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Antioxidant Xanthones from the Pericarp of *Garcinia mangostana* (Mangosteen)

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As part of ongoing research on cancer chemopreventive agents from botanical dietary supplements, *Garcinia mangostana* L. (commonly known as mangosteen) was selected for detailed study. Repeated chromatography of a CH_2Cl_2-soluble extract of the pericarp led to the isolation of two new highly oxygenated prenylated xanthones, 8-hydroxycudraxanthone G (**1**) and mangostingone [7-methoxy-2-(3-methyl-2-butenyl)-8-(3-methyl-2-oxo-3-butenyl)-1,3,6-trihydroxyxanthone, **2**], together with 12 known xanthones, cudraxanthone G (**3**), 8-deoxygartanin (**4**), garcimangosone B (**5**), garcinone D (**6**), garcinone E (**7**), gartanin (**8**), 1-isomangostin (**9**), α-mangostin (**10**), γ-mangostin (**11**), mangostinone (**12**), smeathxanthone A (**13**), and tovophyllin A (**14**). The structures of compounds **1** and **2** were elucidated by spectroscopic data analysis. Except for compound **2**, which was isolated as a minor component, the antioxidant activities of all isolates were determined using authentic and morpholinosydnonimine-derived peroxynitrite methods, and compounds **1**, **8**, **10**, **11**, and **13** were the most active. α-Mangostin (**10**) inhibited 7,12-dimethylbenz[α]anthracene-induced preneoplastic lesions in a mouse mammary organ culture assay with an IC_{50} of 1.0 μg/mL (2.44 μM).

KEYWORDS: ***Garcinia mangostana*; mangosteen; Clusiaceae; prenylated xanthones; antioxidant activity; mouse mammary organ culture assay**

INTRODUCTION

It is well-recognized that consumption of fruits and vegetables can reduce the incidence of degenerative diseases including cancer, heart disease, inflammation, arthritis, immune system decline, brain dysfunction, and cataracts (*1*−*3*). These protective effects are considered mainly to be due to the presence of various antioxidants in fruits and vegetables. Numerous investigations have indicated that free radicals cause oxidative damage to lipids, proteins, and nucleic acids (*4*, *5*). Antioxidants seem to be very important in the prevention of these diseases, because they can inhibit or delay the formation of oxidizable substrate chain reactions (*6*−*8*).

Garcinia mangostana L. (Clusiaceae), commonly known as mangosteen, is a slow-growing tropical evergreen tree with leathery, glabrous leaves. The tree can attain 6−25 m in height and is mainly found in India, Myanmar, Sri Lanka, and Thailand. Mangosteen has dark purple to red-purple fruits. The edible fruit aril is white, soft, and juicy with a sweet, slightly acid taste and a pleasant aroma (*9*). The pericarp of mangosteen has been used in Thai indigenous medicine for the treatment of skin infections, wounds, and diarrhea for many years (*9*−*11*). Recently, products manufactured from *G. mangostana* have begun to be used as a botanical dietary supplement in the United States, because of their potent antioxidant potential (*12*). The major secondary metabolites of mangosteen have been found to be prenylated xanthone derivatives (*10*, *13*−*15*); some members of this compound class isolated from this plant possess antifungal (*16*), antimicrobial (*14*), antioxidant (*17*), and cytotoxic (*18*) activities.

In the course of our ongoing research project on the chemical constituents and biological activity evaluation of popular herbal remedies (*19*), a CH_2Cl_2-soluble partition of the MeOH extract of the pericarp of mangosteen was found to have significant antioxidant activity in a peroxynitrite-scavenging bioassay. This extract was then purified by repeated chromatography, which led to the isolation of two new highly oxygenated prenylated xanthones, 8-hydroxycudraxanthone G (**1**) and mangostingone (**2**), as well as 12 known xanthones. The structure elucidation of compounds **1** and **2**, the antioxidant activity evaluation of all isolates obtained in this investigation except compound **2**, and the evaluation of α-mangostin (**10**) and γ-mangostin (**11**)

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in a mouse mammary organ culture ex vivo assay were carried out.

