# Chemical Constituents from the Branches of *Garcinia schomburgkiana* and Their Cytotoxic and Alpha-glucosidase Inhibitory Activities

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## Abstract

*Garcinia schomburgkiana* is a medium-sized tree found in Thailand, Laos, Cambodia, and Vietnam as an endemic plant. This plant has long been used as folk medicine. In this paper, the phytochemical study of *Garcinia schomburgkiana* branches collected in Thailand leads to the isolation of thirteen known compounds, comprising two polyprenylated benzoylphloroglucinols, seven xanthones, two chalcones, one benzophenone, and one biphenyl, and the evaluation of their cytotoxic properties and $\alpha$-glucosidase inhibitory activities. The isolated compounds are 7-epiclusianone (**1**), oblongifolin C (**2**), pancixanthone A (**3**), euxanthone (**4**), 1,4,5-trihydroxyxanthone (**5**), osajaxanthone (**6**), 1,2,7-trihydroxyxanthone (**7**), 1,3,7-trihydroxy-2,4-diprenylxanthone (**8**), cudratricusxanthone K (**9**), 2'-hydroxydihydrochalcone (**10**), 1-(2',6'-dihydroxyphenyl)-3-phenyl-1-propanone (**11**), clusiacitran B (**12**), and aucuparin (**13**). This study applied the analysis of all isolated compounds' NMR spectroscopic data ($^{1}$H and $^{13}$C NMR) with the literature to enact their chemical structures. Moreover, this investigation yields three compounds that have never been discovered from the genus *Garcinia*, namely cudratricusxanthone K, 2'-hydroxydihydrochalcone, and 1-(2'-6'-dihydroxyphenyl)-3-phenyl-1-propanone). The cytotoxic and $\alpha$-glucosidase inhibitory activities were tested by using the MTT assay and rat small intestine method, respectively. The evaluation of the cytotoxic properties towards Hep G2, MCF-7, HeLa S-3, KB, and HT-29 cell lines showed that oblongifolin C possessed the strongest activities with $IC_{50}$ values ranging from 5.15 to 7.09 $\mu$M. Meanwhile, among all of the compounds tested for $\alpha$-glucosidase inhibitions, aucuparin showed moderate inhibitory effects in sucrose and maltose substrates with the $IC_{50}$ values of 49.23 $\mu$M and 98.20 $\mu$M, respectively.

***Keywords*****:** *Garcinia schomburgkiana*, *Cytotoxicity*, *α-glucosidase*

## 1. Introduction

*Garcinia schomburgkiana* (Clusiaceae family), a medium-sized tree with its edible sour tasting fruits, is an indigenous plant commonly found in the Southeast Asian region including Thailand, Laos, Cambodia, and Vietnam. In Thailand, this plant is mainly distributed in the northern and central areas and has been used as an herbal medicine for expectorant, laxative, cough, and diabetes treatment. Previous phytochemical investigations revealed that genus *Garcinia* contains a rich source of bioactive chemical constituents such as xanthones, biphenyls, depsidones, and polyprenylated benzoylphloroglucinols (PPBPs) with several pharmacological activities, especially as anticancer candidates (Boonyong, Pattamadilok, Suttisri, & Jianmongkol, 2017; Kaennakam, Mudsing, Rassamee, Siripong, & Tip-pyang, 2019; Le, Nishimura, Takenaka, Mizushina, & Tanahashi, 2016; Siridechakorn et al., 2014; Sukandar, Siripong, Khumkratok, & Tip-Pyang, 2016) and as potential antidiabetic agents (Chen et al., 2021; Jin, Kim, Lee, Tan, & Park, 2019; Karim, Rahman, Changlek, & Tangpong, 2020; Raksat et al., 2020; Ryu et al., 2011). In the previous study on the branches of *Garcinia schomburgkiana*, it was reported that the acetone (polar) extract resulted in the isolation of xanthones and flavonoids with their antioxidant potential (Meechai, Phupong, Chunglok, & Meepowpan, 2016, 2018). As part of this extensive project to search bioactive substances from this plant (Kaennakam et al., 2019; Sukandar et al., 2016), the authors investigated the dichloromethane extract of *G. schomburgkiana* branches, which resulted in the isolation of thirteen known compounds. Hence, the isolation, structure elucidation, and bioactivities of the isolated compounds are described.

