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Research Article

Garciniaxanthone E and 12b-Hydroxy-des-D-garcigerrin A from The Tree Bark *Garcinia dulcis* and their Inhibitory Properties against Receptor Tyrosine Kinases

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Abstract
Two xanthone derivatives, garciniaxanthone E (**1**) and 12b-Hydroxy-des-D-garcigerrin A (**2**) have been isolated from ethyl acetate extract of the tree bark of *Garcinia dulcis*. The Ultraviolet (UV), Infrared (IR), Nuclear Magnetic Resonance (NMR), and Mass Spectrometry (MS) data analysis elucidated the structure of the isolated compounds. This study represents the first evaluation of compounds **1** and **2** in terms of their efficacy against receptor tyrosine kinases. The results showed that compound **1** exhibited weak activity with 12% inhibition against Insulin Receptor (InsR), while compound **2** showed moderate activity with 29% inhibition against epidermal growth factor receptor (EGFR). A molecular docking study targeting EGFR-TK suggests that the hydroxyl group at C-4 on compound **2** can be demolished to raise the inhibitory activity in future research.

Keywords: EGFR; *Garcinia dulcis*; garciniaxanthone E; 12b-Hydroxy-des-D-garcigerrin A; Receptor tyrosine kinases

1. INTRODUCTION

The treatment of cancer remains a difficult mission. To date, the search effort for new anticancer compounds through cytotoxicity evaluation is a crucial research activity [1,2,3]. Recently, a growing focus has been on tyrosine kinases (TKs) as potential targets for developing therapeutic anticancer drugs [4,5]. These enzymes participate in various cellular signaling pathways in humans by catalyzing a phosphate transfer from ATP to the tyrosine residues of other proteins. When TK is not functioning correctly, generative disorders can develop, whereas tumors and malignancies can arise when TK is expressed too much. Tyrosine kinases (TKs) can be classified into two distinct families: receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) [6]. Several examples of receptor tyrosine kinases (RTKs) may be identified. These include epidermal growth factor receptors (EGFR), such as HER2 and HER4, also known as Human Epidermal Growth Factor Receptor 2 and -4. It has been demonstrated that these RTKs are associated with the development of numerous malignancies and cancers[5].

One of the Indonesian plants that has the potential to be a source of bioactive chemicals is the family of Clusiaceae, also known as the mangosteen family, and *Garcinia* is one of the prominent genus within the Clusiaceae family, encompassing over 300 species [7]. The *Garcinia* species is recognized for its significant content of phenolic compounds, including flavonoids, phenolic acids, xanthones, biflavonoids, and benzophenones [8]. Various isolated compounds from the genus *Garcinia* have been identified as containing chemical diversity and potential for medicinal use, particularly in anti-inflammatory,[9,10,11] antimicrobial,[12] diabetes [13], cardiovascular disease [13], and cancer [8,11,14,15]. *Garcinia dulcis,* or mundu, has been reported to heal several illnesses, including ulcers and wound infections[16]. It is additionally commonly utilized to treat struma, lymphangitis, and parotitis[17] .

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Previous studies on this species revealed that the flowers and seeds possess antibacterial and antioxidant properties, the branches have an antimalarial effect, and the leaves and fruits are antibacterial[18] and antioxidant[19]. Since most TK inhibitors are synthetic compounds, isolated compounds derived from plant inhibitors are still limited [5]. Based on our knowledge, no xanthone derivatives from *Garcinia dulcis* have been tested for inhibitory properties against receptor tyrosine kinases (RTKs). In this paper, we report the isolation, structure elucidation of the two xanthone derivatives, and inhibitory properties of **1**-**2** from the tree bark of *Garcinia dulcis* against eight RTKs (EGFR, HER2, HER4, IGFR, InsR, KDR, PDGFRα, and PDGFRβ due to correlate with several tumor/cancer diseases [20,21]

