α-Glucosidase inhibitory tetraoxygenated xanthones from the twig extract of Garcinia cowa Roxb. ex Choisy

Thi Kim An Nguyen
Hanoi University of Industry
Thanh Tra Nguyen
Vietnam Academy of Science and Technology
Lan Phuong Doan
Vietnam Academy of Science and Technology
Thi Tham Pham
Hanoi University of Industry
Tran Thi Thu Thuy
thuy.tran@ich.vast.vn

Vietnam Academy of Science and Technology https://orcid.org/0000-0002-6770-3291

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Abstract

Phytochemical investigation of the twigs of *Garcinia cowa* Roxb. ex Choisy (Clusiaceae), collected in Vietnam, led to the isolation of five tetraoxygenated xanthones, including three new compounds, namely norrubraxanthone (**1**), garcinone G (**2**), and garcinone H (**3**), together with two known compounds, *α*-mangostin (**4**) and rubraxanthone (**5**). The structures of the new compounds were elucidated by comprehensive spectroscopic analyses, including 1D and 2D NMR and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS), and by comparison with literature data. All isolated compounds were evaluated for their *in vitro α*-glucosidase inhibitory activity. Compounds **1**–**5** exhibited potent inhibitory effects, with IC_{50} values ranging from 0.39 to 1.62 μM, which were significantly stronger than that of the positive control acarbose (IC_{50} = 263.01 ± 10.92 μM). Among them, compounds **3** and **4** showed the most pronounced activity, with IC_{50} values of 0.43 ± 0.01 and 0.39 ± 0.01 μM, respectively.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent postprandial hyperglycemia and insulin resistance, representing a major global health burden. Inhibition of *α*-glucosidase, a key intestinal enzyme responsible for the terminal hydrolysis of carbohydrates into absorbable glucose, is an established therapeutic strategy to control postprandial blood glucose levels (Van de Laar, 2008). Although several synthetic *α*-glucosidase inhibitors, such as acarbose and miglitol, are clinically available, their long-term use is often associated with gastrointestinal side effects, prompting continuous interest in the discovery of safer and more effective inhibitors from natural sources (Derosa et al, 2012; Rahimi et al, 2005).

Among natural secondary metabolites, xanthones constitute a structurally diverse class of polyphenolic compounds predominantly found in plants of the family Clusiaceae (Guttiferae). Xanthones have attracted considerable attention due to their wide spectrum of biological activities, including antioxidant, anti-inflammatory, anticancer (Oriola et al, 2024; Wahyuni et al, 2016), and antidiabetic effects (Bui et al, 2023; Yang et al, 2022; Nguyen et al, 2017). The genus *Garcinia* is recognized as one of the richest natural sources of oxygenated and prenylated xanthones, with numerous compounds displaying potent enzyme inhibitory and antidiabetic properties (Santos et al, 2018). The structure–activity relationship studies have suggested that highly oxygenated xanthones, particularly those bearing multiple free hydroxyl and/or methoxy substituents in A and B rings of the xanthone core display more efficacy for *α*-glucosidase inhibitory activity (Ryu et al, 2011).

Garcinia cowa Roxb. ex Choisy, widely distributed in Southeast Asia including Vietnam, has been traditionally used in folk medicine for the treatment of inflammation, infections, and metabolic disorders (Pham, 1999). Phytochemical investigations of *G. cowa* have mainly focused on its bark (Ritthiwigrom et al, 2013), latex (Nguyen et al, 2022), root (An et al, 2023), fruits, flower (Sriyatep et al, 2015) and leaves (Raksat et al, 2020), leading to the identification of various oxygenated xanthones with notable biological

activities. However, the chemical constituents of the twigs of *G. cowa*, particularly tetraoxygenated xanthones and their *α*-glucosidase inhibitory potential, remain insufficiently explored.

In the present study, we report the isolation and structural elucidation of three new and two known tetraoxygenated xanthones from the twigs of *Garcinia cowa* collected in Vietnam, employing comprehensive chromatographic separation and spectroscopic analyses (1D and 2D NMR, HR-ESI-MS). Furthermore, the isolated compounds were evaluated for their *in vitro α*-glucosidase inhibitory activity to assess their potential as natural antidiabetic agents. This work not only expands the phytochemical knowledge of *G. cowa* but also highlights tetraoxygenated xanthones as promising leads for the development of novel *α*-glucosidase inhibitors of natural origin.

