

A GERANYLATED BIPHENYL DERIVATIVE FROM *GARCINIA MANGOSTANA*

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Extracts of root bark, stem bark and the latex collected from the green fruits of *Garcinia mangostana* gave α -mangostin, β -mangostin, γ -mangostin, garcinone-E, methoxy- β -mangostin and a new geranylated biphenyl derivative 3-hydroxy-4-geranyl-5-methoxybiphenyl. The latex of *G. mangostana* consists of more than 75% of xanthenes which have strong antibacterial (anti-MRSA and -VRE), anti-inflammatory, antifungal and a number of other biological activities. Hence the presence of the above highly bioactive compounds in large quantities should be the causative factor for *G. mangostana*'s medicinal value in indigenous medicine.

Keywords: *Garcinia mangostana*; Root bark; Stem bark; Latex; α -mangostin; β -mangostin; γ -mangostin; 3-hydroxy-4-geranyl-5-methoxybiphenyl

INTRODUCTION

Garcinia mangostana L. (Clusiaceae) is a tree found in Sri Lanka and other South East Asian countries, which is very popular due to its delicious fruits. Medicinal uses such as for the treatment of diarrhea, dysentery, skin infections and as an anti-inflammatory agent are reported [1]. Extensive chemical investigations have been conducted on the fruit hull and the leaves of *G. mangostana*. So far, over forty natural products belonging to xanthenes, terpenoids and sugars are reported from this species [1–8] with a variety of biological activities [1,9–13]. Among them, antibacterial activity against MRSA and VRE of α -mangostin is significant [12,13]. Considering the above medicinal applications and biological activities, further studies on the chemistry and biological activity of untested extracts from different plant parts of *G. mangostana* were carried out.

RESULTS AND DISCUSSION

As a continuation of our search for bioactive compounds from Sri Lankan flora [13–15], in the present study we have chemically investigated the root bark, stem bark and the latex extracts of *G. mangostana*. Silica gel column chromatography followed

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by PTLC gave a number of yellow crystalline compounds and their structures were elucidated using spectroscopic data. *n*-Hexane extract of the root bark of *G. mangostana* gave α -mangostin (1) and β -mangostin (2) as the major compounds and two unidentified compounds. Stem bark extract gave α -mangostin (1), β -mangostin (2) and γ -mangostin (3) as the major compounds and methoxy- β -mangostin (4) and a number of unidentified compounds as minor products. Latex collected from the green fruits gave α -mangostin (1), β -mangostin (2), γ -mangostin (3), methoxy- β -mangostin (4) and garcinone-E (5). ^{13}C -NMR spectrum of the yellow semi-solid compound (6) isolated from the hexane extract of the root bark of *G. mangostana* indicated the presence of 23 carbon atoms, and HMQC experiments showed seven of them to be nonprotonated carbon atoms. Further studies on HMQC and HMBC experimental data indicated that five of the nonprotonated carbon atoms which appeared at δ_{C} 114, 141.1, 141.7, 156.2 and 158.7 were aromatic; and the remaining two at δ_{C} 132.3 and 138.5 to be olefinic. In the ^1H -NMR spectrum of the compound 6, appearance of three methyl groups as singlets at δ 1.67, 1.76 and 1.89; two olefinic protons as a multiplets at δ 5.15 and a doublet of a triplet at 5.36, two 2H multiplets at δ 2.14 and 2.19 for four allylic protons and another doublet at δ 3.53 ($J=7.0$ Hz) for two allylic-benzylic protons indicated the presence of a geranyl group in the molecule. Observation of HMBC correlations clearly showed the connectivities within the geranyl group (see Table I). The considerably deshielded 2H allylic type protons appeared at δ_{H} 3.53 and their correlations with three aromatic carbons at δ_{C} 114.9, 156.2 and 158.3 clearly showed the direct attachment of the geranyl group to an aromatic nucleus in the molecule (see Fig. 1). Further ^1H -NMR spectral studies showed the presence of an aryl OMe at δ_{H} 3.94, a hydroxyl group and an unsubstituted phenyl group attached to an aromatic ring, and their positions of attachments were identified and confirmed as C-5, C-3 and C-1 respectively, using HMBC correlations (see Fig. 1). Hence the position of the geranyl group which is attached to the substituted aromatic nucleus was