2. RESEARCH METHODS

General experimental procedures

The experimental procedures involved the measurement of UV-visible spectra using a Shimadzu UV-1240 spectrophotometer and IR spectra using a Thermo Scientific Nicolet iS50 FTIR+NIR Spectrophotometer, respectively. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired using a spectrometer from the Agilent DD2 system. The measurements were conducted in $CDCl_3$, and the spectrometer operated at 500 MHz and 125 MHz for the ^{1}H and ^{13}C NMR spectra, respectively. The ESI-TOF (Electrospray Ionization Time-of-Flight) Waters LCT Premier XE mass spectrometer (MS) was utilized to obtain high-resolution mass spectra. The experimental procedures of vacuum liquid chromatography (VLC) and centrifugal planar chromatography (CPC) were performed using Merck silica gel 60 GF_{254} art. 7731 and 7749, respectively. The investigation of thin layer chromatography (TLC) was conducted with silica gel plates that were pre-coated with a layer of Merck Kieselgel 60 GF_{254}, with a thickness of 0.25 mm. UV irradiation identified the spot on TLC and then heated after being sprayed with 20% MeOH in H_2SO_4. MeOH, acetone, EtOAc, and *n*-hexane were technical-grade solvents distilled before extraction, fractionation, and purification. During the purification, pro-analytical grade analytical $CHCl_3$ was used. The Kinase Selectivity Profiling System (KSPS) for Receptor Tyrosine Kinases TK1 (including EGFR, HER2, HER4, IGF1R, InsR, KDR, PDGFR α, and PDGFR β) was acquired from Promega and after that stored at a temperature of -80°C for single-use purposes. Utilize aliquots. A pipetmax automatic liquid handler (Gilson) was used for the kinase enzyme assay, and GloMax Exploreruse aliquots were used for luminous measurements. The kinase enzyme test was conducted utilizing a pipe max automatic liquid handler manufactured by Gilson. Subsequently, luminescent measurements were performed employing a GloMax Explorer.

Plant collection and determination

The tree bark of *G. dulcis* was collected in December 2022 from Mekarsari Fruit Garden, West Java Province, Indonesia. The herbarium voucher number 20230110 is deposited at The Universitas Negeri Jakarta Herbarium (JUNJ) Experiment.

Extraction and isolation

The dried and powdered tree bark of *G. dulcis* (1.5 kg) was extracted with ethyl acetate (2×3.5 L) at room temperature to give a dried extract (57g) after solvent evaporation. The EtOAc extract was fractionated by VLC (Si gel, *n*-hexane: acetone of increasing polarity) into seven major fractions, namely the A-I fraction. Then, the E fraction (2.6 g) was separated by VLC (*n*-hexane: ethyl acetate = 9.5/0.5 to 8/2), resulting in 7 fractions, namely fractions E1-E7. The E4 fraction (850 mg) was then purified by radial chromatography with silica as stationary phase (eluted $CHCl_3$), resulting in 11 fractions, namely E41-E411. From E48 fractions, garciniaxanthone E (**1**) (27.6 mg) was obtained. Fraction D (4.9 g) was fractionated using VLC and eluted with n-hexane: acetone with increasing polarity to give 11 major fractions (D_1–D_{11}). Fraction D_{11} (0.43 g) was fractionated using radial chromatography and purified with Sephadex LH-20 to give compound **2** (32 mg).

Instrumental analysis

Garciniaxanthone E (1) Yellowish solid. UV (MeOH) λ_{max} nm: 202, 252, 327; IR (KBr) υ_{max} cm^{-1}: 3522, 3460, 3269, 2913, 1647, 1575, 1452, 1253, 1152,1007, 827; ^{1}H & ^{13}C NMR ($CDCl_3$) see Table 1; HRESITOF–MS (negative mode) m/z ($[M-H]^-$ 463.2125, (calcd. $[M-H]^-$ for $C_{28}H_{31}O_6$ 463.2121).