Materials and Methods

General Experimental Procedures

Column chromatography (CC) was carried out on silica gel 60 (Merck, 5–40 μm), silica gel 100 (Merck, 63–200 μm), Sephadex LH-20 (GE Healthcare), and C_{18}-reversed-phase silica gel (RP-18, Merck, 15–25 μm). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum plates (Merck, Germany). Visualization of TLC plates was performed under UV light (*λ* 254 and 365 nm), staining with 5% vanillin/H_2SO_4 in ethanol or 10% H_2SO_4 solutions. NMR spectra were recorded on a AV 600 MHz spectrometer (Bruker, Germany). Chemical shifts are reported in *δ* (ppm) with tetramethylsilane (TMS) as an internal reference and coupling constants (*J*) are given in Hertz (Hz). HR-ESI-MS spectra were performed on an Sciex X500 Q-TOF LC/MS system. The UV spectra were recorded on a V-630 UV-VIS spectrophotometer (Jasco, Japan). Melting point was measured on a Büchi B-545 (USA) melting point apparatus (without correction). Industrial-grade solvents (China) used for column chromatography were distilled and dried over sodium sulfate just prior to use.

Plant Material

Fresh twigs of *Garcinia cowa* Roxb. ex Choisy were collected at Ba Vi, Hanoi, Vietnam in July 2024. The plant material was identified by Dr. Nguyen Quoc Binh, Vietnam National Museum of Nature, Vietnam Academy of Science and Technology (VAST). A voucher specimen No. GC072024 has been deposited at the Institute of Chemistry, VAST.

Extraction and Isolation

The twigs of *G. cowa* (5.0 kg) were dried in an oven at 45 ^{o}C for 3 days and subsequently ground into a fine powder. The powder materiel was extracted with ethanol (3 x 3 L) under ultrasonic vibration for 6 h at room temperature. The combined extract were filtred and concentrated under reduced pressure to yield a crude extract (312.4 g). The crude extract was then suspended in water and successively

partitioned with *n*-hexane and ethyl acetate (EtOAc), and concentrated to afford the *n*-hexane fraction (98.1 g), the EtOAc fraction (182.4 g), and the remaining aqueous residue (31.8 g).

The EtOAc fraction was separated by column chromatography (CC) over silica gel using gradient solvent systems of *n*-hexane/EtOAc (10/0 to 3/1, v/v) and dichloromethane/methanol (DCM/MeOH) (15/1 to 0/10, v/v) to provide seven main fractions (Frs. F1–F7). Fraction F3 (21.0 g) was fractioned using silica gel CC eluted with *n*-hexane/EtOAc (50/1 to 1/2, v/v) to obtain compound **4** (12.2 mg) and compound **5** (25.0 mg). Fraction F4 (35.9 g) was fractioned using silica gel CC eluted with *n*-hexane/acetone (30/1 to 0/10, v/v) to obtain six subfractions (Frs. F4.1-F4.6). Compound **1** (14.6 mg) was isolated from subfraction F4.5 by repeated CC over silica gel using DCM/MeOH (40/1, v/v) as the eluent, followed by crystallisation from a mixture of DCM/MeOH to appear as pale-yellow needles. Fraction F5 (13.8 g) was chromatographed on a silica gel column eluting with DCM/MeOH (50/1 to 3/1), v/v) to give five subfractions (Frs. F5.1-F5.5). Subfraction F5.3 was first separated on a Sephadex LH-20 column using eluent of 5% DCM/MeOH and then further purified by silica gel CC eluted with DCM/MeOH (35/1, v/v) to obtaine compound **2** (23.6 mg) as pale-yellow solid. Fraction F6 (8.6 g) was loaded onto a silica gel column eluted with DCM/MeOH (40/1–3/1, v/v) to yield five subfractions (Frs. F6.1-F6.5). Repeated chromatography of subfraction F6.2 by silica gel CC with DCM/MeOH (30/1, v/v) and further purification in a Sephadex LH-20 column using 5% DCM/MeOH to provide compound **3** (16.2 mg) which was recrystallized from methanol as pale-yellow needles.

Norrubraxanthone (**1**): Pale yellow needles (MeOH-DCM). m.p. 216–217°C. IR (KBr) ν_{max}: 3392, 2936, 1643, 1610, 1583, 1482, 1449, 1286, 1181, 1100, 768 cm 1. UV (MeOH) λ_{max} (log□): 203 (4,90), 212 (4,88), 244 (4,79), 260 (4,76), 316 (4,63), 353 (4,10). ^{1}H and ^{13}C NMR (CD_3OD): see Table 1. HR-ESI-MS (pos.): *m/z* 397.1646 $[M + H]^+$; calcd for $C_{23}H_{25}O_6^+$, 397.1646.