MATERIALS AND METHODS

General Experimental Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The UV spectra were obtained with a Beckman DU-7 spectrometer, and the IR spectra were run on an ATI Mattson Genesis Series FT-IR spectrophotometer. NMR spectroscopic data were recorded at room temperature on a Bruker Advance DPX-300 or a DRX-400 MHz spectrometer with tetramethylsilane (TMS) as internal standard. Standard pulse sequences were employed for the measurement of 2D NMR spectra (^{1}H−^{1}H COSY, HMQC, HMBC, and NOESY). Electrospray ionization (ESI) mass spectrometric analysis was performed with a 3-T Finnigan FTMS-2000 Fourier transform mass spectrometer. Column chromatography was carried out with Purasil (230−400 mesh, Whatman, Clifton, NJ). Analytical thin-layer chromatography (TLC) was performed on 250 μm thickness Merck Si gel 60 F_{254} aluminum plates. A SunFire PrepC_{18}OBD column (5 μm, 150 × 19 mm i.d., Waters, Milford, MA) and a SunFire PrepC_{18} guard column (5 μm, 10 × 19 mm i.d., Waters) were used for HPLC, along with two Waters 515 HPLC pumps and a Waters 2487 dual λ absorbance detector.

Chemicals. L-Ascorbic acid, DL-2-amino-3-mercapto-3-methylbutanoic acid (DL-penicillamine), diethylenetriaminepentaacetic acid (DTPA), and 3-morpholinosydnonimine (SIN-1) were purchased from Sigma Chemical Co. (St. Louis, MO). Dihydrorhodamine 123 (DHR 123) and peroxynitrite ($ONOO^-$) sodium salt were obtained from Molecular Probes (Eugene, OR) and Cayman Chemicals Co. (Ann Arbor, MI), respectively.

Plant Material. The freeze-dried powder of the pericarp of *G. mangostana* used in this study was obtained from Nature's Sunshine Products, Inc. A representative sample (lot 0112824) was deposited as a powder in the Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University.

Extraction and Isolation. The dried and milled pericarp of *G. mangostana* (1 kg) was extracted by maceration with MeOH (3 × 5 L) at room temperature, for 3 days each. After filtration and evaporation of the solvent under reduced pressure, the combined crude methanolic extract (324.3 g) was suspended in H_2O (700 mL) to produce an aqueous solution, then partitioned in turn with *n*-hexane (3 × 500 mL), CH_2Cl_2 (3 × 500 mL), EtOAc (3 × 500 mL), and *n*-BuOH (3 × 500 mL) to afford dried *n*-hexane (36.9 g), CH_2Cl_2 (111.2 g), EtOAc (69.3 g), *n*-BuOH (141.7 g), and H_2O-soluble (~7.3 g) extracts. The CH_2Cl_2-soluble partition was found to have significant antioxidant activity in a $ONOO^-$ scavenging bioassay. Therefore, this extract was selected for further detailed purification.

