Natural Product Research
Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Thiruventhan Karunakaran, Gwendoline Cheng Lian Ee, Intan Safinar Ismail, Siti Mariam Mohd Nor & Nor Hisam Zamakshshari (2017): Acetyl- and O-alkyl- derivatives of β-mangostin from Garcinia mangostana and their anti-inflammatory activities, Natural Product Research, DOI: 10.1080/14786419.2017.1350666

To link to this article: http://dx.doi.org/10.1080/14786419.2017.1350666

NATURAL PRODUCT RESEARCH, 2017
https://doi.org/10.1080/14786419.2017.1350666

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Acetyl- and *O*-alkyl- derivatives of β-mangostin from *Garcinia mangostana* and their anti-inflammatory activities

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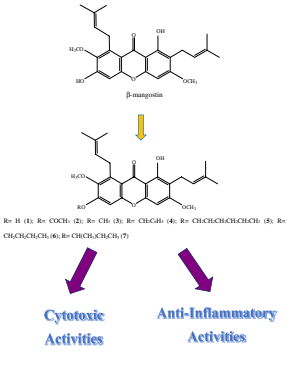
ABSTRACT

Pure β-mangostin (1) was isolated from the stem bark of *Garcinia mangostana* L. One monoacetate (**2**) and five *O*-alkylated β-mangostin derivatives (**3–7**) were synthesised from β-mangostin. The structures of these compounds were elucidated and determined using spectroscopic techniques such as 1D NMR and MS. The cytotoxicities and anti-inflammatory activities of these five compounds against RAW cell 264.7 were tested. The structural-activity relationship studies indicated that β-mangostin showed a significant activity against the LPS-induced RAW cell 264.7, while the acetyl- as well as the *O*-alkyl- β-mangostin derivatives did not give good activity. Naturally occurring β-mangostin demonstrated comparatively better anti-inflammatory activity than its synthetic counterparts.



ARTICLE HISTORY
Received 27 March 2017
Accepted 12 June 2017

KEYWORDS
Acetyl- and *O*-alkyl- β-mangostin; anti-inflammation; β-mangostin

1. Introduction

Garcinia is a plant genus from the family Clusiaceae. It is a large genus of evergreen trees and shrubs distributed in tropical Asia, Africa and Polynesia. The genus *Garcinia* is known to be a rich source of xanthones and polyisoprenylated benzophenones (Ee et al. 2006, 2012;

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Supplemental data for this article can be accessed at https://doi.org/10.1080/14786419.2017.1350666.

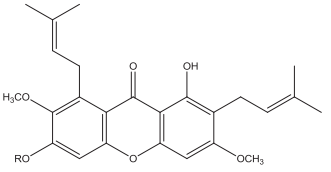
Zhao et al. 2012; Zhou et al. 2015). *G. mangostana* has a vast history of its use as a medicinal plant especially in some parts of South-east Asia (Ee et al. 2014) and has been reported for its anti-inflammatory and cytotoxic properties and is used in therapy for various conditions such as urinary disorders, gonorrhoea and skin disorders (Han et al. 2009; Mohamed et al. 2014). The major bioactive secondary metabolites of *G. mangostana* are xanthone derivatives which consist of α-mangostin and β-mangostin. (Zhao et al. 2010; Dharmaratne et al. 2013; Morelli et al. 2015). β-mangostin was reported to possess several bioactivities such as cytotoxicity towards selective cancer cell lines, anti-microbial and anti-inflammatory (Obolskiy et al. 2009). Much research has also been focused on the potential bioactivities of α-mangostin as it is an equally dominant constituent as β-mangostin. There have been attempts to produce semi-synthetic derivatives of α-mangostin and their structural-activity relationship studies are conducted. It is reported that β-mangostin is a very potent anti-inflammatory agent and suppresses LPS-induced inflammatory response in RAW 264.7 macrophage (Syam et al. 2014). In this study, naturally occurring β-mangostin was modified to six semi-synthetic derivatives (**2**–**7**) via acetylation and *O*-alkylation reactions. β-mangostin (**1**) and compounds **2**–**5** were tested for cytotoxicity and reduction of nitrite production (NO) on RAW 264.7 macrophages for anti-inflammatory activity and the structure-activity relationship studied.

