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Benzophenones and Biflavonoids from *Garcinia livingstonei* Fruits

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A series of 13 known compounds, including seven benzophenones [guttiferone A (**1**), guttiferone K (**2**), xanthochymol (**3**), guttiferone E (**4**), cycloxanthochymol (**5**), isoxanthochymol (**6**), and gambogenone (**7**)], five biflavonoids [amentoflavone (**8**), 3,8″-biapigenin (**9**), (+)-volkensiflavone (**10**), (+)-morelloflavone (**11**), and (+)-fukugiside (**12**)], and the xanthone derivative alloathyriol (**13**), were identified from the fruits of *Garcinia livingstonei* (Clusiaceae). This is the first time that compounds **2**−**7**, **9**, **12**, and **13** have been reported in this species. The cytotoxicity of benzophenones **1** and **2** was assessed for their effect on HCT-116, HT-29, and SW-480 human colon cancer cell lines. Both compounds exhibited strong activity against HCT-116 and HT-29 cell lines with IC_{50} values between 5 and 10 μM, and somewhat weaker activity with SW-480 cells (IC_{50} values ranging from 18 to 25 μM).

KEYWORDS: ***Garcinia livingstonei*; cytotoxicity; benzophenones; biflavonoids**

INTRODUCTION

Over the past decade, we have established a multidisciplinary research program focused on the discovery of active principles from edible plants useful in the prevention and/or treatment of colon cancer (*1*−*4*). We have found that the Clusiaceae family is an important source of bioactive prenylated benzophenones with cytotoxic/antiproliferative activities (*5*).

Garcinia livingstonei T. Anderson (Clusiaceae), commonly known as African mangosteen or imbe, is a widespread plant in the warmer parts of Africa, from the north of Durban as far as Somalia and Guinea. In southern Africa, it is distributed widely in the Limpopo and Zambezi Valleys (*6*, *7*). *G. livingstonei* is a small tree that grows to 1.8 m and bears small (10−40 mm diameter) yellowish-orange fruits containing a sticky juice. The fruits are edible and have a pleasant flavor. The pulp can be eaten fresh, made into a jam or jellies, or used to prepare ice cream or alcoholic beverages (*7*−*9*).

Previous chemical and pharmacological investigations on the root bark, leaves, and fruits of *G. livingstonei* have reported the presence of several xanthones, biflavonoids, and benzophenones, with antiparasitic, antiviral, antifungal, antibacterial, and cytotoxic activities (*10*−*16*). On the basis of these reports and our continuing research interest in edible plants with cancer chemopreventive potential, the present investigation was undertaken to determine the chemical composition of the MeOH extract of *G. livingstonei* fruits using high-performance liquid chromatography−photodiode array (HPLC-PDA) and electrospray ionization time-of-flight mass spectrometry (ESI-ToF-MS) analyses, and to evaluate the cytotoxic effect against HCT-116, HT-29, and SW-480 human colon cancer cell lines of the major constituents. The fruits of *G. livingstonei* were selected for this study because of their long-recorded use by humans as food (*6*−*9*) and thus their likely safety.

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Table 1. LC-MS Analysis (Retention Time, UV Spectra, and Molecular Masses) of Phenolic Compounds in the EtOAc Extract of *G. livingstonei*

compound	$t_R \pm$ SD[a] (min)	λ_{max} (nm)	MW (*m/z*)
guttiferone A (**1**)	28.11 ± 0.03	279.3	601 [M − H]
guttiferone K (**2**)	28.11 ± 0.03	279.3	601 [M − H]
xanthochymol (**3**)	28.67 ± 0.05	229.6, 278.1	601 [M − H]
guttiferone E (**4**)	28.67 ± 0.05	229.6, 278.1	601 [M − H]
cycloxanthochymol (**5**)	35.49 ± 0.02	233.1, 275.7	601 [M − H]
isoxanthochymol (**6**)	35.76 ± 0.01	232.0, 275.7	601 [M − H]
gambogenone (**7**)	16.73 ± 0.04	220.2, 281.7, 321.0	451 [M − H]
amentoflavone (**8**)	17.25 ± 0.03	229.6, 268.6, 288.8, 334.1	539 [M + H]
3,8″-biapigenin (**9**)	19.99 ± 0.01	217.8, 269.8, 331.7	539 [M + H]
(+)-volkensiflavone (**10**)	19.53 ± 0.04	222.5, 287.6, 323.3	541 [M + H]
(+)-morelloflavone (**11**)	17.40 ± 0.03	226.1, 288.8, 331.7	557 [M + H]
(+)-fukugiside (**12**)	14.79 ± 0.02	271.0, 291.2, 331.7,	719 [M + H]
alloathyriol (**13**)	18.65 ± 0.02	237.9, 254.4, 315.0, 363.7	273 [M − H]

[a] Mean ± SD (n = 3).