The CH_2Cl_2-soluble extract was subjected to chromatography over a silica gel column, eluted with $CHCl_3$/MeOH (from 100:1 to 1:1), to give 21 fractions (F01−21). F08 (200 mg) was chromatographed over a silica gel column with a *n*-hexane/EtOAc solvent system (20:1 to pure EtOAc) to give ten subfractions (F0801−F0810). Tovophyllin A (**14**; 10 mg) was obtained as a yellow solid from the solution ($CHCl_3$/MeOH, ~10:1) of F0807. Subfractions F0804−F0806 were combined and successively chromatographed over a reversed-phase HPLC column with H_2O/CH_3CN (15:85) at a flow rate of 7.0 mL/min to afford cudraxanthone G (**3**; 5 mg; t_R = 34.0 min) and 8-hydroxycuderaxanthone G (**1**; 6 mg; t_R = 42.5 min). A portion of fraction F10 (600 mg of 3.4 g) was chromatographed over a silica gel column with a *n*-hexane/EtOAc solvent system (20:1 to pure EtOAc) to yield the pure compounds 8-deoxygartanin (**4**; 30 mg) and gartanin (**8**; 340 mg). Garcinone E (**7**; 30 mg) was isolated from F11 by silica gel column chromatography with *n*-hexane/CH_2Cl_2/EtOAc (65:30:5) as the eluting solvent mixture. α-Mangostin (**10**; 13 g) was isolated as a major component from combined fractions F12 (4.8 g) and F13 (20 g) by silica gel chromatography eluted with *n*-hexane/EtOAc (6:1) and on Sephadex LH-20 column chromatography with pure MeOH as solvent. The subfractions of F13 were then combined and chromatographed over a silica gel column eluted with *n*-hexane/EtOAc (5:1 to EtOAc) to give an additional amount of α-mangostin (**10**, 650 mg) and the further subfractions, F1301−F1305. Subfraction F1303 was finally purified by semipreparative reversed-phase HPLC [H_2O/CH_3CN (30:70); flow rate = 6.0 mL/min] to afford a minor new compound, mangostingone (**2**; 1.2 mg; t_R = 15.8 min). Fraction F17 (3.8 g) was chromatographed over a Sephadex LH-20 column using MeOH as eluent, yielding seven subfractions (F1701−F1707). F1702 (200 mg) was purified over a silica gel column with *n*-hexane/EtOAc (4:1) as solvent system to afford 1-isomangostin (**9**, 35 mg) and garcimangosone B (**5**, 3 mg), in order of polarity. F1705 was separated using a semipreparative reversed-phase HPLC column with H_2O/CH_3CN (15:85) at a flow rate of 7.0 mL/min to give mangostinone (**12**; 6 mg; t_R = 28.0 min) and smeathxanthone A (**13**; 8 mg; t_R = 45.0 min). F1706 was purified with a Sephadex LH-20 column using pure MeOH as solvent, to give γ-mangostin (**11**, 600 mg). Fraction F18 was fractionated over a silica gel column with $CHCl_3$/acetone (40:1) as solvents, resulting in 12 subfractions (F1801−F1812). The major subfraction, F1805 (6 g), was chromatographed over a Sephadex LH-20 column, eluting with pure MeOH, to afford another major isolate, γ-mangostin (**11**; 2 g), and seven subfractions (F180501−F180507). F180502 (100 mg) was purified over a silica gel column with $CHCl_3$/acetone (35:1) as solvent, to afford an additional amount of 1-isomangostin (**9**; 20 mg). F180504 (90 mg) was chromatographed over a reversed-phase silica gel column eluted with MeOH/H_2O (7:3), to yield garcinone D (**6**; 10 mg).

8-Hydroxycudraxanthone G (1) was obtained as a yellow solid: UV (MeOH) λ_{max} (log ϵ) 238 (4.28), 263 (4.38), 279 (4.34), 351 (3.97) nm; IR (dried film) ν_{max} 3384, 1623, 1584, 1490, 1217, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.16 (OH), 11.22 (OH), 7.25 (1H, d, J = 9.0 Hz, H-6), 6.69 (1H, d, J = 9.0 Hz, H-7), 5.24 (2H, m, H-2′ and H-2″), 3.81 (3H, s, OCH_3-3), 3.54 (2H, d, J = 6.2 Hz, H-1″), 3.41 (2H, d, J = 6.9 Hz, H-1′), 1.87 (3H, s, H-5″), 1.81 (3H, s, H-5′), 1.74 (3H, s, H-4″), 1.71 (3H, s, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4 (C-9), 164.4 (C-3), 158.8 (C-1), 153.8 (C-8), 152.7 (C-4a), 142.8 (C-10a), 135.9 (C-5), 132.3 (C-3′), 132.2 (C-3″), 123.0 (C-6), 123.0 (C-2″), 122.2 (C-2′), 118.2 (C-2), 113.0 (C-4), 109.8 (C-7), 107.3 (C-9a), 104.9 (C-1a), 62.1 (OCH_3-3), 25.7 (C-4′), 25.5 (C-4″), 23.0 (C-1″), 22.5 (C-1′), 18.0 and 17.9 (C-5′ and C-5″); HRESIMS *m*/*z* 433.16114 $[M + Na]^+$ (calcd for $C_{24}H_{26}O_6Na^+$, 433.16216).

