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Garcixanthones B and C, new xanthones from the pericarps of *Garcinia mangostana* and their cytotoxic activity

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ABSTRACT

Two new prenylated xanthones, garcixanthones B (**1**) and C (**2**) and six known metabolites: gartanin (**3**), 1,3,8-trihydroxy-2-(3-methyl-2-butenyl)-4-(3-hydroxy-3-methylbutanoyl)-xanthone (**4**), rubraxanthone (**5**), 1,3,6,7-tetrahydroxy-8-prenylxanthone (**6**), garcinone C (**7**), and xanthone I (9-hydroxycalabaxanthone) (**8**) were separated from the EtOAc-soluble fraction of the air-dried pericarps of *Garcinia mangostana* (Clusiaceae). Their structures were verified on the basis of spectroscopic data analysis as well as by comparison with the literature. The cytotoxic activity of the new compounds was assessed against MCF7, A549, and HCT116 cell lines using sulforhodamine B (SRB) assay. Compounds **1** and **2** showed significant cytotoxic potential against MCF7 (human breast adenocarcinoma) and A549 (lung carcinoma) cell lines with IC_{50}s 4.27 and 2.65 and 3.08 and 3.91 μM, respectively compared to doxorubicin (0.06 and 0.44 μM, respectively). However, they exhibited moderate activity towards HCT116 (colon carcinoma) cell line.

1. Introduction

Recently, increasing evidence has supported that diet plays an important role in preventing the development of cancer (Wang et al., 2015; Di Francia et al., 2016). Fruits are one of the main dietary components for daily consumption. It is popularly believed that increasing fruit consumption will contribute to the reduced risk of oral cavity, pharynx, esophagus, larynx, stomach, and lung cancers due to the intake of some specific active substances as we consume fruit every day (Grundy et al., 2016). The genus *Garcinia* (Clusiaceae) includes up to 800 species, the fruits of many of which are edible and serve as a substitute for tamarinds in curries (Chen et al., 2008). *G. mangostana* L. (mangosteen, the queen of fruits) is famous for its flavorful and nutritious values in the Southeast Asian countries (Khumsupan and Gritsanapan, 2014). It is known to be a rich source of oxygenated and prenylated xanthones (Ibrahim et al., 2018a,b; Mohamed et al., 2017; Bui et al., 2014). Xanthones are a class of heterocyclic metabolites with a xanthene-9-one frame-work, which connected to different functional groups: hydroxyl, methoxy, prenyl, and dihydrofuran (Liu et al., 2015). They are commonly found in the Moraceae, Guttiferae, Gentianaceae, Polygalaceae and Clusiaceae families (Ibrahim et al., 2018b). These metabolites possessed a wide variety bioactivities: anti-leishmanial, anti-HIV, antimicrobial, antimicrobial, antitumor, anti-inflammatory, antimalarial, anti-quorum sensing, antioxidant, advanced glycation end-products inhibitory, cytotoxic, and antihypertensive (Abdallah et al., 2016a,b, 2017; Mohamed et al., 2014; Auranwiwat et al., 2014; Mahamodo et al., 2014). Its pericarp or ripe fruit has been utilized in Chinese and Ayurvedic medicines for treating various ailments such as: dysentery, gonorrhea, urinary tract infections, chronic ulcers, wounds, suppurations, hyperkeratosis, eczema, psoriasis, and leucorrhoea (Mohamed et al., 2017; Upaganlawar and Badole, 2012). Moreover, its root decoction is helpful in treating menstrual disorders (Ibrahim et al., 2018a,b; Khumsupan and Gritsanapan, 2014). Our previous phytochemical study of *G. mangostana* revealed the existence of xanthones, flavonoids, and phenolics (Mohamed et al., 2014; Abdallah et al., 2016a,b, 2017; Ibrahim et al., 2018a,b). In the course of our search for bioactive metabolites from *G. mangostana*, the EtOAc-soluble fraction of the fruit pericarps was subjected to a phytochemical investigation,