MATERIALS AND METHODS

Standards and Chemicals. The reference standards of compounds **3**−**13** were previously isolated in our laboratory from the related species *Garcinia xanthochymus* and were identified by spectral data (UV, IR, MS, and one- and two-dimensional NMR) (*1*). All isolates have purities of ≥98% by HPLC-PDA analyses. ACS grade ammonium acetate, dimethyl

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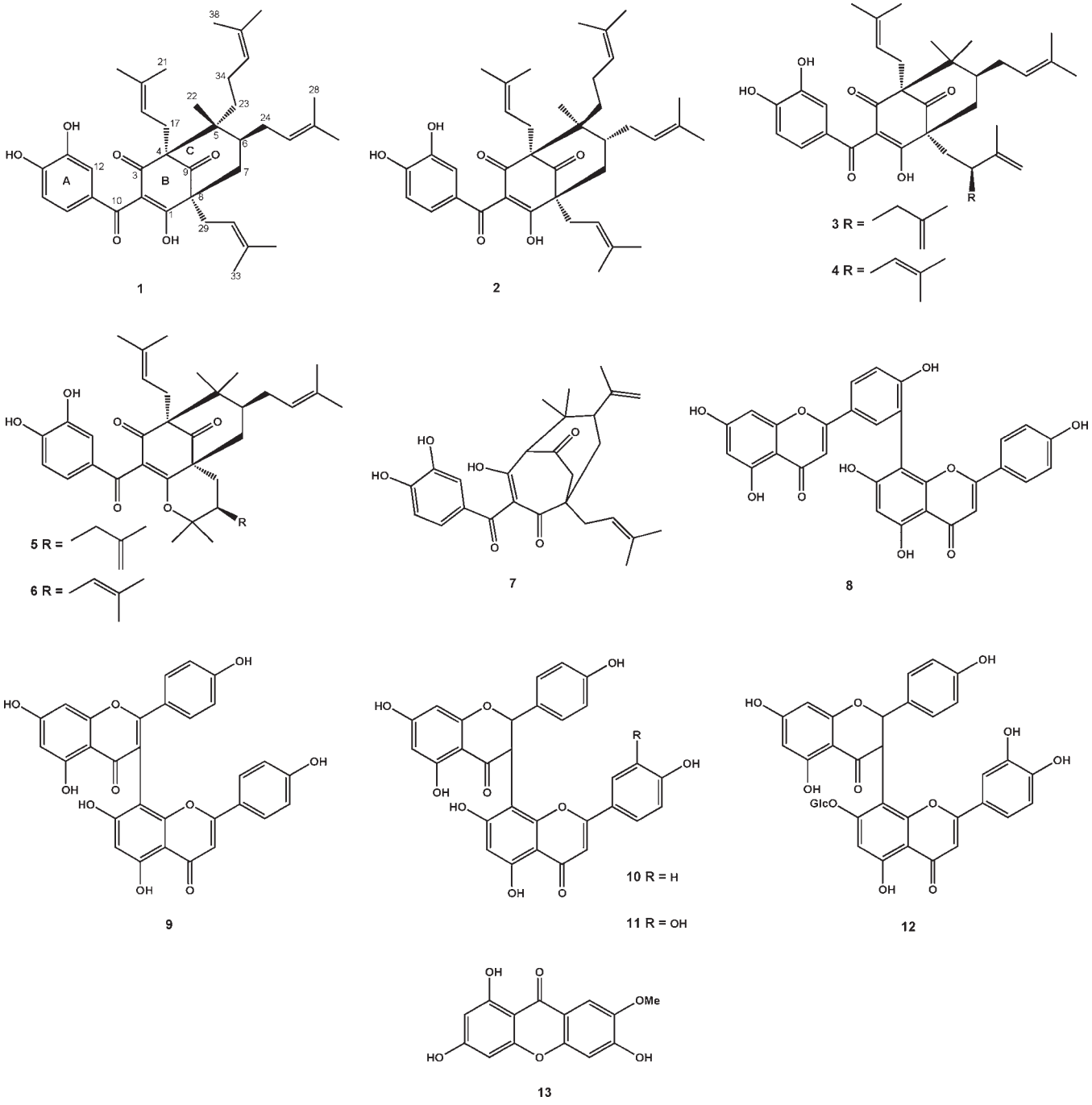