Mangostingone (2) was obtained as a yellow solid: UV (MeOH) λ_{max} (log ϵ) 243 (3.84), 320 (3.65), 354 (3.32) nm; IR (dried film) ν_{max} 3365, 1608, 1578, 1465, 1284, 1162, 1081 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 13.50 (OH), 6.86 (1H, s, H-5), 6.39 (1H, s, H-4), 6.23 (1H, s, H-4″a), 5.86 (1H, s, H-4″b), 5.24 (1H, t, J = 6.8 Hz, H-2′), 4.75 (2H, s, H-1″), 3.73 (3H, s, OCH_3-3), 3.30 (2H, d, J = 6.8 Hz, H-1′), 1.92 (3H, s, H-5″), 1.75 (3H, s, H-4′), 1.61 (3H, s, H-5′); ^{13}C NMR (75 MHz, acetone-d_6) δ 199.1 (C-2″), 182.2 (C-9), 163.3 (C-3), 161.4 (C-1), 161.1 (C-6), 156.1 (C-4a), 155.8 (C-10a), 145.8 (C-3″), 145.7 (C-7), 131.4 (C-8), 131.2 (C-3′), 123.6 (C-2′), 123.6 (C-4″), 111.0 (C-9a), 111.0 (C-2), 103.3 (C-5), 103.2 (C-1a), 93.4 (C-4), 61.3 (OCH_3-3), 37.9 (C-1″), 25.9 (C-4′), 22.0 (C-1′), 18.1 (C-5″), 17.9 (C-5′); HRESIMS *m*/*z* 447.14323 $[M + Na]^+$ (calcd for $C_{24}H_{24}O_7Na^+$, 447.14142).

Measurement of Peroxynitrite Scavenging Activity. $ONOO^-$ scavenging activity was measured by monitoring the oxidation of nonfluorescent DHR 123 to highly fluorescent rhodamine 123 using the modified method of Kooy et al. (*20*). Briefly, DHR 123 (5 mM) in EtOH, purged with nitrogen, was stored at −80 °C as a stock solution. This solution was not exposed to light, prior to the study. The rhodamine buffer (pH 7.4) consisted of 50 mM sodium phosphate dibasic, 50 mM sodium phosphate monobasic, 90 mM sodium chloride, 5 mM potassium chloride, and 100 μM DTPA. The final concentration of DHR 123 was 5 μM. The buffer in this assay was prepared before use and placed on ice. The concentrations of compounds tested were in the range from 0.2 to 100 μM in 10% DMSO. The background and final fluorescent intensities were measured 5 min after treatment with and without the addition of authentic $ONOO^-$ in 0.3 N sodium hydroxide (10 μM) or SIN-1 in deionized water (10 μM). DHR 123 was oxidized rapidly by $ONOO^-$, superoxide anion ($O_2^{\bullet -}$), and nitric oxide ($NO^{\bullet}$). The fluorescence intensity of oxidized DHR 123 was measured with an LS55 luminescence spectrometer (Perkin-Elmer, Boston, MA) at the excitation and emission wavelengths of 480 and 530 nm, respectively. Values of $ONOO^-$ scavenging activity (50% inhibition, IC_{50}) were expressed as the mean (n = 3) for the final fluorescence intensity