12b-Hydroxy-des-D-garcigerrin A (2) Yellowish solid. UV (MeOH) λ_{max} nm: 201, 263, 317; IR (KBr) υ_{max} cm^{-1}: 3279, 2969, 1580, 1437, 1282, 1230, 1175, 1010; ^{1}H & ^{13}C NMR (aceton-d_6) see Table 2. HRESITOF–MS (positive mode) m/z ($[M-H]^+$ 313.1069, (calcd. $[M-H]^+$ for $C_{18}H_{17}O_5$ 313.1076). The purity of compounds **1**-**2** was assessed by nuclear magnetic resonance (NMR) and found to be greater than 95%

Kinase enzyme assay

The ADP-Glo Kinase Assay was used to quantify kinase activity obtained from Promega. The experimental procedure was conducted using the methods previously outlined[22]. In the tested isolated compounds, the percentage of kinase activity was determined by subtracting the fluorescence of the background from all kinase events, as shown in Table 3. This study employed erlotinib as the positive control at a concentration of 1 μM.

Table 1. ^{1}H and ^{13}C NMR data of compound **1** in $CDCl_3$

No	δ_H (multipl, *J* in Hz)	δ_C	HMBC
1		164.7	
2	6.18 (*d*, 2)	98.0	C-1, C-3, C4, C-9a
3		165.0	
4	6.35 (*d*, 2.3)	93.0	C-2, C-3, C-4a, C-9a,
4a		157.5	
5		130.6	
6		150.1	
7		126.2	
8		135.6	
8a		111.9	
9		183.4	
9a		103.8	
10a		146.3	
11	3.48 (*d*, 6.2)	25.1	C-6, C-8, C-12, C-13
12	5.07 (*t*, 6.4)	123.9	C-14, C-20
13		134.9	
14	1.99 (*t*, 7.15)	40.3	C-11, C-13, C-15, C-16
15	2.09 (*t*, 7.2)	27.3	C-14
16	5.11 (*t*, 6.3)	125.4	C-18, C-14
17		131.6	
18	1.56 (*s*)	25.8	
19	1.61 (*s*)	17.7	C-18
20	1.79 (*s*)	16.5	C-14
21	4.11 (*d*, 6)	29.0	C-7, C-8, C-8a, C-23
22	5.09 (*m*)	125.0	C-24
23		130.6	
24	1.66 (*s*)	25.8	C-25
25	1.79 (*s*)	18.3	C-24
1-OH	13.61		C-2, C-9a

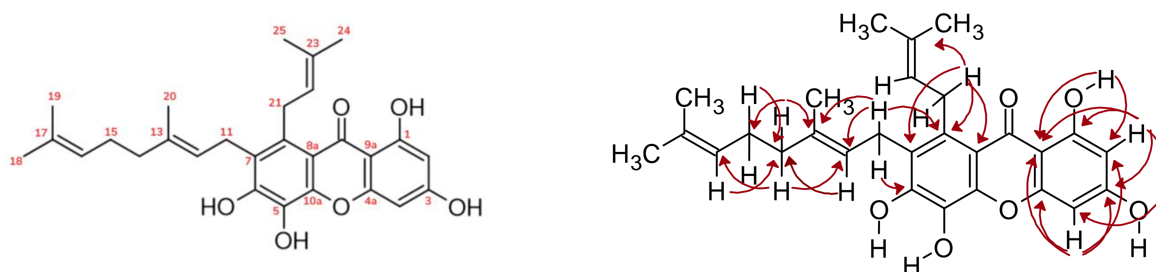

Figure 1. Structure of garciniaxanthone E (**1**) and selected HMBC correlations in compound **1**

Molecular Docking Study

Compound **2** and erlotinib investigated the binding interaction using a molecular docking study. The docking was conducted using YASARA based on the algorithm of AutoDock Vina (version 21.6.17)[23] and BIOVIA discovery studio software for visualization. TheEGFR-TK crystal structure was obtained from the Protein Data Bank (PDB: 1M17)[24]. The EGFR-TK was pretreated by removing water molecules, adding missing hydrogen atoms, and distributing the Gasteiger charges, with all other parameters set to their default values. The ligand was bound to the active site, and the docking model with the lowest binding energy was selected as the optimal configuration for analysis.