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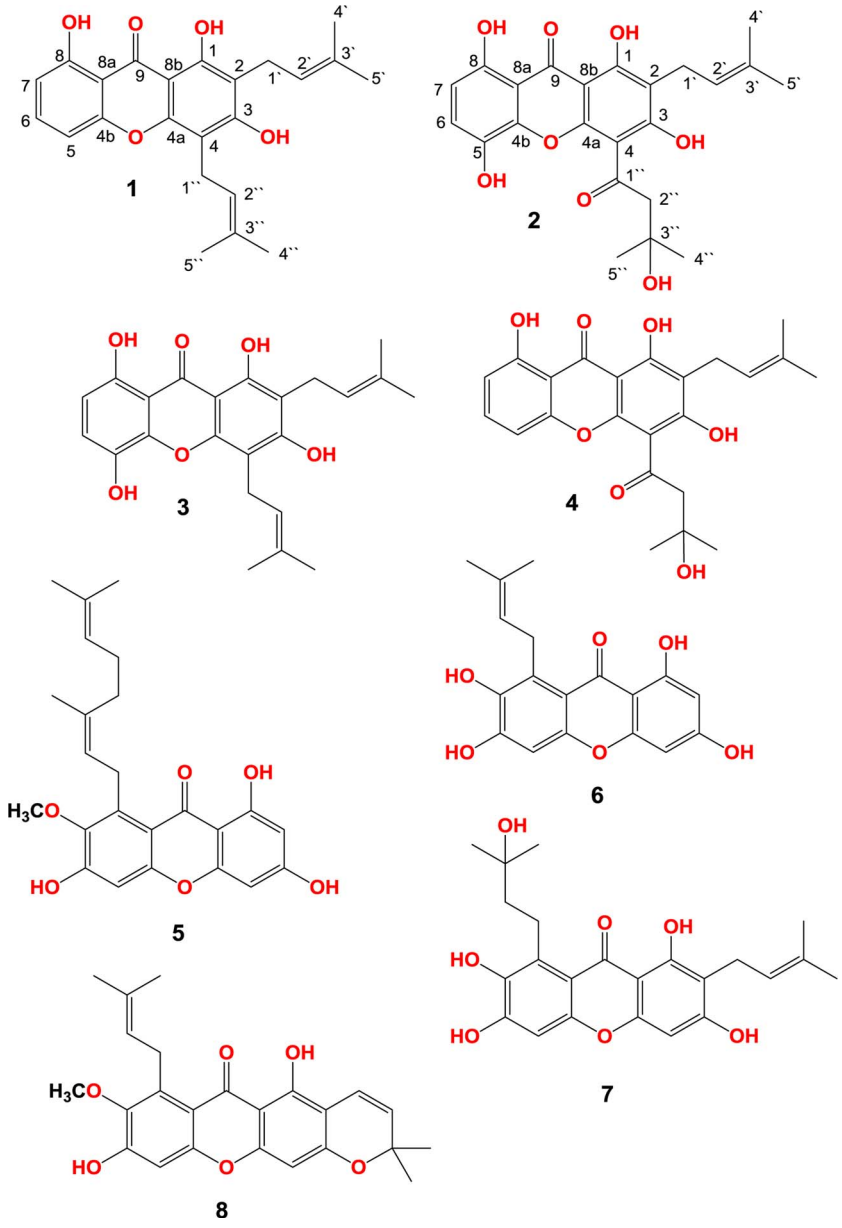

Fig. 1. Structures of compounds **1–8**.

leading to the isolation and structural characterization two new xanthones: garcixanthones B (**1**) and C (**2**) and six known metabolites (**3-8**) (Fig. 1). Their structures were determined unambiguously by one and two dimensional NMR techniques in conjunction with the comparison with data for the known related compounds. Moreover, their cytotoxic capacities towards MCF7, A549, and HCT116 using sulforhodamine B (SRB-U) assay were evaluated.

2. Results and discussion

The powdered fruit pericarps were extracted with acetone. The acetone extract was mixed with water and partitioned with *n*-hexane and EtOAc. The EtOAc soluble-fraction was successfully chromatographed over sephadex LH-20, SiO_2, and RP_{18} columns to furnish two new (**1** and **2**) and 6 known metabolites (**3-8**) (Fig. 1).

Compound **1** was separated as a yellow amorphous powder and gave positive $FeCl_3$ test. It had a molecular formula $C_{23}H_{24}O_5$ based on the observed HRESIMS pseudo-molecular ion peak at *m/z* 381.1698 $[M+H]^+$ (calcd for 381.1702, $C_{23}H_{25}O_5$), requiring twelve degrees of unsaturation. The characteristic UV absorptions at λ_{max} 241, 267, 320, and 358 nm, indicated that **1** was a xanthone derivative (Xu et al., 2014). The IR spectrum exhibited bands at 1658 (chelated C=O), 3436 (phenolic OH), 2946 (C−H aliphatic), 1629 and 895 (olefinic double bond), 1592 (C−O), and 1439 (C=C aromatic) cm^{-1} (Suksamrarn et al., 2002). The HSQC and ^{13}C spectra displayed twenty three carbons resonances: five methines, four methyls, two methylenes, and twelve quaternary carbons, including five oxygen-bonded aromatic carbons and one carbonyl (C-9, δ_C 181.2). The ^1H and ^1H-^1H COSY spectra showed three coupled aromatic protons at δ_H 7.77 (dd, J = 8.5, 1.7 Hz, H-5), 7.25 (t, J = 8.5 Hz, H-6), and 7.30 (dd, J = 8.5, 1.7 Hz, H-7). They correlated to the carbons resonating at δ_C 117.0, 123.9, and 119.8, respectively in the HSQC spectrum characteristic for a *tri*-substituted phenyl moiety (Table 1). This assignment was secured by the HMBC cross peaks of H-7/C-5, H-6/C-4a and C-8, and H-5/C-7 and C-8a (Fig. 2). Moreover, a C-1 chelated OH group's signal was observed at δ_H 13.20. Its location was assured based on its HMBC cross peaks to C-2 (δ_C 109.1), C-8b, and C-1 (δ_C 158.7). The ^1H and ^{13}C NMR spectra exhibited signals for two *tri*-substituted olefinic double bonds at δ_H 5.29