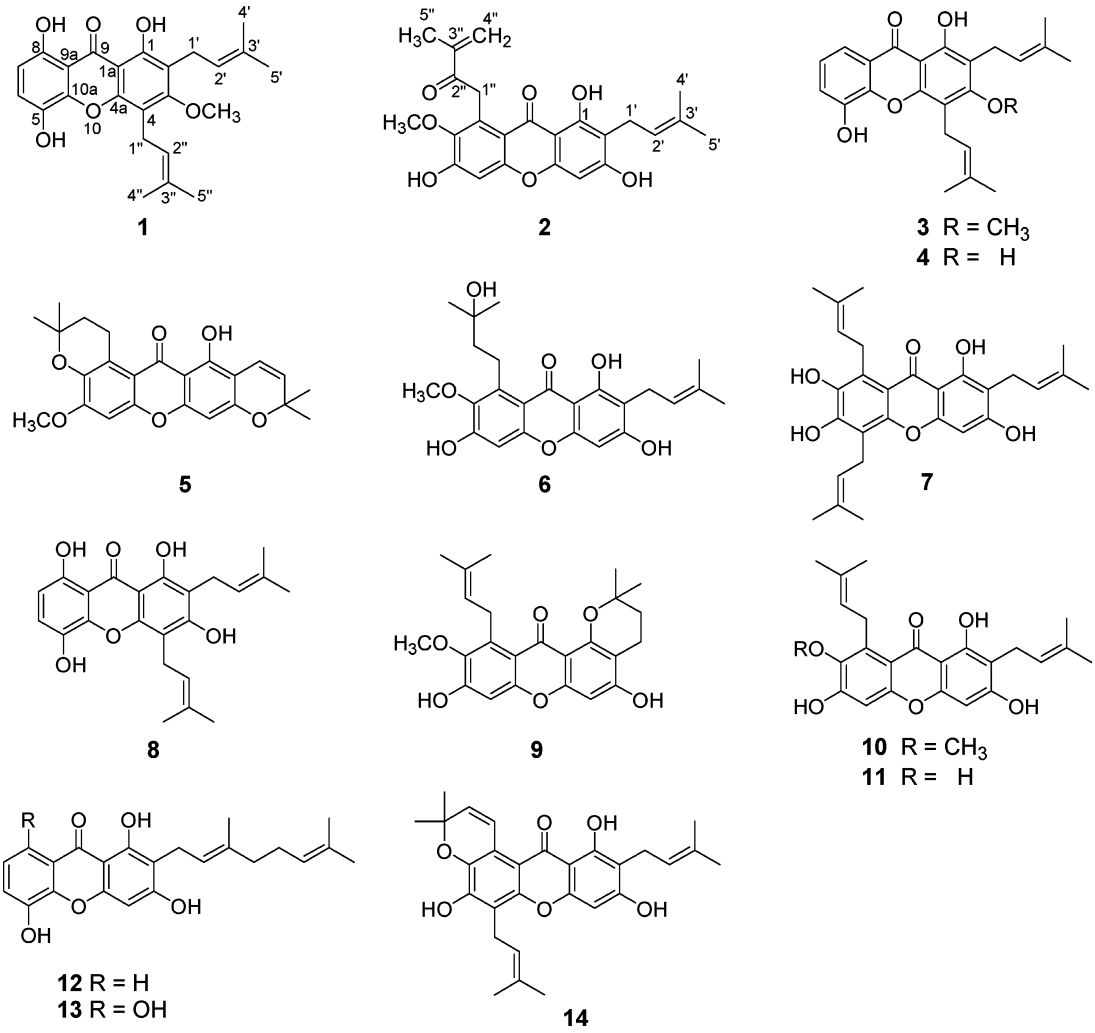

Figure 1. Structures of compounds isolated from the pericarp of *G. mangostana*.

minus background fluorescence by the detection of oxidation of DHR 123. DL-Penicillamine was used as a positive control.