TABLE I NMR spectral data of compound 6 in CDCl_3

^1H (δ)	^{13}C (δ)	HMBC ^1H - ^{13}C (δ)	H/C-Assignment
1.67 s	18.1	26.9, 124.4, 132	8'-H
1.76 s	26.1	18.7, 124.4, 132	9'-H
1.89 s	16.6	40.19, 122, 138	10'-H
2.14 m	40.2	16.6, 24.4, 26.94, 122.3, 138.1	4'-H
2.19 m	26.9	40.19, 124.4, 138.05, 132.27	5'-H
3.53 d ($J=7.0$ Hz)	22.7	114.9, 122.3, 138.5, 156.2, 158.7	1'-H
3.94 s	56.3	158.65	5-OCH ₃
5.15 m	124.4	-	6'-H
5.36 td ($J=1.12$ and 7.1 Hz)	122.3	16.6, 22.65, 40.2	2'-H
5.56 br s	-	108.4, 114.9, 156.2	3-OH
6.77 d ($J=1.49$ Hz)	102.9	108.4, 114.9, 141.1, 158.7	6-H
6.79 d ($J=1.53$ Hz)	108.4	102.9, 114.9, 141.1, 156.7	2-H
7.37 m	127.7	127.4	4''-H
7.47 m	129.1	129.1, 141.7	2''-H, 6''-H
7.62 m	127.4	127.7, 141.7	3''-H, 5''-H
-	114	-	C-4
-	132.3	-	C-7'
-	138.5	-	C-3'
-	141.1	-	C-1
-	141.7	-	C-1''
-	156.2	-	C-5
-	158.7	-	C-3

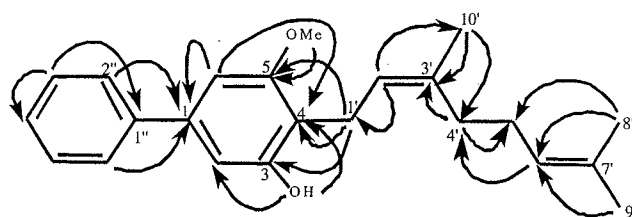
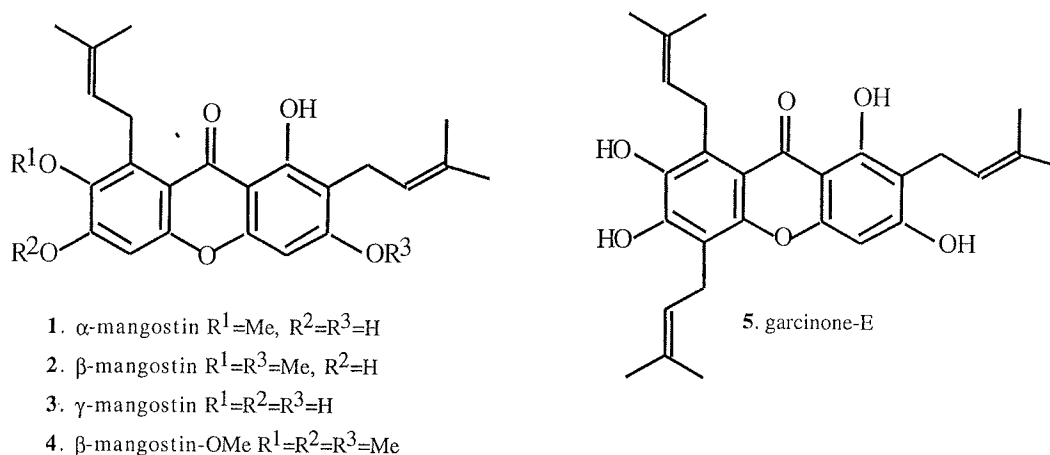
HMBC correlations of **6**

FIGURE 1.

identified as C-4. The CIMS of the compound **6** had M^+ of m/z 336 with m/z 337 $[M+1]^+$ as the base peak, consistent with the proposed molecular formula $C_{23}H_{28}O_2$. All the above information are well in agreement with the structure of the compound (**6**) as 3-hydroxy-4-geranyl-5-methoxybiphenyl. Structures of the known compounds α -mangostin (**1**), β -mangostin (**2**), γ -mangostin (**3**), methoxy- β -mangostin (**4**) and garcinone-E (**5**) were confirmed by comparison with authentic samples and literature data [1–12].

EXPERIMENTAL

General Procedure

1H - and ^{13}C -NMR spectra were recorded on Bruker Avance DPX-300 (300 MHz for 1H -NMR and 75.45 MHz for ^{13}C -NMR) and Bruker Avance DPX-500 (500 MHz for 1H -NMR and 125 MHz for ^{13}C -NMR) spectrometers using TMS as internal standard in $CDCl_3$. Low resolution MS analysis was performed on a AQA LCMS system (Thermoquest, San Jose, CA, USA) and a Finnigan HPLC system.

Plant Material

Garcinia mangostana was collected in December 2000 from Gannoruwa in the Central Province of Sri Lanka and the plant specimens (Number: GM-11-00) were deposited

at the Natural Products Laboratories of the Institute of Fundamental studies, Kandy, Sri Lanka. Plant material was dried, powdered and extracted with *n*-hexane, methylene chloride (CH₂Cl₂) and methanol, respectively and subjected to silica gel column chromatography (Merk Kieselgel 60, 230–400 mesh ASTM with *n*-hexane, CH₂Cl₂ and MeOH as solvents).