3. RESULTS AND DISCUSSION

Compound **1** was acquired in the form of yellow powder. It showed UV and IR absorptions typical of a

substituted xanthone. The absorption bands observed in the UV spectrum were at wavelengths 202, 252, and 327 nm. The infrared spectra exhibited peaks in absorption corresponding to the stretching vibrations of O-H bonds at a wavenumber of 3522 cm^{-1} and C=O bonds at a wavenumber of 1647 cm^{-1}. Its molecular formula,

Table 2. ^{1}H and ^{13}C NMR data of compound **2** in acetone-d_6

No	δ_H (multipl, *J* in Hz)	δ_C	HMBC
1		153.3	
2		129.5	
3	7.33 (*s*)	123.2	C-1, C-4, C-4a, C-11
4		136.8	
4a		142.0	
5		146.6	
6	7.37 (*d*. 8)	121.9	C-8, C-10a
7	7.31 (*d*, 8)	125.1	C-5, C-6, C-8
8	7.7 (*d*, 7.8)	116.5	C-8a, C-9, C-10a
8a		121.8	
9		183.8	
9a		109.2	
10a		145.6	
11		40.9	
12	6.29 (*dd*, 17.4, 10.7)	147.8	C-11, C-14, C-15
13	5.03 (*d*, 17.4)	110.8	C-11, C-12
	5.01 (*d*, 10.6)		
14	1.53 (*s*)	26.9	C-2, C-11, C-12, C-15
15	1.53 (*s*)	26.9	C-2, C-11, C-12, C-14
1-OH	12.87 (*s*)		C-1, C-2, C-9a

Figure 2. Structure of 12b-Hydroxy-des-D-garcigerrin A (**2**) and selected HMBC correlations in compound **2**

$C_{28}H_{31}O_6$, was secured by HR-ESI-TOF–MS (negative mode) data (found $[M-H]^-$ m/z 463.2125, calc. 463.2121). As presented in Table 1, ^{1}H-NMR spectra exhibited distinct signals that revealed a singlet corresponding to a chelated hydroxyl group (1-OH) at δ_H 13.61, a *meta*-coupled (*J*=2 Hz) proton signals were observed (δ_H 6.12 and 6.35) which correspond to H-2 and H-4. HMBC Spectra of compound **1** showed a long-range ^{1}H-^{13}C correlation between the hydroxyl group (1-OH) and C-2 (δ_c 98) as well as C-9a (δ_c 103.8). The correlations were also observed between H-2 and C-9a, C-4 (δ_c 93), and between H-4 and C-2, C-9a confirming the identity of H-2 and H-4, respectively. The NMR data also presented includes the observed signals of a prenyl side chain. These signals comprise an olefinic proton, denoted as H-12 (δ_H 5.07,*t*, *J*= 6.4 Hz). The benzylic methylene protons, labeled as H-21 (δ_H 4.11,*d*, *J* = 6.0 Hz), and the methyl groups (H-24 and H-25) display signals with singlet (3H) at δ_H 1.79 and 1.66, respectively. The positioning of the prenyl group close to the carbonyl group was determined by the low-field chemical shift of the methylene protons H-21 (δ_H 4.11). The remaining signals observed in the spectrum consist of a doublet of methylene protons H-11 (δ 3.48, *J*=6.2 Hz), broad triplets of olefinic protons H-12 and H-16 (δ_H 5.07 and 5.11), and multiplets of methylene protons H-14 and H-15 (δ_H 1.99, and 2.09), respectively. Three singlet signals of methyl groups H-18, H-19, and H-20 were also observed (δ_H 1.56, 1.79, and 1.61). These observed signals are consistent with the presence of a geranyl group. According to the HMBC correlation, it was observed that the geranyl side chain was positioned at C-7 in an ortho orientation to the phenyl group. This conclusion was drawn based on the cross peak observed between the H-11 and H-21, which were connected to C-7 (δ_c126.2) ppm. The structure was modified by introducing hydroxyl groups at positions C-3 (δ_c 165), C-5 (δ_c 130.8), and C-6 (δ_c 149.2) ppm. The HMBC data indicated that the resonances at δ_c 165 and 149.2 ppm corresponded to H-2, H-4, and H-1, respectively. These suggest that C-3 and C-6 have chemical shifts of 165 and 150.1 ppm, respectively. Based on the NMR data and comparison of the spectroscopic data compound **1** to that reported in the literature[25], compound **1** is referred to as garciniaxanthone E.