Mouse Mammary Organ Culture Assay. This assay was carried out according to an established protocol (*21*). In brief, 4-week-old BALB/c female mice (Charles River, Wilmington, MA) were pretreated for 9 days with 1 μg of estradiol and 1 mg of progesterone. On the 10th day, the mice were sacrificed and the second pair of thoracic mammary glands was dissected on silk and transferred to 60 mm culture dishes containing 5 mL of Waymouth's 752/1 MB medium supplemented with streptomycin, penicillin, and L-glutamine. The glands were incubated for 10 days (37 °C, 95% O_2 and 5% CO_2) in the presence of growth-promoting hormones (5 μg of insulin, 5 μg of prolactin, 1 μg of aldosterone, and 1 μg of hydrocortisone per milliliter of medium). Glands were exposed to 2 μg/mL 7,12-dimethylbenz[*a*]anthracene (DMBA) between 72 and 96 h. After their exposure, glands were rinsed and transferred to new dishes with fresh medium. The fully differentiated glands were then permitted to regress by withdrawing all hormones except insulin for 14 additional days. Test compounds were present in the medium during days 1−10 of culture; mammary glands were scored for the incidence of lesions.

RESULTS AND DISCUSSION

Repeated column chromatography of the CH_2Cl_2-soluble fraction of the pericarp of *G. mangostana* led to the isolation of two new (**1** and **2**) and 12 known prenylated xanthones (**Figure 1**). The structures of the known compounds cudraxanthone G (**3**) (*22*), 8-deoxygartanin (**4**) (*23*), garcimangosone B (**5**) (*24*), garcinone D (**6**) (*25*), garcinone E (**7**) (*26*), gartanin (**8**) (*27*), 1-isomangostin (**9**) (*10*), α-mangostin (**10**) (*28*), γ-mangostin (**11**) (*26*), mangostinone (**12**) (*29*), smeathxanthone A (**13**) (*30*), and tovophyllin A (**14**) (*31*) were identified by comparing their physical and spectroscopic data (UV, ^{1}H NMR, ^{13}C NMR, DEPT, and 2D NMR) with those of published values and were confirmed by their HRESIMS data. Compounds **10** and **11** were found to be the major components of the CH_2Cl_2-soluble extract of the pericarp of *G. mangostana*.

A molecular formula of $C_{24}H_{26}O_6$ was determined for compound **1** by its HRESIMS (*m*/*z* 433.16114 $[M + Na]^+$). The ^{1}H NMR spectrum revealed two downfield singlets at δ_H 11.22 and 12.16, suggesting the presence of two hydrogen-bonded hydroxy groups in the molecule of **1**. The ^{1}H NMR spectrum of this compound also displayed the characteristic signals of two ortho-coupled aromatic protons at δ_H 7.25 (1H, d, J = 9.0 Hz, H-6) and 6.69 (1H, d, J = 9.0 Hz, H-7), two olefinic protons at δ_H 5.24 (2H, m, H-2′ and H-2″), one methoxy group at δ_H 3.81 (3H, OMe-3), and four tertiary methyls at δ_H 1.87 (3H, s, H-5″), 1.81 (3H, s, H-5′), 1.74 (3H, s, H-4″), and 1.71 (3H, s, H-4′). The ^{13}C NMR spectrum of compound **1** showed 24 resonance signals. The presence of two 3-methylbut-2-enyl functionalities in compound **1** could be assigned by interpretation of its ^{1}H and ^{13}C NMR spectroscopic data as well as the correlations observed in the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra. In addition to the signals of these two prenyl groups and the signal of a typical methoxy substituent group, only 11 carbon resonance signals composed of two aromatic rings and one doubly conjugated carbonyl carbon (δ_C 185.4)

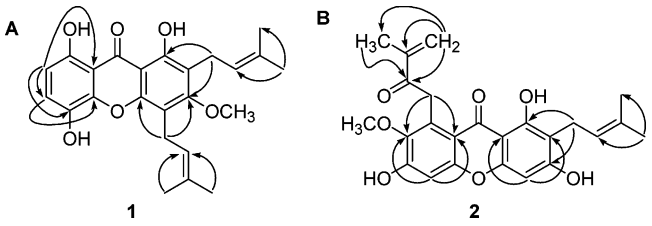

Figure 2. Selected HMBC correlations of compounds **1** and **2**.