Table 1

^{1}H (600 MHz) and ^{13}C (125 MHz) NMR data (in CD_3OD) for compounds **1**–**3**.

Position	1			2		3	
	δ_H (mult., *J*)	δ_C	Position	δ_H (mult., *J*)	δ_C	δ_H (mult., *J*)	δ_C
1		164.6	1		161.5		161.6
2	6.09 (d, 1.8)	98.5	2		111.5		112.3
3		165.4	3		163.6		163.8
4	6.16 (d, 2.4)	93.8	4	6.21 (s)	93.2	6.26 (s)	93.2
4a		158.3	4a		156.1		156.2
5	6.65 (s)	101.0	5	6.68 (s)	103.0	6.73 (s)	103.0
5a		153.3	5a		156.6		156.7
6	65yt	154.1	6		157.8		158.0
7		142.1	7		144.7		144.8
8		129.5	8		137.6		137.7
8a		112.1	8a		112.1		112.1
9		183.3	9		183.1		183.2
9a		104.3	9a		103.7		103.7
1′	4.09 (d, 6.6)	26.4	1′	3.27 (d, 7.2)	22.2	2.70 (m)	28.9
2′	5.25 (td, 6.6, 1.2)	124.8	2′	5.24 (tt, 5.4, 1.8)	123.9	1.70 (m)	43.3
3′		135.3	3′		131.7		71.8
4′	1.94 (m)	40.9	4′	1.79 (s)	17.9	1.29 (s)	18.4
5′	2.02 (m)	16.6	5′	1.67 (s)	26.0	1.29 (s)	29.0
6′	5.01 (m)	125.5	1′	4.13 (d, 6.6)	26.6	4.17 (d, 6.6)	26.6
7′		131.8	2′	5.41 (t, 6.6)	127.8	5.41 (t, 6.6)	127.7
8′	1.54 (s)	25.7	3′		135.3		135.4
9′	1.50 (s)	17.7	4′	4.36 (s)	62.0	4.37 (s)	61.5
10′	1.82 (s)	27.7	5′	1.78 (s)	21.6	1.78 (s)	21.6

Position	1			2		3	
	δ_H (mult., *J*)	δ_C	Position	δ_H (mult., *J*)	δ_C	δ_H (mult., *J*)	δ_C
			7-OMe	3.80 (s)	61.4	3.81 (s)	62.0

Garcinone G (**2**): Pale yellow powder. m.p. 206–207°C. IR (KBr) v_{max}: 3392, 2936, 1643, 1610, 1583, 1482, 1449, 1286, 1181, 1100, 768 cm 1. UV (MeOH) λ_{max} (log□): 210 (4,94), 243 (4.82), 260 (4.71), 316 (4.67), 358 (4.11). ^{1}H and ^{13}C NMR (CD_3OD): see Table 1. HR-ESI-MS (pos.): *m/z* 427.1756 $[M + H]^+$; calcd for $C_{24}H_{27}O_7^+$, 427.1757.

Garcinone H (**3**): Pale yellow needles (MeOH-DCM); m.p. 214–215°C. IR (KBr) v_{max}: 3392, 2936, 1643, 1610, 1583, 1482, 1449, 1286, 1181, 1100, 768 cm 1. UV (MeOH) λ_{max} (log□): 208 (4,73), 243 (4,44), 259 (4,39), 315 (4,27), 346 (3,76). ^{1}H and ^{13}C NMR (CD_3OD): see Table 1. HR-ESI-MS (pos.): *m/z* 445.1866 $[M + H]^+$; calcd for $C_{24}H_{29}O_8^+$, 445.1857.