## 2. Objectives

1) To isolate and purify the phytochemicals from the branches of *G. schomburgkiana*

2) To assess the cytotoxicity amongst all isolated secondary metabolites against five human cancer cell lines

3) To test the $\alpha$-glucosidase inhibitory activity of the isolated compounds

## 3. Materials and Methods

### *3.1 Plant material*

The branches of *Garcinia schomburgkiana* were collected from Taling Chan District, Bangkok, Thailand, in January 2019. The plant material (voucher specimen Khumkratok no. 92–08) was identified by Dr. Suttira Khumkratok, a botanist at the Walai Rukhavej Botanical Research Institute, Mahasarakham University, Mahasarakham, Thailand.

### *3.2 Extraction and isolation of branches of G. schomburgkiana*

The extraction process was done by the maceration of the air-dried branches of *G. schomburgkiana* (14.0 kg) with dichloromethane (2 x 30 L) for six days at room temperature. The solvent was removed *in vacuo* using a rotary evaporator to yield 90.0 g of the crude extract.

Silica gel column chromatography (CC) technique was used to fractionate the dichloromethane crude extract eluted with a gradient of ethyl acetate/hexanes (10/90, 20/80, 30/70, 40/60, 50/50, 60/40, 70/30, 80/20, 90/10, and 100/0), thus fractions A-J were obtained. Subfractions A1-A4 were supplied by Sephadex LH-20 CC with dichloromethane/methanol (50/50) of fraction A (15.0 g). The reversed-phase (RP) C-18 CC eluted in acetonitrile/water (85/15, 150 mL) of subfraction A1 (1.0 g) was done to purified compound **1** (30.7 mg). Compound **10** (4.5 mg) was achieved by loading subfraction A2 (23.0 mg) into chromatotron model 7924 T (Harrison Research) with chloroform/hexanes (5/95 and 10/90, each 50 mL) solvent system. Meanwhile, fraction B (1.0 g) was applied to chromatotron eluted in chloroform/hexanes (65/35, 200 mL) to yield compounds **3** (6.6 mg) and **4** (38.5 mg).

Fraction C (20.0 g) was chromatographed using the Sephadex LH-20 CC with dichloromethane/methanol (50/50) solvent system to provide subfractions C1-C6. Then, subfraction C1 (1.5 g) was subjected to RP C-18 CC with a system of acetonitrile/water (70/30 and 90/10, each 100 mL) to furnish compound **2** (38.2 mg). A step of a solvent gradient of chloroform: hexanes (30/70, 40/60, and 50/50, each 200 mL) eluted in chromatotron was used to chromatograph subfraction C2 (25.0 mg), hence compounds **6** (1.8 mg), **11** (2.1 mg), and **12** (10.6 mg) were isolated. The purification of compounds **5** (2.1 mg), **7** (1.5 mg), **8** (2.9 mg), and **13** (7.4 mg) were concluded from fraction D (1.0 g) using chromatotron with chloroform: hexanes (50/50, 60/40, and 70/30, each 100 mL) as a solvent system. Fraction E (25.0 mg) was applied to chromatotron eluted with chloroform: hexanes (50/50, 100 mL) to collect compound **9** (1.9 mg).

### *3.3 Structure elucidation*

All of the isolated compounds' chemical structures were interpreted based on the comparison of $^{1}$H and $^{13}$C NMR spectroscopic data with the literature. They were identified as 7-epiclusianone (**1**), oblongifolin C (**2**), pancixanthone A (**3**), euxanthone (**4**), 1,4,5-trihydroxyxanthone (**5**), osajaxanthone (**6**), 1,2,7-trihydroxyxanthone (**7**), 1,3,7-trihydroxy-2,4-diprenylxanthone (**8**), cudratricusxanthone K (**9**), 2′-hydroxydihydrochalcone (10), 1-(2′,6′-dihydroxyphenyl)-3-phenyl-1-propanone (**11**), clusiacitran B (**12**), and aucuparin (**13**).

### *3.4 Cytotoxic activity against human cancer cell lines*

The isolated compounds were assessed for their *in vitro* cytotoxic activity against five human cancer cell lines including KB (oral epidermoid carcinoma), HeLa S-3 (cervical carcinoma), HT-29 (colorectal adenocarcinoma), MCF-7 (breast adenocarcinoma), and Hep G2 (hepatocellular carcinoma) with the MTT assay (Sukandar et al., 2016). The reference substance used in this study was doxorubicin. The preparation of stock solution (5 mg/mL) was initiated by dissolving the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-