remained for compound **1**. These NMR data suggested that compound **1** is a prenylated xanthone derivative (*27*, *29*). The two downfield hydrogen-bonded hydroxy singlets at δ_H 11.22 and 12.16 suggested the locations of two of the three hydroxy groups to be at C-1 and C-8 in the molecule of **1**. In the HMBC spectrum (**Figure 2A**), correlations were observed from H-6 to C-5, C-8, and C-10a, from H-7 to C-5, C-6, C-8, and C-9a, from OMe-3 to C-3, and from both H-1′ and H-1″ to C-3. These correlations were used to assign the positions of two prenyl units and the methoxy group. Therefore, compound **1** was determined to be 8-hydroxycudraxanthone G.

A sodiated molecular ion peak at *m*/*z* 447.14323 $[M + Na]^+$ in its HRESIMS was used to assign a molecular formula of $C_{24}H_{24}O_7$ for compound **2**. The UV (λ_{max} at 243, 320, and 354 nm) and IR [ν_{max} at 3365 (O—H), 1608 (C═O), and 1578 (aromatic ring) cm^{-1}] spectroscopic data of compound **2** were very similar to those of **1**. The ^1H and ^{13}C NMR spectroscopic data suggested that compound **2** is also a prenylated xanthone. In the ^1H NMR spectrum of **2**, only one downfield singlet for a hydrogen-bonded hydroxy group was displayed at δ_H 13.50 (OH-1). In addition to a methoxy group and the signals of the xanthone skeleton, ten other resonances were shown in the ^{13}C NMR spectrum of **2**. By interpretation of the chemical shifts and splitting patterns as well as the observed 2D NMR ($^1H-^1H$ COSY, HMQC, and HMBC) correlations of the nonskeletal protons and carbons, the two prenyl units in the molecule of **2** were determined as 3-methylbut-2-enyl and 2-oxo-3-methylbut-3-enyl, respectively. On the basis of the above-mentioned NMR data analysis and the determined molecular formula, the presence of three hydroxyl groups could be deduced. The positions of all substituents, namely, one methoxy group, two prenyl units, and three hydroxy groups, were assigned by careful analysis of the correlations obtained in the HMBC spectrum (**Figure 2B**). The observed key HMBC correlations for the structure assignment were from OH-1 to C-1a, C-1, and C-2, from H-1′ to C-1, C-2, and C-3, from H-1″ to C-7, C-8, and C-9a, and from the methoxy singlet at δ_H 3.73 to C-7. Hence, compound **2**, mangostingone, was determined to be 1,3,6-trihydroxy-7-methoxy-2-(3-methylbut-2-enyl)-8-(2-oxo-3-methylbut-3-enyl)-xanthone.

The antioxidant activities of 13 isolated compounds (**1** and **3**—**14**) were determined using the authentic $ONOO^-$ and SIN-1-derived $ONOO^-$ methods (*20*, *32*). Compound **2** was obtained in insufficient amounts for this testing. The scavenging activities on $ONOO^-$ of the compounds tested are summarized in **Table 1**. Five of the xanthones (**1**, **8**, **10**, **11**, and **13**) were demonstrated to possess potent antioxidant activity in both assays tested. The species $ONOO^-$, generated from $NO^\bullet$ and $O_2^{\bullet-}$ in vivo, has been reported to act as an oxidant and be involved in the initiation of carcinogenesis, along with $NO^\bullet$ (*33*). Because there is a lack of defense systems against $ONOO^-$ in the body and the highly reactive peroxynitrous acid (ONOOH), formed by protonation of $ONOO^-$, easily decomposes to induce more highly reactive oxygen species, such as $^\bullet OH$, there is considerable interest in the development of $ONOO^-$ scavengers (*34*, *35*). Until now, two possible pathways of phenolic compounds to scavenge $ONOO^-$ may be represented by nitration and electron donation. Monohydroxylated phenolic compounds, such as ferulic acid and *p*-coumaric acid, act as $ONOO^-$ scavengers by nitration. On the other hand, compounds with a catechol moiety, such as caffeic acid and chlorogenic acid, reduce $ONOO^-$ generated from $NO^\bullet$ and $O_2^{\bullet-}$ by electron donation (*36*). The presence of two hydroxyl groups at the C-5 and C-8 positions in compounds **1**, **8**, and **13** was consistent with their potent antioxidant effects (*37*, *38*). Compounds **10** and **11** both possess hydroxyl groups at positions C-1, C-3, and C-6.