Figure 1. Compounds identified from *G. livingstonei* fruits.

sulfoxide (DMSO), 5-fluorouracil (5-FU), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma-Aldrich (St. Louis, MO). HPLC- and MS-grade MeCN, MeOH, and water were obtained from J. T. Baker (Phillipsburg, NJ), and ACS-grade *n*-butanol, MeOH, and EtOAc were provided by VWR Inc. (Bridgeport, PA).

Plant Material. Fresh fruits of *G. livingstonei* were collected in the Fruit and Spice Park (Homestead, FL), in July of 2005, and were authenticated by Chris Rollins. A voucher specimen (code Reynertson 78) was deposited at the Steere Herbarium of the New York Botanical Garden (Bronx, NY).

General Methods. UV spectra were obtained on a Lambda 2 UV/vis spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz), including correlation spectroscopy, nuclear Overhauser effect spectroscopy, heteronuclear multiple quantum coherence, and heteronuclear multiple bond correlation experiments, were recorded on a Bruker Avance 300 NMR spectrometer in acetone-d_6 or MeOH-d_4. Column chromatography was carried out on Sephadex LH-20 (25−100 μm; Pharmacia Fine Chemicals, Piscataway, NJ). Thin-layer chromatography (TLC) analyses were performed on Si gel plates (F_{254}, 250 μm, Type 60) supplied by EM Science Co. (Darmstadt, Germany), using a mobile phase composed of *n*-hexane−EtOAc−EtOH−formic acid (40:10:1.25:0.2). HPLC analyses were conducted on a Waters 2695 HPLC instrument equipped with a PDA detector (Waters, Milford, MA). All analyses were performed on a Synergi Hydro RP column (250 mm × 4.6 mm i.d., 4 μm) (Phenomenex, Torrance, CA) with a guard column (4 mm × 3 mm i.d.) of the same material (Phenomenex). An elution gradient (flow rate, 1 mL/min) was used with the mobile phases (A) 10 mM ammonium acetate and (B) MeCN. The gradient schema was initially 90% A for 4 min, then changed to 100% B in 34 min, and was isocratic until 45 min. Finally, it returned to initial conditions in 10 min. The injection volume was 10 μL in all cases, the detection was at 280 nm, and the column was kept at 30 °C throughout analysis. Control of the equipment, data acquisition, processing, and management of chromatographic information were performed by the