α -Mangostin (**4**): Yellow powder. ^{1}H NMR ($CDCl_3$) *δ* (ppm): 13.77 (1H, OH), 6.77 (1H, s, H-5), 6.25 (1H, s, H-4), 5.28 (2H, m, H-2□, H-2□), 4.07 (2H, d, *J* = 6.6 Hz, H-1□), 3.80 (3H, s, OMe), 3.42 (2H, d, *J* = 6.6 Hz, H-1□), 1.85 (6H, s, H-4□, H-4□), 1.75 (3H, s, H-5□), 1.69 (3H, s, H-5□).^{13}C NMR ($CDCl_3$) *δ* (ppm): 182.0 (C-9), 161.5 (C-3), 160.5 (C-1), 155.7 (C-6), 155.0 (C-5a), 154.6 (C-4a), 142.6 (C-7), 137.1 (C-8), 135.2 (C-3□), 132.1 (C-3□), 123.2 (C-2□), 121.6 (C-2□), 112.1 (C-8a), 108.8 (C-2), 103.6 (C-9a), 101.6 (C-5), 93.3 (C-4), 62.0 (7-OMe), 26.6 (C-1□), 25.8 (C-4□, 4□), 21.4 (C-1□), 18.2 &17.9 (C-5□, 5□).

Rubraxanthone (**5**): Yellow powder. ^{1}H NMR ($CDCl_3$) *δ* (ppm): 6.63 (1H, s, H-5), 6.13 (1H, d, *J* = 1.8 Hz, H-4), 6.06 (1H, d, *J* = 1.8 Hz, H-2), 5,19 (1H, td, *J* = 6.0, 0.6 Hz, H-2□), 4.99 (1H, td, *J* = 6.6, 1.2, H-6□), 4.01 (2H, d, *J* = 6.6 Hz, H-1□), 3.76 (3H, s, 7-OMe), 2.03 (2H, m, H-5□), 1.95 (2H, m, H-4□), 1.79 (3H, s, H-10□), 1.54 (3H, s, H-8□), 1.50 (3H, s. H-9□). ^{13}C NMR ($CDCl_3$) *δ* (ppm): 181.5 (C-9), 164.3 (C-3), 163.2 (C-1), 156.9 (C-4a), 156.5 (C-6), 155.3 (C-5a), 143.4 (C-7), 137.2 (C-3□), 133.9 (C-7□), 130.5 (C-8), 124.1 (C-6□), 123.9 (C-2□), 110.8 (C-8a), 102.5 (C-9a), 101.5 (C-5), 97.4 (C-2), 92.7 (C-4), 60.0 (7-OMe), 39.4 (C-4□), 26.2 (C-10□), 25.6 (C-1□), 24.4 (C-8□), 16.4 (C-9□), 15.3 (C-5□).

α -Glucosidase inhibition assay

The *α*-glucosidase inhibitory assay was performed following a previously reported method with minor modifications (An et al, 2023; Hakamata et al, 2009). The test compounds were initially dissolved in dimethyl sulfoxide (DMSO) and subsequently diluted with phosphate buffer (100 mM, pH 6.8) to final concentrations of 16, 4, 1, 0.25 and 0.06 μg/mL. In a 96-well microplate, each reaction well contained 40 μL of phosphate buffer (100 mM, pH 6.8), 10 μL of the test compound solution, and 25 μL of *α*-glucosidase (0.4 U/mL, Sigma). The mixture was pre-incubated at 37°C for 10 min, after which 25 μL of *p*-nitrophenyl-*α*-*D*-glucopyranoside (pNPG, 2.5 mM, Sigma) was added to initiate the reaction. Following

incubation at 37°C for 30 min, the reaction was terminated by the addition of 100 µL of Na_2CO_3 (0.2 M). A reaction mixture without test compound served as the negative control, while acarbose was used as the positive control. All experiments were conducted in triplicate. The amount of *p*-nitrophenol released was quantified by measuring absorbance at 410 nm using a microplate reader (BioTek, USA).

α-Glucosidase inhibitory activity was expressed as percentage inhibition and calculated using the following equation: Inhibition (%) = [(OD control – OD sample) / OD control] x 100.

The IC_{50} value, defined as the concentration of compound required to inhibit 50% of *α*-glucosidase activity, was determined using TableCurve software.

Statistical analysis

All quantitative data are presented as mean ± standard deviation (SD) from at least three independent experiments (n ≥ 3). IC_{50} values were calculated using TableCurve 2D v4 (Systat Software), in accordance with the original protocol. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Isolation and structure elucidation

The ethyl acetate extract of the twigs of *G. cowa* was separated by column chromatography to afford five tetraoxygenated xanthones, including 3 new xanthones, namely norrubraxanthone (**1**), garcinone G (**2**), and garcinone H (**3**), and two known xanthones, α-mangostin (**4**) and rubraxanthone (**5**) (Fig. 1).