2. Results and discussion

β-mangostin (**1**) (about 300 mg/3 kg) was isolated from the hexane and chloroform extracts of the stem bark of *Garcinia mangostana* through column chromatographic techniques. The structural elucidation of β-mangostin (**1**) using 1D NMR and MS as well as by comparison with previous reported data was carried out (Yahayu et al. 2013). For the acetylation reaction, β-mangostin (**1**) (20 mg) was treated with pyridine and acetic anhydride at room temperature for 48 h to give 6-monoacetate-β-mangostin (**2**) (12 mg, Figure 1). For the *O*-alkylation reaction, β-mangostin (**1**) (20 mg) was reacted with 0.02 mL of the following alkanes: iodomethane or iodohexane or bromomethylbenzene or 1-bromobutane and 2-bromobutane and K_2CO_3 (1.5 g). The reactions yielded 6-*O*-methyl β-mangostin (**3**) (7 mg), 6-*O*-benzyl β-mangostin (**4**) (10 mg), 6-*O*-hexyl β-mangostin (**5**) (14 mg), 6-*O*-sec-butyl β-mangostin (**6**) (5 mg) and 6-*O*-isobutyl β-mangostin (**7**) (3 mg), respectively. The reaction equation and summary of results are shown in Figure 2 and Table S1.

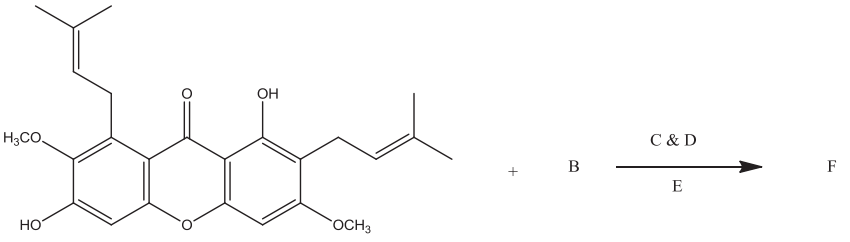
Compounds **4**–**7** are newly synthetised derivatives of β-mangostin. From the ^{13}C NMR spectra, it was observed that the signals of C-5 in the *O*-alkylated derivatives of β-mangostin had shifted 2–3 ppm upfield as the presence of the alkyl chain causes shielding to C-5 (δ_C 101.5) (Ha et al. 2009). For the 6-*O*-monoacetate β-mangostin (**2**) the change in the proton chemical shift for H-5 by 1.2 ppm towards downfield, i.e. δ_H 7.09 (s, 1H) compared to H-5 (δ_H 6.81) for pure β-mangostin (**1**) is due to the electron withdrawing effect of the carbonyl carbon from the acyl group. The same goes for the carbon peak at position 5 (C-5) δ_C 110.4 which was shifted by 9.9 ppm in 6-*O*-monoacetate β-mangostin (**2**). The ^{13}C NMR data for compounds **4**–**7** are summarised in Table S2. Compounds **1**–**5** were subjected to biological evaluation for cytotoxicity and anti-inflammatory effects, while compounds **6** and **7** were not tested for these biological activities due to the low yield which is below 5 mg.

Cytotoxic tests indicated β-mangostin (**1**) to be toxic towards the RAW 264.7 macrophages in a concentration ranging from 500 to 125 µg/mL. The concentration of β-mangostin



R= H (**1**); R= $COCH_3$ (**2**); R= CH_3 (**3**); R=$CH_2C_6H_5$ (**4**); R= $CH_2CH_2CH_2CH_2CH_2CH_3$ (**5**); R= $CH_2CH_2CH_2CH_3$ (**6**); R= $CH(CH_3)CH_2CH_3$ (**7**)

Figure 1. Structures of β-mangostin (**1**), monoacetylated (**2**) and *O*-alkylated β-mangostin.