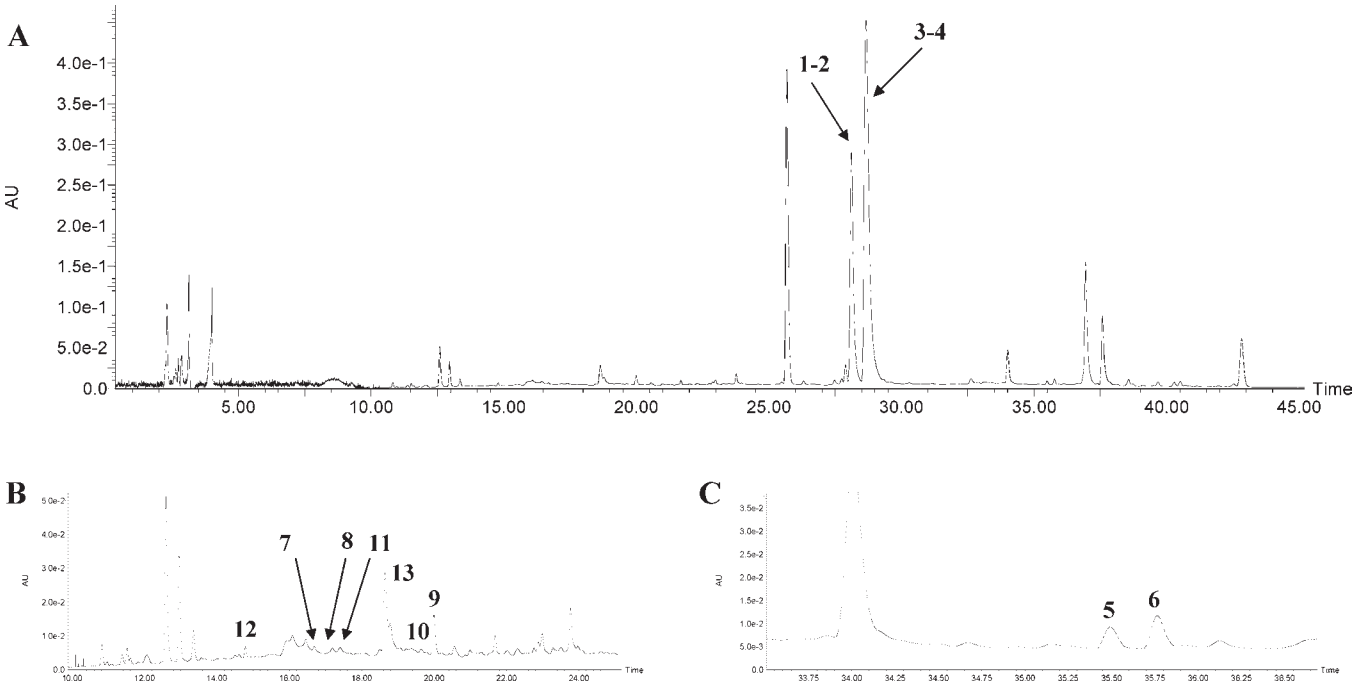

Figure 2. (**A**) HPLC-PDA chromatogram of the EtOAc-soluble fraction of *G. livingstonei* fruits. (**B** and **C**) Close up of selected regions of the chromatogram. For peak assignments, see **Table 1**.

Empower 2 software (Waters). Preparative HPLC separations were carried out using a Waters 600 instrument with a 486 tunable absorbance detector (Waters) on a C18 Nucleosil column (250 mm × 21.1 mm i.d., 10 μm) (Phenomenex). The mobile phase consisted of water (A) and MeOH (B) at 20 mL/min, with a linear gradient from 30 to 5% of (A) in 45 min run time at room temperature. Liquid chromatography−mass spectrometry (LC-MS) analyses were performed with a Waters LCT Premier XE time-of-flight (ToF) mass spectrometer equipped with an ESI source (Waters). The equipment was operated in both negative and positive ion modes, and was controlled by MassLynx 4.1 software (Waters) using the following parameters: source temperature, 120 °C; capillary temperature, 400 °C; capillary voltage, 3000 V; sample cone voltage, 20 V; and desolvation gas flow, 600 L/h. Measurements were performed in the W mode, and the data were collected in the full-scan mode from 100 to 1000 m/z. Lock spray containing leucine−enkephalin (554.261 m/z) was used for accuracy and reproducibility.

Extraction and Isolation. The frozen fruits (4.3 kg) of *G. livingstonei* were deseeded, and the pulp (2.8 kg) was exhaustively extracted in a blender with MeOH (3.0 L) at room temperature. The combined MeOH extracts were concentrated under reduced pressure to dryness to give a dark brown residue (306.3 g), which was suspended in water (1.0 L) and then partitioned between water and EtOAc (GLE, 5.5 g) and *n*-butanol (GLB, 18.4 g), sequentially. The GLE fraction (5.2 g) was separated over Sephadex LH-20 (200.0 g) and eluted with MeOH to afford nine fractions (GLE-I−GLE-IX) pooled according to their HPLC and TLC profiles. Fraction GLE-IV (4.1 g) was subjected to further separation over Sephadex LH-20 using MeOH to give seven fractions [GLE-IV(a)−GLE-IV(g)]. The preparative HPLC of fraction GLE-IV(e) (550 mg) afforded 18.8 mg of **1** (t_R = 19.9 min) and 20.0 mg of **2** (t_R = 36.3 min). The GLE fraction was also analyzed by LC-ToF-MS, by means of the same analytical conditions used for the identification of the GLE fraction components and by comparison of their relative retention times and spike profiles with those of authentic samples previously isolated from the related species *G. xanthochymus* (*1*). Briefly, accurately weighed appropriate amounts of GLE fraction (5 mg) or reference compounds **1**−**13** (0.5 mg) were dissolved in MeOH in a 1 mL volumetric flask. All solutions before LC-MS analyses were filtered through nylon membranes (0.45 μm; Phenomenex) and were stored at 4 °C in the dark. The GLE sample solution (10 μL) was spiked separately with each of the 13 standard solutions (2 μL) using the HPLC autoinjector. Retention time, UV spectrum, and ESI positive and negative ions were recorded for each injection (**Table 1**). The standard and GLE sample solutions were tested by means of the standard addition method and independently assaying concentrations of both stock standard and GLE sample solution, in triplicate (**Figure 2**).

