase have homologous proteins in the MAP kinase signal transduction pathway in human. No inhibitors in the extracts were found in these screenings. Type 1 protein serine/threonine phosphatase (GLC7) in yeast was used to screen inhibitors against PP1 inhibitors and no inhibitor was found. None of the fungal extracts showed any inhibitory activities in all the screening systems. No Ras/Raf inhibitor was found in the *in vivo* Ras/Raf interaction with the yeast two-hybrid screening system, which used to screen for inhibitor against Ras/Raf protein interaction inhibitor. There were 11 actinomycetes extracts that showed toxicity against yeast strain LZ (transformant of Ras/Raf). H7667, a *Streptomyces* toxic to yeast is further screened for inhibitors of the GSK3-beta pathway. H7763, a *Streptomyces* species that showed positive in the primary screen for inhibitor of isocitrate lyase (ICL) which is not itaconic acid (known ICL inhibitor). H7240

showed the strongest susceptibility towards the resin in which the concentration of 5g/l of resin is sufficient to produce growth inhibition of the bacteria.