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Studies on bioactive Quassinoids isolated from Simaroubaceous Plants

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Simaroubaceous plants contain many quassinoids with various biological activities, such as antitumor, antimalarial, antifeedant, insecticidal, antiinflammatory, amoebicidal, andherbicidal effects. We are interested in such biologically active compounds and have isolated many quassinoids from plants, such as *Brucea antidysenterica*, *Picrasma ailanthoides*, and *Brucea javanica*. As part of these studies, we investigated the isolation of quassinoids from Ailanthus altissima SWINGLE (Simaroubaceae).

Three new quassinoids, ailantinol E, ailantinol F , and ailantinol G, and related compounds were isolated from Ailanthus altissima grown in Taiwan. Their structures were elucidated from spectral evidence. Each new quassinoid was evaluated for its antitumor promoting effects against Epstein-Barr virus early antigen activation introduced by 12-*O*-tetradecanoylphorbol-13-acetate in Raji cells. The new quassinoids were found to show potent activity without showing any cytotoxicity. The screening for inhibitors against nitric oxide donor action was also conducted using the new quassinoids and some standard samples.

The aerial parts of A. altissima were extracted with MeOH to afford a crude extract. After evaporation of the solvent, the crude extract was dissolved in aqueous MeOH and re-extracted with *n*-hexane, chloroform, and then *n*-BuOH. The $CHCl_3$ extract was further fractionated using combination Sigel and Sephadex LH-20 column chromatography and pre-parative HPLC to give three new quassinoids and several known quassinoids. In this paper, we report on the isolation and structural elucidation of three new quassinoids, ailantinol E, ailantinol F, and ailantinol G, from A. altissima grown in Taiwan. The known quassinoids chapparin, amarolide-11-acetate, shinjulactone A, shinjulactone C, shinjulactone H, and shinjulactone L, were also isolated from this plant. Each new quassinoid was evaluated for its antitumor promoting effects against Epstein-Barr virus early antigen activation introduced by 12-*O*-tetradecanoylphorbol-13-acetate in Raji cells. The new quassinoids were found to show potent activity without showing any cytotoxicity.

A series of shinjulactone C derivatives were synthesized and evaluated for their anti-tumor promoting effects against Epstein-Barr virus early antigen activation introduced by 12-*O*-tetradecanoylphorbol-13-acetate in Raji cells. Succinate and 3',3'-dimethylsuccinate of shinjulactone C displayed higher activities than shinjulactone C.

The anti-tumor-promoting activity of shinjulactone C (1) and derivatives was tested in a short-term in vitro assay of TPA-induced EBV-EA activation in Raji cells. All of the compounds tested showed an inhibitory effect on EBV activation, and only weak cytotoxicity against Raji cells was observed for all compounds, even at the 1000 mol ratio. Among all compounds tested 3',3'-dimethylsuccinate demonstrated strongest inhibitory effect. Succinate of shinjulactone C (2) and 3',3'-dimethylsuccinate (4) demonstrated higher inhibitory activities against EBV-EA activation than starting material with IC_{50} values of 162 and 155, respectively. Compound 3, 5 and 6 showed

almost equivalent and slightly weaker activity than starting material with IC_{50} values of 204, 232 and 263 respectively. In contrast, compound 7 and 8 showed weak activity with IC_{50} values of 345 and 316, respectively. In point of structure-activity relationship, succinates produced better potency than glutarates. Among 3'-substituted glutaryl shinjulactone C, compounds which do not have bulky moiety, as in glutarate (3), 3'-methylglutarate (5) and 3',3'-dimethylgulutare (6), showed similar or slightly lower inhibitory activities in comparison to starting material. As substituted moieties of glutarate became bulky, as in the case of 3'-ethyl-3'-methylglutarete (7) and 3'-tetramethylene-glutarate (8), activities significantly decreased. These results indicate that appropriate size ester group at C-20 position of shinjulactone C is important for enhancement of the inhibitory activity.

Key words: quassinoid, *Ailanthus altissima*, Simaroubaceae, inhibitory effect on Epstein-Barr virus early antigen (EBV-EA) activation