Table 1. Peroxynitrite Scavenging Activity of Compounds Isolated from the Pericarp of *G. mangostana* (Mangosteen)[a]

	peroxynitrite	
compound	authentic $ONOO^-$ (IC_{50}, μM)	SIN-1-derived $ONOO^-$ (IC_{50}, μM)
1	4.6	10.0
3	>30	3.2
4	>30	11.9
5	15.9	>30
6	26.4	15.1
7	14.1	>30
8	9.1	9.3
9	19.2	24.1
10	12.2	<0.49
11	8.0	3.1
12	>30	>30
13	2.2	9.7
14	>30	>30
DL-penicillamine[b]	3.1	7.4

[a] Compound **2** was not evaluated in these assays because it was isolated in insufficient quantity. A compound is considered to be inactive if its IC_{50} value is >30 μM. [b] Positive control.

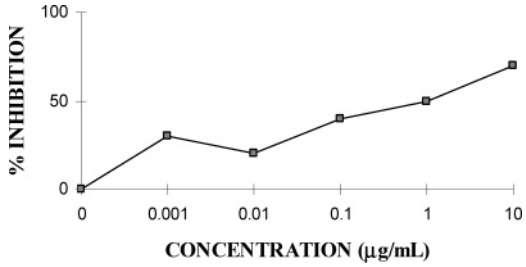

Figure 3. Dose-dependent inhibition activity of α-mangosteen (**10**) in a mouse mammary organ culture assay.

The above results are supportive of the use of the pericarp of *G. mangostana* as an antioxidant botanical dietary supplement. It is worth noting that two of the active isolates obtained in the present investigation, α-mangostin (**10**) and γ-mangostin (**11**), were found to be major components of the CH_2Cl_2-soluble extract of the pericarp of *G. mangostana*. Therefore, these two compounds may be used as marker components for quality control of this botanical dietary supplement.

In addition to their peroxynitrite antioxidant activity, α-mangostin (**10**) and γ-mangostin (**11**) were evaluated for their potential to inhibit DMBA-induced preneoplastic lesions in a mouse mammary organ culture (MMOC) assay (*39*, *40*). At a concentration of 10 μg/mL, the percent inhibitions of compounds **10** and **11** were 57.1 and 42.9, respectively. The more active compound, α-mangostin (**10**), was then further evaluated in a dose—response MMOC assay, and it exhibited an IC_{50} of 1.0 μg/mL (2.44 μM) (**Figure 3**). As noted previously (*21*), substances active in this model system are considered to be good candidates for further investigation in full-term cancer chemo-

preventive studies in experimental animal models. In recent work, a crude α-mangostin (**10**) preparation was found to have efficacy in inhibiting preneoplastic lesions in a rat colon carcinogenesis model (*41*). Accordingly, the further investigation of extracts of magosteen pericarp and α-mangostin as potential cancer chemopreventive agents seems to be warranted.

α-Mangostin (**10**) has been reported as a significant antimycobacterial substance against *Mycobacterium tuberculosis* with a minimum inhibitory concentration value of 6.25 μg/mL (*12*). In addition, this xanthone was found to be a histamine H_1 receptor antagonist (*42*). α-Mangostin (**10**) was also reported as a selective inhibitor against bovine brain-derived acidic sphingomyelinase (*43*). Recently, synthetic methods for this prenylated xanthone have been reported (*44*, *45*).

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