Norrubraxanthone (**1**) was obtained as pale-yellow needles, m.p. 215–216 ^{o}C. The positive ion HR-ESI-MS spectrum of **1** exhibited a protonated molecular ion peak at *m/z* 397.1646 $[M + H]^+$, consistent with molecular fomular $C_{23}H_{24}O_6$. The ^{1}H and ^{13}C NMR spectra displayed characteristic resonances of a 1,3,6,7-tetraoxygenated xanthone, including a conjugated carbonyl carbon (δ_C 183.3, C-9), three isolated aromatic methines [δ_H 6.65 (1H, s, H-5)/δ_C 101.0 (C-5), δ_H 6.16 (1H, d, J = 2.4 Hz, H-4)/δ_C 93.8 (C-4) and δ_H 6.09 (1H, d, J = 1.8 Hz, H-2)/δ_C 98.5 (C-2)], and six oxygenated aromatic carbons resonating at δ_C 142.1-165.6. The presence of a geranyl side chain was established from HSQC and HMBC data, which revealed two olefinic methines [δ_H 5.25 (1H, td, J = 6.6, 1.2 Hz, H-2′)/δ_C 124.8 (C-2′) and δ_H 5.01 (1H, m, H-6′)/δ_C 125.5 (C-6′)], three methylene groups [δ_H 4.09 (2H, d, J = 6.6, H-1′)/ δ_C 26.4 (C-1′), δ_H 2.02 (2H, m, H-5′)/δ_C 16.6 (C-5′) and δ_H 1.94 (2H, m, H-4′)/δ_C 40.9 (C-4′)], three methyl groups [δ_H 1.82 (s, 3H, H-10′)/δ_C 27.7 (C-10′), δ_H 1.54 (s, 3H, H-8′)/δ_C 25.7 (C-8′) and δ_H 1.50 (s, 3H, H-9′)/δ_C 17.7(C-9′)] and two quaternary olefinic carbons [δ_C 135.3 (C-3′) and δ_C 131.8 (C-7′)]. The attachment of the geranyl side chain at C-8 was confirmed by HMBC correlations from H-1′ to C-7 (δ_C 142.1), C-8 (δ_C 129.5) and C-8a (δ_C 112.1) (Fig. 2). Furthermore, the spectroscopic data of compound **1** (Table 1) were closely comparable to those reported for 1,3,6-trihydroxy-7-methoxy-8-(3,7-dimethyloct-2,6-dienyl)xanthone

(rubraxanthone) previously isolated from *G. cowa* and *G. nitida* (Wahyuni et al, 2016), except for the absence of a methoxyl group. On the basis of detailed 1D and 2D NMR analyses and comparison with literature data, compound **1** was identified as 1,3,6,7-tetrahydroxy-8-(3,7-dimethyloct-2,6-dien-1-yl)xanthone.

Garcinone G (**2**) was obtained as a pale-yellow powder, m.p. 206–207 ^{o}C. Its molecular formula was determined to be $C_{24}H_{26}O_7$ based on (+)HR-ESI-MS data, which showed a protonated molecular ion at *m/z* 427.1756 $[M + H]^+$. The ^{1}H, and ^{13}C NMR spectra, together with HSQC data (Table 1), revealed the presence of two isolated aromatic methines [δ_H 6.68 (1H, s, H-5)/δ_C 103.0 (C-5), δ_H 6.21 (1H, s, H-4)/δ_C 93.2 (C-4)], two olefinic methines [δ_H 5.41 (1H, t, *J* = 6.6 Hz, H-2′)/δ_C 127.8 (C-2′), δ_H 5.24 (1H, tt, *J* = 5.4, 1.8 Hz, H-2″)/δ_C 123.9 (C-2″)], one methoxy group [δ_H 3.80 (3H, s, -OCH_3)/δ_C 61.4], one oxygenated methylene [δ_H 4.36 (2H, s, H-4′)/δ_C 62.0 (C-4′)] and three methyl groups [δ_H 1.79 (3H, s, H-4″)/δ_C 17.9 (C-4″), δ_H 1.78 (3H, s, H-5′)/δ_C 21.6 (C-5′) and δ_H 1.67 (3H, s, H-5″)/δ_C 26.0 (C-5″)]. In addition, the presence of a conjugated carbonyl carbon at (δ_C 183.1, C-9) and six oxygenated aromatic carbons resonating at δ_C 144.7-163.6 supported a tetraoxygenated xanthone skeleton bearing a prenyl and a hydroxylated prenyl side chain. The HMBC correlation between the methoxy protons and C-7 (δ_C 144.7) established the position of the methoxy substituent. The prenyl group was assigned to C-2 based on long-range HMBC correlations from H-1′ (δ_H 3.27 (2H, d, *J* = 7.2 Hz) to C-1 (δ_C 161.5), C-2 (δ_C 111.5), and C-3 (δ_C 163.6). Furthermore, the attachment of the 4-hydroxy-3-methylbut-2-en-1-yl side chain at C-8 was confirmed by HMBC cross-peaks from H-1″ (δ_H 4.13 (2H, d, *J* = 6.6 Hz) to C-7, C-8 (δ_C 137.6) and C-8a (δ_C 112.1) (Fig. 2). Accordingly, compound **2** was identified as 1,3,6-trihydroxy-7-methoxy-2-(3-methylbut-2-en-1-yl)-8-(4-hydroxy-3-methylbut-2-en-1-yl)xanthone and was named garcinone G.