Cytotoxic Assay. The cytotoxicity of the tested compounds **1**, **2**, and mixtures of both **1** and **2** (at ratios of 1:1, 1:2, and 2:1) was determined using the MTT colorimetric assay, as previously reported (*1*, *2*). In brief, HCT-116, HT-29, and SW-480 colon cancer cells were plated at 1 × 10^4 cell/well in 96-well microtiter plates with 100 μL of RPM1-1640 growth medium and incubated for 24 h at 37 °C, with 5% CO_2 in a humidified atmosphere, during which period a partial monolayer was formed. The medium was then removed, and fresh growth medium containing different concentrations (3.125, 6.5, 12.5, 25, 50, and 100 μg/mL) of the sample was added. After 2 days of incubation at 37 °C with 5% CO_2, the growth medium was removed, and 10 μL of a MTT solution (5 mg/mL in PBS) was added. After it was incubated at 37 °C for 4 h, the MTT reagent was removed, and DMSO (100 μL) was added to each well and then shaken for another 15 min. The absorbance was measurement at 490 nm. Controls wells received only the media without the tested sample. 5-FU was used as a positive control. The IC_{50} value was defined as the concentration of the sample, which reduced absorbance by 50% relative to the vehicle-treated control. The cytotoxicity (C) of the samples evaluated was calculated as:

$$C\,(\%) = [(A_{490}\text{ of untreated cells} - A_{490}\text{ of treated cells}) / A_{490}\text{ of untreated cells}] \times 100$$

Statistical Analysis. All of the results are expressed as the means of six experiments ± standard deviations (SDs). The statistical significance ($p < 0.05$) of differences between means was assessed by a one-way analysis of variance followed by Duncan's test.

RESULTS AND DISCUSSION

The genus *Garcinia* of the Clusiaceae family is well-known to be a rich source of bioactive prenylated benzophenones, xanthones, triterpenes, and biflavonoids, among others (*5*). To identify the chemical composition of the fruits of *G. livingstonei*, an organic extract was prepared by blending fruits with MeOH at room temperature. The crude MeOH extract was initially fractionated by solvent−solvent partitioning to yield two primary fractions