Powdered root bark (575 g) of *G. mangostana* was successively extracted with cold *n*-hexane and CH₂Cl₂ to give 13 g (2.26%) of *n*-hexane extract and 38 g (6.6%) of CH₂Cl₂ extract. The *n*-hexane extract of the root bark (6.5 g) when subjected to medium pressure column chromatography (MPLC) followed by preparative thin layer chromatography (PTLC) gave **6** (30 mg, 0.01%) and unidentified products. The CH₂Cl₂ extract of the root bark of *G. mangostana* when subjected to MPLC followed by PTLC gave **1** and **2** as the major compounds, and **3** and sitosterol as minor compounds. Powdered stem bark of *G. mangostana* (1 kg) was successively extracted with cold *n*-hexane and CH₂Cl₂ to give 21 g (2.1%) of *n*-hexane extract and 56 g (5.6%) of CH₂Cl₂ extracts. The *n*-hexane extract of the stem bark (11 g) when subjected to MPLC followed by PTLC gave **1** (707 mg, 0.13%), **2** (2.47 g, 0.47%) and unidentified products. The CH₂Cl₂ extract of the stem bark (25 g) when subjected to MPLC followed by PTLC gave **1** (10.1 g, 2.26%), **2** (3.2 g, 0.72%) and **3** (10 mg, 0.002%). Latex was tapped from the immature green fruits of *G. mangostana* and dried to give a greenish yellow solid. Dried latex was completely dissolved in methanol, filtered to remove plant debris, evaporated and dried to give a greenish yellow solid (11.2 g), which on MPLC followed by PTLC gave **1** (5.08 g, 54.7%), **2** (930 mg, 9.1%), **3** (1.07 g, 10.11%), **5** (70 mg, 0.64%) and **4** (2 mg, 0.02%). Identity of known compounds were confirmed by comparison of spectral and physical data with literature values, and direct comparison with authentic samples. β -mangostin (**2**) was methylated with diazomethane and directly compared with methoxy- β -mangostin-OMe (**4**). Methylation of **1** and **3** also gave **4**.

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References

- [1] S. Suksamrarn, N. Suwannapoch, P. Ratananukul, N. Aroonlerk and A. Suksamrarns (2002). *J. Nat. Prod.*, **65** (5), 761.
- [2] N. Chairungsrierd, K. Takeuchi, Y. Ohizumi, S. Nozoe and T. Ohta (1996). *Phytochemistry*, **43**, 1099–1102.
- [3] F. Asai, H. Tosa, T. Tanaka and M. Jinuma (1995). *Phytochemistry*, **39**, 943–948.
- [4] A.K. Sen, K.K. Sarkar, P.C. Maiumder and N. Banerji (1981). *Phytochemistry*, **20**, 183–185.
- [5] A.J. MacLeod and N.M. Pieris (1982). *Phytochemistry*, **21**, 117–119.
- [6] W. Mahabusarakam and P. Wiriyachitra (1987). *J. Nat. Prod.*, **50**, 474–478.
- [7] M. Parveen, N.U. Khan, B. Achari and P.K. Dutta (1991). *Phytochemistry*, **30**, 361–362.
- [8] K. Balasubramanian and K. Rajagopalan (1988). *Phytochemistry*, **27**, 1552–1554.
- [9] S-X. Chen, Min Wan and Boon-Nee Loh (1996). *Planta Medica*, **62**, 381–382.
- [10] W. Mahabusarakum, S. Phongpaichitra and P. Wiriyachitra (1983). *Warasan Songkhla Nakkharin*, **5**(4), 341 [SciFinder Scholar].
- [11] G. Gopalakrishnan, B. Banumathi and G. Suresh (1997). *J. Nat. Prod.*, **60**, 519–524.

- [12] M. Iinuma, H. Tosa, T. Tanaka, F. Asai, Y. Kobayashi, R. Shimano and K. Miyauchi (1996). *J. Pharm Pharmacology*, **48**, 861.
- [13] Y. Sakagami, M. Iinuma, K.G.N.P. Piyasena and H.R.W. Dharmaratne (2004). *Phytomedicine* (in press).
- [14] H.R.W. Dharmaratne, W.M.N.M. Wijesinghe and V. Thevanasem (1999). *J. Ethnopharmacology*, **66**, 339–342.
- [15] H.R.W. Dharmaratne, W.M.A.P. Wanigasekera, E. Mata-Greenwood and J.M. Pezzuto (1998). *Planta Medica*, **64**, 460–461.