Garcinone H (**3**) was isolated as pale-yellow needles, m.p. 214–215 ^{o}C. The (+)HR-ESI-MS spectrum of **3** exhibited a protonated molecular ion peak at m/z 445.1866 $[M + H]^+$, corresponding to the molecular formula $C_{24}H_{28}O_8$. The ^{1}H and ^{13}C NMR data of **3** (Table 1) showed characteristic signals of a tetraoxygenated xanthone bearing two prenyl-derived side chains, closely resembling those of compound **2**. These included a conjugated carbonyl carbon (δ_C 183.2, C-9), two isolated aromatic methines [δ_H 6.73 (1H, s, H-5)/δ_C 103.0 (C-5), δ_H 6.26 (1H, s, H-4)/δ_C 93.2 (C-4)], one olefinic methine [δ_H 5.41 (1H, t, *J* = 6.6 Hz, H-2′)/δ_C 127.7 (C-2′)], one methoxy group [δ_H 3.81 (3H, s, -OCH_3)/δ_C 61.0], one oxygenated methylene [δ_H 4.37 (2H, s, H-4′)/δ_C 61.5 (C-4′)], three methyl groups [δ_H 1.78 (3H, s, H-5′)/δ_C 21.6 (C-5′), δ_H 1.29 (6H, s, H-4″, H-5″)/δ_C 18.4 (C-4″), 29.0 (C-5″)] and six oxygenated aromatic carbons resonating at δ_C 144.8-163.8. The major difference between compounds **2** and **3** was that the prenyl group attached at C-2 in **3** was hydroxylated and fully saturated. This was supported by the presence of two methylene groups [δ_H 2.70 (2H, m, H-1″)/δ_C 28.9 (C-1″), δ_H 1.70 (2H, m, H-2')/δ_C 43.3 (C-2″)], two methyl groups [δ_H 1.29 (6H, s, H-4', H-5')/δ_C 18.4 (C-4″), 29.0 (C-5″)] and an sp^3 oxygenated quaternary carbon at δ_C 71.8 (C-3″). Further support was provided by HMBC correlations from H-1″ to C-1 (δ_C 161.6), C-2 (δ_C 112.3), and C-3 (δ_C 163.8). All remaining spectroscopic features of compound **3** were

identical to those of compound **2**. Accordingly, compound **3** was identified as 1,3,6-trihydroxy-7-methoxy-2-(3-hydroxy-3-methylbut-1-yl)-8-(4-hydroxy-3-methylbut-2-en-1-yl)xanthone (Fig. 2).

Compounds **4** and **5** were identified as *α*-mangostin (Khaw et al, 2020) and rubraxanthone (Wahyuni et al, 2016) respectively.

α-Glucosidase inhibition effects

All isolated compounds (**1**–**5**) exhibited potent *α*-glucosidase inhibitory activity, with IC_{50} values ranging from 0.39 to 1.62 μM (Table 2). These values indicate substantially stronger inhibition compared to the positive control acarbose (IC_{50} = 263.01 ± 10.92 μM).

Table 2
α-Glucosidase inhibition of compounds **1**–**5**

Compound	**IC_{50} (μM)**
1	1.62±0.05
2	0.94±0.14
3	0.43 ± 0.01
4	0.39 ± 0.01
5	0.56 ± 0.03
Acarbose	263.01±10.92

Among the tested compounds, compounds **3** and **4** displayed the strongest inhibitory activity, with IC_{50} values of 0.43 ± 0.01 μM and 0.39 ± 0.01 μM, respectively. These findings suggest that subtle structural differences among the tetraoxygenated xanthones influence their interaction with the enzyme active site. Compounds **2** and **5** also showed strong inhibition, with IC_{50} values below 1 μM, whereas compound **1** exhibited comparatively weaker activity (IC_{50} = 1.62 ± 0.05 μM), though still markedly more potent than acarbose. The low IC_{50} values observed for these tetraoxygenated xanthones are consistent with previous reports describing highly oxygenated xanthones from *Garcinia* species, which have been shown to act as competitive or mixed-type α-glucosidase inhibitors (An et al, 2023, Nguyen et al, 2017; Tran et al, 2025, Yang et al, 2022).

