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Inhibition of Hepatitis C Virus Replication by Chalepin and Pseudane IX Isolated from Ruta angustifolia Leaves

○Tutik Sri WAHYUNI[1,2], Aty WIDYAWARUYANTI[2], Maria Inge LUSIDA[2], Achmad FUAD[2], Soetjipto SOETJIPTO[2], 渕野 祐之[3], 川原 信夫[3], 林 祥剛[1], 青木 千恵[1], 堀田 博[1]（[1]神戸大院医, [2]アイルランガ大, インドネシア, [3]医薬基盤研究所 薬用植物資源研セ）

[Objective]: The development of complementary and/or alternative drugs for treatment of hepatitis C virus (HCV) infection is still needed. Medicinal plants are promising sources for several pharmaceutical agents, either in the form of traditional preparations or as pure active principles. A variety of plants have been tested and proven to be beneficial as antiviral drug candidates against HCV. In this study, we examined extracts, their subfractions and isolated compounds of *Ruta angustifolia* leaves for anti-HCV activities [Method]: *R. angustifolia* leaves were successively extracted with n-hexane, dichloromethane and methanol. The dichloromethane extract which is revealed strong inhibition was performed for further purification. Anti-HCV activities were determined by a cells culture system using Huh 7.5 cell and HCV J6/JFH1 strain. [Result and discussion]: Bioactivity guided isolation and structure determination by using HPLC, LC-MS and NMR were identified six compounds, chalepin, scopoletin, γ-fagarine, arborinine, kokusaginine and pseudane IX. Among them, chalepin and pseudane IX showed strong anti-HCV activities with 50% inhibitory concentration (IC_{50}) of 1.7 ± 0.5 and 1.4 ± 0.2 μg/ml, respectively, without apparent cytotoxicity. Their anti-HCV activities were stronger than that of ribavirin (2.8 ± 0.4 μg/ml), which has been widely used for the treatment of HCV infection. Mode-of-action analyses revealed that chalepin and pseudane IX inhibited HCV at the post-entry step and decreased the levels of HCV RNA replication and viral protein synthesis. We also observed that arborinine, kokusaginine and γ-fagarine possessed moderate levels of anti-HCV activities with IC_{50} values being 6.4 ± 0.7, 6.4 ± 1.6 and 20.4 ± 0.4 μg/ml, respectively, whereas scopoletin did not exert significant anti-HCV activities at 30 μg/ml. These results suggest that chalepin and pseudane IX would be good candidates for seed compound to develop antiviral against HCV.