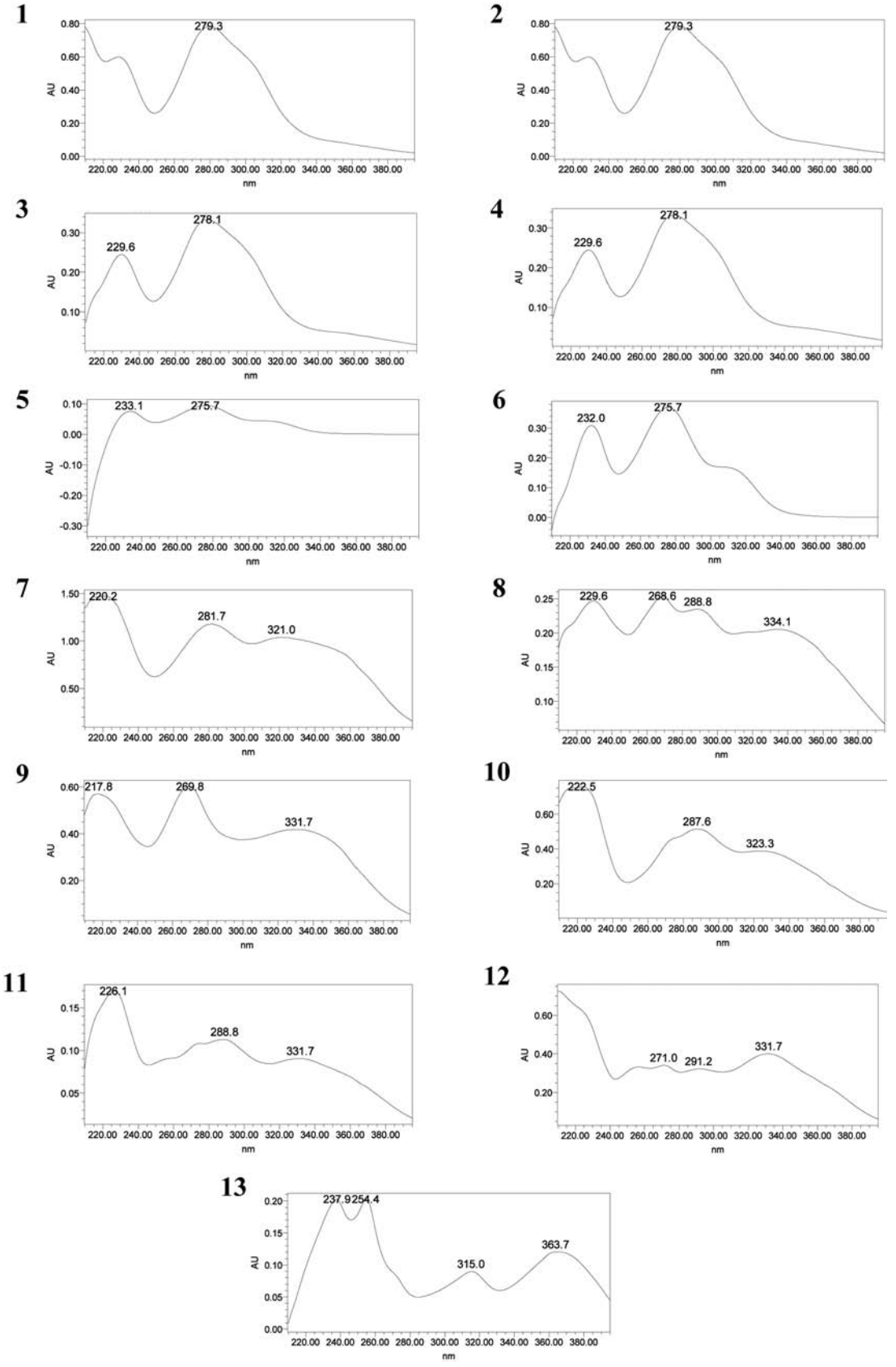

Figure 3. Typical UV profiles (280 nm) of compounds **1**−**13** identified in the *G. livingstonei* extract.

GLE (5.5 g) and GLB (18.4 g). Extensive chromatographic separation of the GLE fraction yielded benzophenones **1** and **2**, which were identified as the known compounds guttiferones A and K, respectively, by comparison of their physical properties, ^{1}H, ^{13}C, and two-dimensional NMR, and MS data with those previously reported (*13*, *17*−*19*).

Additionally, LC-ToF-MS analyses of the GLE fraction led to identification of the known compounds guttiferone A (**1**),