Overall, these findings suggest that the twigs of *Garcinia cowa* represent a promising source of bioactive xanthones and warrant further mechanistic studies, including enzyme kinetics, molecular docking, and *in vivo* evaluation.

Conclusions

In summary, a phytochemical investigation of the twigs of *Garcinia cowa* collected in Vietnam led to the isolation of five xanthone derivatives, among which three compounds (**1**–**3**) were identified as new natural products. Their structures were unambiguously elucidated using extensive spectroscopic analyses, including 1D and 2D NMR and HR-ESI-MS techniques. All isolated xanthones exhibited remarkably potent *α*-glucosidase inhibitory activity, with IC_{50} values in the low micromolar to submicromolar range (0.39–1.62 μM), demonstrating activities several hundred times stronger than that of the reference drug acarbose. Notably, compounds **3** and **4** showed the most pronounced inhibitory effects, underscoring the importance of highly oxygenated xanthone frameworks in *α*-glucosidase inhibition.

These findings not only expand the chemical diversity of xanthones reported from *Garcinia cowa* but also identify tetraoxygenated xanthones as promising lead compounds for the development of novel antidiabetic agents. Further studies focusing on enzyme inhibition mechanisms, structure-activity relationships, and *in vivo* antidiabetic efficacy are warranted.

Declarations

Author contributions NTKA, and TTTT contributed to the isolation and structure elucidation. DLP, PTT and NTT were responsible for testing and analysis of bioactivity assessments. NTKA, and TTTT worked on methods, software and prepared the manuscript. All authors approved the final manuscript and agreed to the submission.

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Ethics approval
All experimental procedures involving plant materials were conducted in accordance with institutional, national, and international ethical standards. This study did not involve experiments with human participants or animals.

Consent to participate
Not applicable.

Consent to publish
Not applicable.

Competing interests
The authors declare that they have no financial or personal conflicts of interest that could have influenced the work reported in this paper.