Compound **2** was isolated as a yellow solid powder. The absorption bands observed in the UV spectrum were at wavelengths 201, 263, and 317 nm. The IR spectra compound **2** showed absorption bands at 3279 cm^{-1} (O-H stretching) and 1580 cm^{-1} (C=O stretching). Its molecular formula, $C_{18}H_{17}O_5$, was secured by HR-ESI-TOF–MS (positive mode) data (found $[M-H]^+$ m/z 313.1069, *calc*. 313.1076). The ^{1}H-NMR spectrum shows signals of a chelated hydroxyl proton 1-OH (δ_H 12.87) and a singlet aromatic proton H-3 (δ_H 7.33). The appearance of proton signals of the methyl groups H-14 and H-15 at δ_H 15.3 (s), H-15E (δ_H 5.03, *d*, *J* = 17.4 Hz) and H-15Z (δ_H 5.01, *d*, *J* = 10.6 Hz), and H-14 (δ_H 6.26, *dd*, *J* = 17.4; 10.7 Hz) shows the presence of a 1,1-dimethylallyl group. The substitution of the 1,1-dimethylallyl group at C-2 was supported by the HMBC correlation of 1-OH to C-2 (δ_C 129.5), H-3 to C-1 (δ_C 153.3), C-4 (δC 136.8), C-4a (δ_C 142), and C-11 (δ_C 40.9), as well as the correlation of the H-14 and H-15 methyl proton signals to C-2. The resonances of H-6, H-7, and H-8 at δ_H 7.37 (*d*, *J* = 8), δ_H 7,31 (*d*, *J* = 8 Hz), δ_H 7,7 (d, J = 7,8 Hz) were identified as ABM systems attributed to 1,2,3-trisubstituted benzene. The positions of H-6, H-7, and H-8 are supported by the HMBC correlation, where the H-6 proton is correlated with C-8 (δ_C 116.5) and C-10a (δ_C 145.6), H-7 to C-5 (δ_C 146.6) and C-6 (δ_C 121.9), and H-8 to C-8a, C-9 (δ_C 183.8) and C-10a. Two hydroxyl groups are substituted at C-4 and C-5 to fulfill the structure of compound **2**. Based on ^{1}H-NMR and ^{13}C-NMR analysis, compound **2** was identified to be 12b-Hydroxy-des-D-garcigerrin A. Furthermore, comparing NMR data between compound **2** and 12b-Hydroxy-des-D-garcigerrin A[26] reveals similarities (Table 2).

Moreover, compounds **1** and **2** underwent screening for their inhibitory effects on the phosphoryl transfer activity of eight receptor tyrosine kinases (RTKs), specifically EGFR, HER2, HER4, IGF1R, InsR, KDR, and PDGFRα. The results are presented in Table 3, and erlotinib is employed as the positive control.

Compound **1** exhibited weak activity (12% inhibition) against InsR (the Insulin-like growth factor (IGF)), an insulin receptor that has also been linked to specific tumors, specifically IGF-driven brain tumors[27]. Meanwhile, compound **2** showed moderate activity (29% inhibition) against EGFR. EGFR is a member of the family of epidermal growth factor receptors (EGFR). These results demonstrate that their overexpression is associated with the development of numerous malignancies, including breast, lung, prostate, and Colonic malignancies[28].

