Cytotoxicity and Synergistic Effect of the Constituents from Roots of Aglaia odorata (Meliaceae)

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Twelve compounds were isolated from the roots of Aglaia odorata. Their structures were established on the basis of NMR and MS data as rocaaglaol (1), rocaaglamide (2), eichlerialactone (3), sapelins A (4), isofouquierone (5), eichlerianic acid (6), shoreic acid (7), agladupol E (8), 3-epimeliantriol (9), cleomiscosins B (10), 2β,3β-dihydroxy-5α-pregnane-16-one (11) and β-D-glucopyranos-1-yl N-methylpyrrole-2-carboxylate (12). Among them, compounds 1 and 2 showed significant cytotoxicity against human cancer cell (HL-60, SMMC-7721, A-549, MCF-7 and SW480) with IC50 values of 0.007–0.095 μM, while compounds 3–5 and 10 and 11 showed moderate to no cytotoxicity (IC50 0.43 to values >40 μM). Compound 6 showed only weak cytotoxicity (IC50 6.87 to >40 μM) and its epimer 7 was completely inactive (IC50 > 40 μM) in the assay. However, potent synergistic effect was observed when the molar ratio of 6 to 7 is between 4:1 and 1:1.

**Keywords:** Aglaia odorata; cytotoxicity; flavaglines; epimer; synergistic effect

1. Introduction

The genus Aglaia (Meliaceae) comprised about 120 species primarily distributed in tropical and subtropical Asia as well as tropical Australia and Pacific islands, with eight species being distributed in China (Peng & Caroline 2008). During the past decades, species in the genus have attracted considerable attention as a prolific source of new natural products with promising bioactive. A number of flavaglines, triterpenoids and other compounds have been isolated from Aglaia (Ishibashi et al. 1993; Ohse et al. 1996; Nugroho et al. 1999; Cai et al. 2005; Su et al. 2006; Ebada et al. 2011; Zhang et al. 2012; Pan et al. 2014). Aglaia odorata, known as Mi-Zi-Lan or Shu-Lan in Chinese folklore, has been used as heart stimulant and febrifuge, or as an herb to treat cough, inflammations, injuries and toxin-causing vomiting (Proksch et al. 2001).
In previous study, some flavaglines (Ohse et al. 1996), triterpenoids (Wang & Yang 2013; Liu et al. 2014), aminopyrrolidine-diamides (Hayashi et al. 1982; Inada et al. 2001) and essential oils (Joycharat et al. 2014) have been reported from *A. odorata*. In the current investigation, 12 compounds (1–12) including 2 epimeric (6 and 7) were isolated from the roots of *A. odorata*. The cytotoxicity of the 12 compounds against five human cancer cell lines and synergistic cytotoxicity effect of the epimers 6 and 7 were investigated.

2. Results and discussion

2.1. Chemical identification

Twelve compounds were isolated from the roots of *A. odorata*, and their structures were determined by comparison of their spectral data reported. They are rocaaglaol (1) (Su et al. 2006), rocaaglamide (2) (Ishibashi et al. 1993), eichlerialactone (3) (Phongmaykin et al. 2008), sapelins A (4) (Jolad et al. 1980), isofouquierone (5) (Waterman & Ampofo 1985), two epimers – eichlerianic acid (6) and shoreic acid (7) (Roux et al. 1998), agladupol E (8) (Xie et al. 2007), 3-epimeliantriol (9) (Lyons & Taylor 1975; Xie et al. 2007), cleomiscosins B (10) (Ray et al. 1982), 2β,3β-dihydroxy-5α-pregnane-16-one (11) (Inada et al. 1997) and β-D-glucopyranos-1-yl N-methylpyrrole-2-carboxylate (12) (Pailee et al. 2011) (see Figure 1).

2.2. Cytotoxicity

All compounds were evaluated for their cytotoxic activities against the five human tumour cell lines (A-549, MCF-7, SW480, SMMC-7721 and HL-60). The results (Table 1) indicated that rocaaglaol (1) and rocaaglamide (2) exhibited significant cytotoxic activities against the five human tumour cell lines, with IC50 values 0.007–0.095 μM. Compound 5 showed cytotoxic activities with IC50 values between 0.43 and 2.65 μM, while the other compounds 3, 4, 6, 10 and 11 showed only weak or no cytotoxic activities, and compounds 7–9 and 12 showed no cytotoxicity (IC50 > 40 μM) in the assay (Tables 1 and 2).

Figure 1. Structures of isolated compounds 1–12.
2.3. Synergistic effect of the emiperics 6 and 7

Although compound 6 showed only weak (IC\textsubscript{50} 6.87–16.15 µM) or no cytotoxicity (IC\textsubscript{50} > 40 µM) and its epimer 7 was completely inactive (IC\textsubscript{50} > 40 µM, Table 2), pronounced cytotoxicity was observed for their mixtures containing molar ratio of 3:2 (6 and 7) (IC\textsubscript{50} of 0.32–0.48 µM for cell lines except SW480, Table 1). Further investigation showed that the two epimers possessed potent synergistic effect against the five human cancer cell lines when the molar ratio of 6 to 7 was between 4:1 and 1:1 (Table 2). Dramatic cytotoxicity enhancement (IC\textsubscript{50} 0.45–0.76 µM) was also observed for the SW480 cell line, which was in essence resistant to both epimers (IC\textsubscript{50} > 40 µM, Table 1). The mechanisms governing the molar ratio-dependent cytotoxic effects are under investigation.

3. Conclusions

The cytotoxicity activity-guided chromatographic separation of A. odorata led to isolation of 12 compounds (1–12), which are as follows: two flavaglines (1 and 2), seven triterpenoids (3–9),
one coumarinolignan (10), one steroid (11) and one alkaloid (12). Among them, flavaglines (1 and 2) showed significant cytotoxicity against five human cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7 and SW480) with values in the range of 0.007–0.039 μM, and some triterpenoids (3–6), coumarinolignan (10) and steroid (11) exhibited moderate to no cytotoxicity with values from 0.43 to values > 40 μM. So it is suggested that flavaglines and triterpenoids are the major types of compounds responsible for the significant anticancer activities of A. odorata. The epimeric triterpenoids (6 and 7) exhibited potent synergistic cytotoxicity with values (IC₅₀) ranging from 0.38 to 2.69 μM with weight ratio (6:7) from 4:1 to 1:1. Compounds 4, 5 and 8–12 are reported for the first time from the genus Aglaia.

**Supplementary material**

Supplementary material relating to this article is available online: experiments (S1), ¹H and ¹³C NMR spectra of 6, 7, two mixtures 6a (6:7 = 3:2), 7a (6:7 = 2:3) S2 and S3.

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**References**