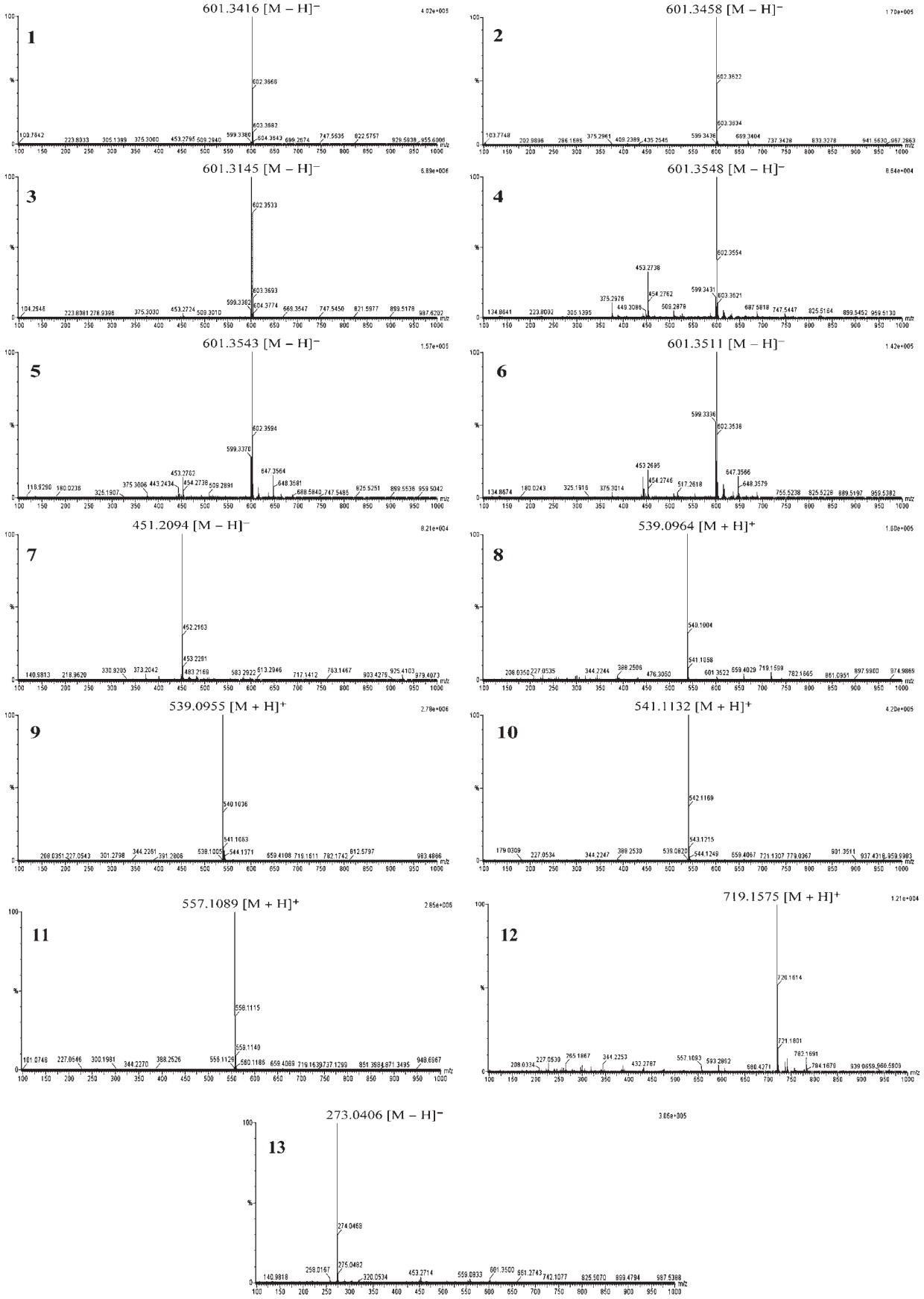

Figure 4. ESI-ToF-MS spectra of compounds **1**−**13** identified in negative mode (compounds **1**−**7** and **13**) and positive mode (compounds **8**−**12**).

guttiferone K (**2**), xanthochymol (**3**), guttiferone E (**4**), cycloxanthochymol (**5**), isoxanthochymol (**6**), gambogenone (**7**), amentoflavone (**8**), 3,8″-biapigenin (**9**), (+)-volkensiflavone (**10**), (+)-morelloflavone (**11**), (+)-fukugiside (**12**), and alloathyriol (**13**) (**Figure 1**) by comparison of the retention times and the UV spectra with those of the standard compounds

Table 2. Cytotoxic Activity of Compounds **1** and **2** Isolated from *G. livingstonei* Fruits

	IC_{50} (μM)		
compound	HCT-116	HT-29	SW-480
1	5	5	21 ± 4.0^a
2	10	25	23 ± 2.6^a
1 + **2** (1:1)			21 ± 3.1^a
1 + **2** (2:1)			22 ± 5.6^a
1 + **2** (1:2)			18 ± 8.9^a
5-FU	45.4	46.1	21 ± 7.0^a

[a] No statistical differences were observed.

previously isolated from the related species *G. xanthochymus* (*1*, *17*, *20*, *21*) using HPLC-PDA analysis. Identified peaks were further confirmed by spiking sample with standard mixtures using both HPLC-PDA and mass spectra in LC-ToF-MS methods. UV spectra from 210 to 400 nm of the 13 compounds analyzed are shown in **Figure 3**. All compounds showed wavelength absorption maxima at 280 nm and revealed typical absorptions for these polyphenol derivatives.