Table 3. The tyrosine kinase activity of compounds **1** and **2** at 10 μM

Compounds	% Activity							
	EGFR	HER2	HER4	IGFIR	InsR	KDR	PDGFRα	PDGFRβ
1	102	100	101	99	88	102	93	102
2	71	97	98	96	91	89	79	88
Erlotinib	0	42	37	94	47	9	28	17

[a] positive control at concentration 1 μM.

[b]strong <20%, moderate; 20-60%, weak or not active>60%

Table 4. Docking Score of compound **2** and erlotinib

Compound	Binding Energy (Kcal/mol)	Hydrogen Bond
Erlotinib	-7.66	MET769
2	-8.36	PRO770

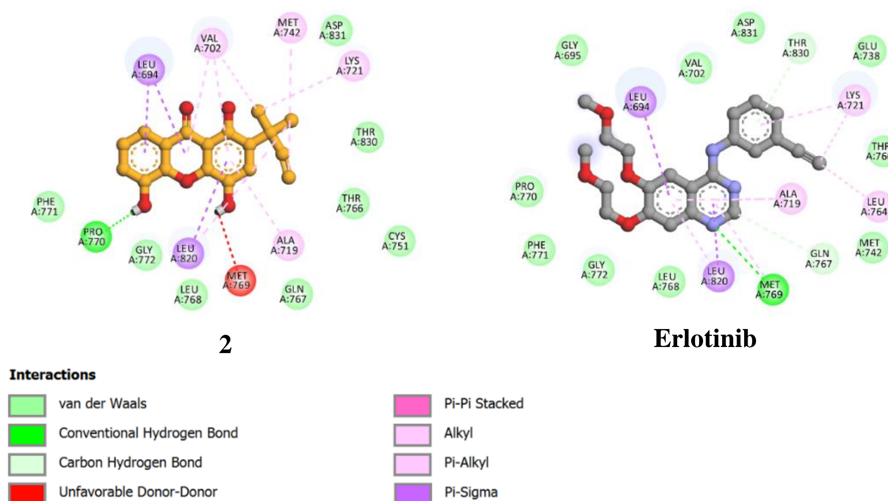

Figure 3. Two-dimensional ligand–protein interactions of investigated compounds (**2** and Erlotinib) in complex with EGFR.

Molecular docking was performed further to investigate the interaction between compound **2** and EGFR-TK. Erlotinib was used as the positive control. The result showed that the binding energy of compound **2** was lower than erlotinib, namely -8.36 and -7.97 kcal/mol (Table 3), respectively. However, compound **2** formed an H-bond between a hydroxyl group at C-5 with PRO770 and a steric clash interaction between a hydroxyl group at C-4 with MET769. Erlotinib, as the native ligand, exhibited an H-bond with MET769, as presented in Figure 1. Hydrogen bonding with MET769 and PRO770 is pivotal to stabilizing the inhibitor in the active site of EGFR[29]. This demonstrates that a functional group at C-5 in compound **2** can significantly decrease inhibitory activity against EGFR-TK. This result was in line with the previous work.[30, 31, 32]

4. CONCLUSIONS

In conclusion, as referred to in the data analysis structure, two xanthone derivatives, garciniaxanthone E (**1**) and 12b-Hydroxy-des-D-garcigerrin A (**2**), have been isolated from an ethyl acetate extract of *Garcinia dulcis* tree bark. Among eight receptor tyrosine kinases (RTKs), compound **1** exhibited weak activity against InsR, and compound **2** showed moderate activity against EGFR. The result of the molecular docking study showed that the absence of hydroxyl group at C-4 on compound **2** can potently enhance the inhibitor activity against EGFR-TK. Therefore, compound **2** is potent for future research with xanthone as the core structure for anticancer by targeting receptor tyrosine kinases.

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