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Figures

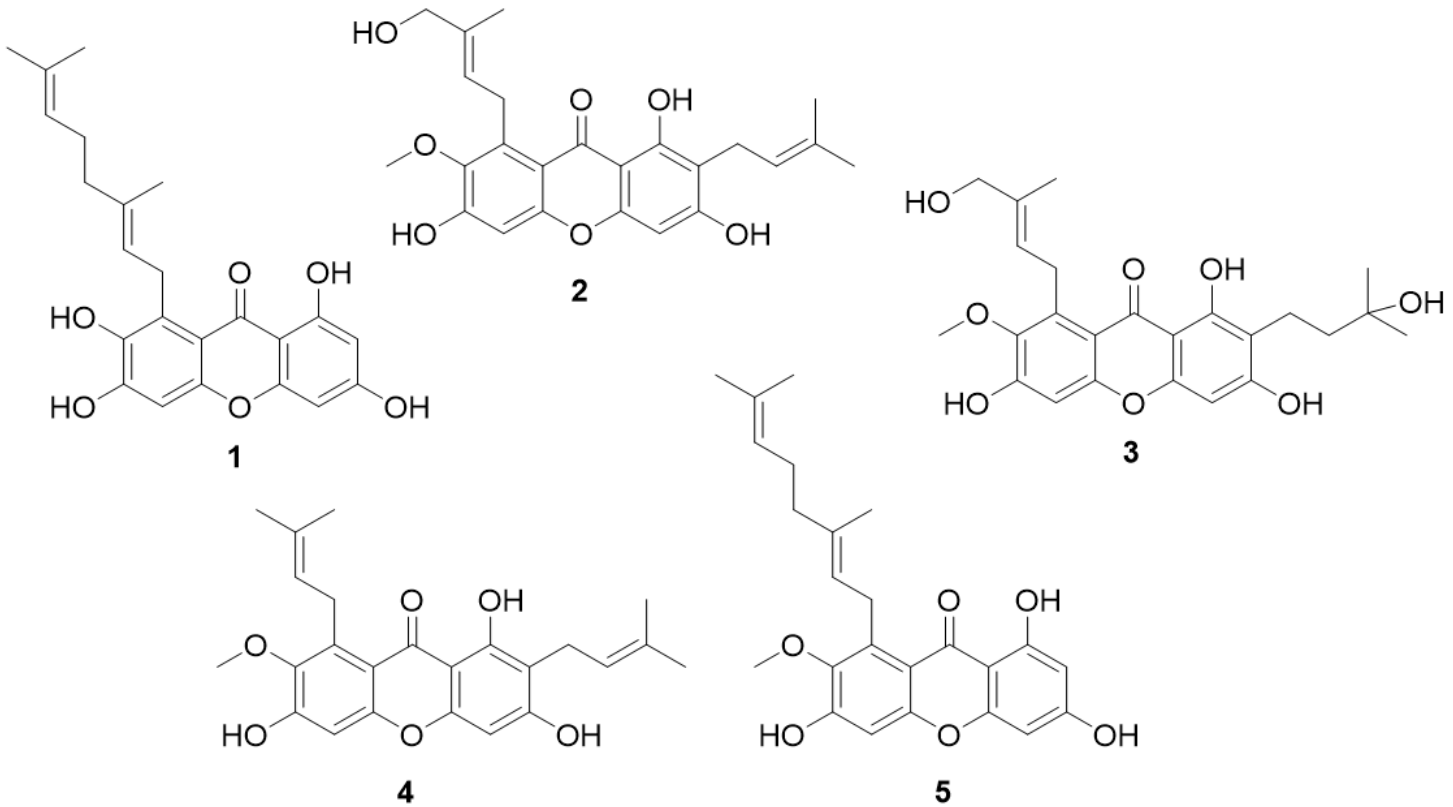

Figure 1

Structure of compounds **1**-**5**

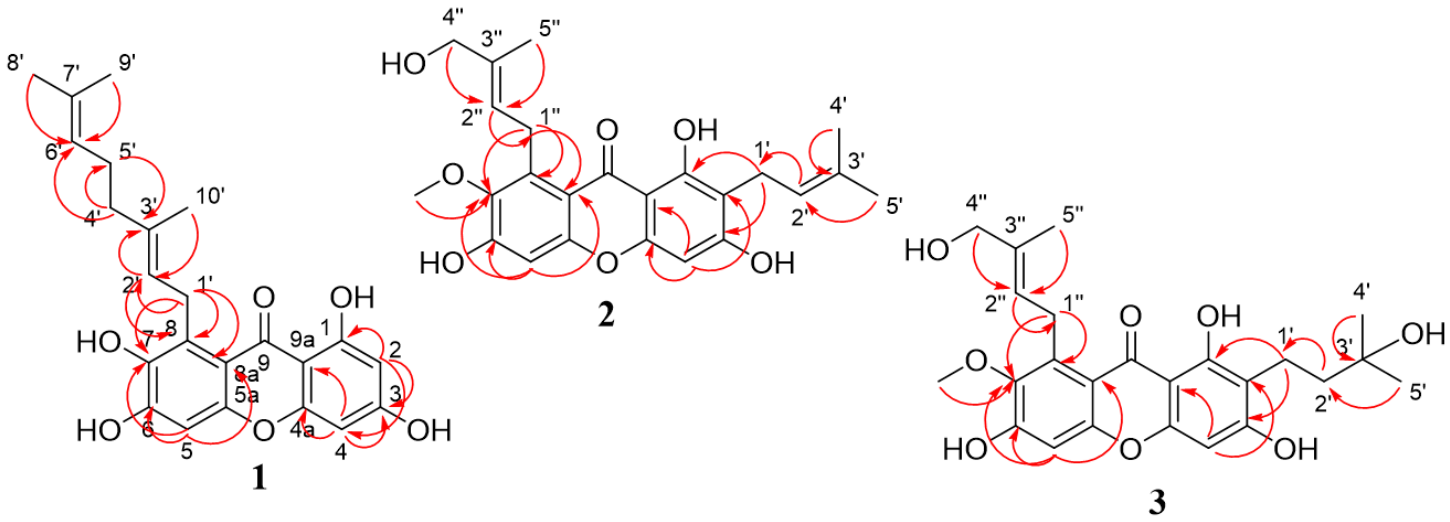

Figure 2

Selected HMBC correlations in compounds **1**-**3**.

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