The ESI-ToF-MS analyses were performed with positive and negative ESI modes to cover a broad range of metabolites (**Figure 4**), and all 13 constituents gave unequivocal signals in both experiments. The predominant chromatographic peaks of prenylated benzophenones **1** and **2** were observed with both ionization modes (m/z 601 [M − H] and 603 [M + H]). Compounds **3**−**6** were also found to be an isomeric series of benzophenones with m/z 601 [M − H]. Compounds **8** and **9** belong to an isomeric series of known biflavonoids with m/z 539 [M + H]. Finally, five different compounds, **13**, **7**, and **10**−**12**, with m/z 275 [M − H], 451 [M − H], 541 [M + H], 557 [M + H], and 719 [M + H], respectively, were also identified and comprised of xanthones, benzophenones, and biflavonoids. Detailed analysis of the MS spectra of benzophenones **1**−**6**, all isomers displaying m/z 603 $[M + H]^+$, depicted two structural characteristic fragments signals: (I) the isoprenyl groups losses, consisting of fragments ions at m/z 547 $[M + H - 54]^+$ and 535 $[M + H - 68]^+$ attributed to the loss of C_4H_8 and C_5H_8 (molecular formula $C_{34}H_{43}O_6$ and $C_{33}H_{43}O_6$, respectively), and (II) the 3,4-dihydroxy benzoyl group loss, consisting of the fragment ion at m/z 467 $[M + H - 136]^+$ attributed to the loss of $C_7H_4O_3$ (molecular formula $C_{31}H_{47}O_3$). Compounds **2**−**7**, **9**, **12**, and **13** are all new to *G. livingstonei*.

Previously, we reported the antioxidant and cytotoxic activities of the organic extract and isolates (**3**−**6**) from the fruits of the related species *G. xanthochymus*. These compounds displayed potent cytotoxicity in the SW-480 human colon cancer cell line, with IC_{50} values of 8.3, 7.5, 16.6, and 16.6 μM, respectively (*1*).

To investigate the potential cytotoxic activity of the *G. livingstonei* and the main isolates **1** and **2**, we used the MTT assay with HCT-116, HT-29, and SW-480 colon cancer cells, and the results are summarized in **Table 2**. Compounds **1** and **2** displayed a selective activity against HCT-116 (IC_{50} = 5 μM each) and HT-29 (IC_{50} = 10 and 25 μM, respectively), being about five times more active than 5-FU, a well-known synthetic drug used in the chemotherapy of colon cancer (IC_{50} = 46 μM). Compounds **1** and **2** showed weaker activity in the SW-480 colon cancer cell line (IC_{50} = 21 and 23 μM, respectively).

A previous study by Kumar and collaborators (*22*) on benzophenones from *Garcinia indica* showed that xanthochymol (**3**) and isoxanthochymol (**6**), two prenylated benzophenone isomers, showed maximal cytotoxicity in a ratio of 1:2 in three human cancer cell lines including MCF-7 (breast), COLO-320-DM (colon), and WRL-68 (liver). Therefore, we initiated studies on **1** and **2** in the SW-480 cell line at ratios of 1:1, 2:1, and 1:2 to determine if we could detect a synergistic relationship with these two prenylated isomers in a manner similar to Kumar (*22*). However, all of the mixtures of **1** and **2** showed similar activity against SW-480 cell line (IC_{50} = 21, 22, and 18 μM, respectively) as each of the single constituents. This may be due to differences in the cancer cell lines used or the polyprenylated benzophenones tested. Other research groups have reported that compound **1** has weak cytotoxic activity in A2780 human ovarian cancer cell line (*17*). The question of whether certain mixtures of benzophenones may be more effective than a purified compound needs further research.

In conclusion, from the edible fruits of *G. livingstonei*, we isolated and identified a series of compounds, including benzophenones with cytotoxic activity. Nine of these compounds have been isolated and identified from the species for the first time. *G. livingstonei* fruits are edible and pleasant testing and therefore could be an attractive dietary source of unique principles with potential to impact human health.

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