*B (Reactant), C (Base), D (Solvent), E (Condition), F (Product)

Figure 2. Reaction scheme for semisynthetic β-mangostin derivatives.

showed more than 80% cell viability from a concentration of 62.5 µg/mL and below. For the β-mangostin derivatives **2**–**5**, all the compounds showed more than 80% cell viability for concentrations ranging up to 500 µg/mL. It can be deduced that semi-synthetic modifications of β-mangostin resulted in reduction of the toxicity of pure β-mangostin. The cytotoxicity of compounds **1**–**5** against RAW 264.7 macrophages with concentrations ranging from 500 to 7.8125 µg/mL is plotted in the line graph in Figure 3.

The anti-inflammatory tests conducted using Griess assay showed that β-mangostin (**1**) is still the best candidate to inhibit nitric oxide production at a low IC_{50} value of 11.72 ± 1.16 µM compared to the selected derivatives of β-mangostin **2**–**5** which gave IC_{50} values more than 50 µM. Thus, it can be concluded that the acetylation and *O*-alkylation reactions of β-mangostin did not improve the anti-inflammatory property possessed by pure β-mangostin (**1**) even though the toxicity of compound **1** has been decreased for higher concentrations up to 500 µg/mL. From the structure-activity relationship studies predicted through comparison of the biological activities, the OH is an important functional group that determines the bioactivity of the compound. Replacement of the OH functional group at position C-6 with acetyl or alkyl group decreases or makes it inactive against the inflammation. The anti-inflammatory test results are summarised in Table 1.

3. Experimental

See supplementary data.

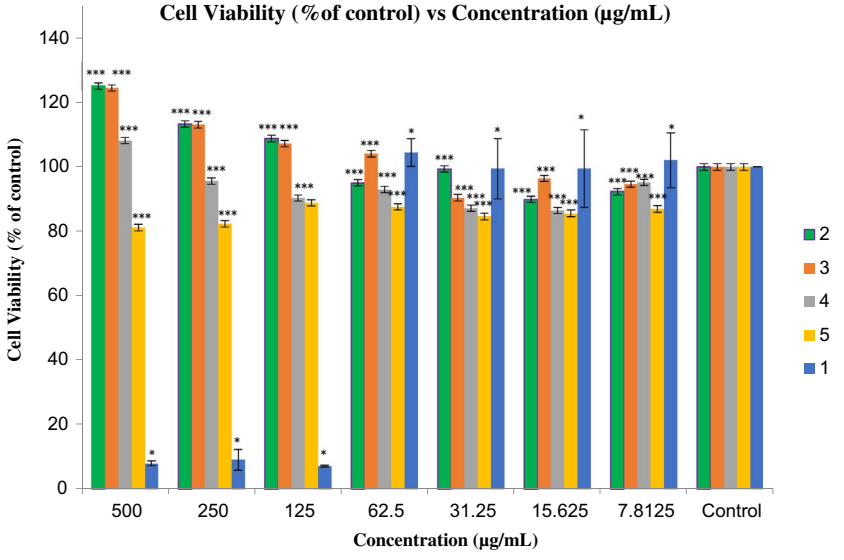


Figure 3. Cell Viability of Compounds **1**–**5**.
Notes: All experiments were conducted in triplicate and results are expressed as mean ± SD. *p*-values were determined by one way analysis of variance followed by Dunnett test (*** $p < 0.0001$, ** $p < 0.005$ and * < 0.05 vs. control (0 µg/mL)). Statistically, *p*-values < 0.05 were considered to be significant.

Table 1. IC_{50} values of compounds **1**–**5**.

Compounds	IC_{50} (µM)
1	11.72 ± 1.16
2	>50
3	>50
4	>50
5	>50
Curcumin	20.0 ± 00

Note: Each value of IC_{50} represented mean ± S.E.M of three independent experiments.

Acknowledgements

The authors wish to express gratitude to the Malaysian Ministry of Higher Education for providing financial support under the FRGS research grant and Universiti Putra Malaysia for providing research facilities and technical support.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Malaysian Ministry of Higher Education.

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