tetrazolium bromide (Sigma Chemical Co., USA) in saline water. All five human cancer cell lines were maintained in MEM and high glucose DMEM medium, respectively, supplemented with 10% fetal bovine serum and Penicillin-Streptomycin, in a humidified atmosphere with 5% $CO_2$ (37°C). The cancer cells (100 $\mu$l/wells) were seeded in a 96-well culture plate (Costar, Corning Incorporated, NY, USA) at a density of $3 \times 10^3$ cells per well. The pre-incubation was undergone for 24 h at 37°C in a humidified atmosphere of 5% $CO_2$/95% air to allow cellular attachment. Within the same condition, 10 $\mu$L/well of various test solution concentrations (0–100 $\mu$M) were added and incubated for 72 h. After the first incubation was completed, each well was filled with 10 $\mu$L of tetrazolium reagent and further incubated at 37°C for 4 h. The formazan solubilization occurred after the supernatant was decanted and added with 100 $\mu$L/well of DMSO. A Microplate reader was used to detect each well's optical density at 550 nm and correction at 595 nm. Each determination served as an average mean of six replicates. The inhibitory concentration ($IC_{50}$) was calculated using SigmaPlot software version 10.0.

*3.5 $\alpha$-glucosidase inhibitory activity*

The rat small intestinal method's $\alpha$-glucosidase inhibitory assay was accomplished (Potipiranun, Worawalai, & Phuwapraisirisan, 2018). First, the crude enzyme was prepared by diluting the rat intestinal powder (1.0 g) in 30 mL of saline water and sonicated for 15 min. Next, the suspension was homogenized by centrifugation (9000 rpm x 30 min) at 4°C. The supernatant that occurred was applied as the enzyme solution. Maltose (10 mM) and sucrose (100 mM) were used as the substrates, which each of them was dissolved in the phosphate buffer (pH 6.9). The 160 $\mu$L assay mixture abided of 10 $\mu$L of the tested sample, 30 $\mu$L of 0.1 M phosphate buffer (pH 6.9), 20 $\mu$L of the substrate solution, 80 $\mu$L of glucose kit liquid (Human, Germany), and 20 $\mu$L of the enzyme solution. The mixture was incubated at 37°C for 10 min in maltose or 40 min in sucrose. Lastly, the absorbance (520 nm) was evaluated to measure the enzymatic activity. Moreover, the positive control, acarbose, was assessed within the above condition. Enzyme inhibition reactions for all samples were fulfilled in triplicates and repeated in two independent experiments. Besides, the percentage inhibition was calculated using $[(A_0–A_1):A_0] \times 100$, whereas $A_0$ and $A_1$ were the absorbances without and with the sample, respectively. The $IC_{50}$ value was obtained by plotting the percentage of inhibitions versus sample concentration.

## 4. Results and Discussion

Various chromatography methods were conducted to fractionate the dichloromethane extract of *G. schomburgkiana* branches including silica gel CC, Sephadex LH-20 CC, RP C-18 CC, and radial chromatography (chromatotron) to exhibit thirteen known compounds. Their chemical structures were identified by employing their spectroscopic data ($^1$H and $^{13}$C NMR) from the previous studies. Those isolated compounds were determined as 7-epiclusianone (**1**) (Derogis et al., 2008; Piccinelli et al., 2005), oblongifolin C (**2**) (Hamed et al., 2006), pancixanthone A (**3**) (Ito, Miyamoto, Rao, & Furukawa, 1996), euxanthone (**4**) (Tanus Jorge Nagem & Oliveira, 1997), 1,4,5-trihydroxyxanthone (**5**) (Iinuma, Tosa, Tanaka, Asai, & Shimano, 1995), osajaxanthone (**6**) (Lopes, Lopes, Gilbert, & Bonini, 1977), 1,2,7-trihydroxyxanthone (**7**) (Tanus J. Nagem, Da Silva, & Da Silveira, 1992), 1,3,7-trihydroxy-2,4-diprenylxanthone (**8**) (Iinuma, Tosa, Tanaka, & Riswan, 1996), cudratricusxanthone K (**9**) (Hwang et al., 2007), 2′-hydroxydihydrochalcone (**10**) (Kostrzewa-Susłow, Dmochowska-Gładysz, Białońska, & Ciunik, 2008), 1-(2′,6′-dihydroxyphenyl)-3-phenyl-1-propanone (**11**) (Hambley, Rideout, & Taylor, 1990), clusiacitran B (**12**) (Gonzalez, Olivares, & Monache, 1995), and aucuparin (**13**) (Kokubun, Harborne, Eagles, & Waterman, 1995), as shown in Figure 1.



*Proceedings of RSU International Research Conference (2021)*

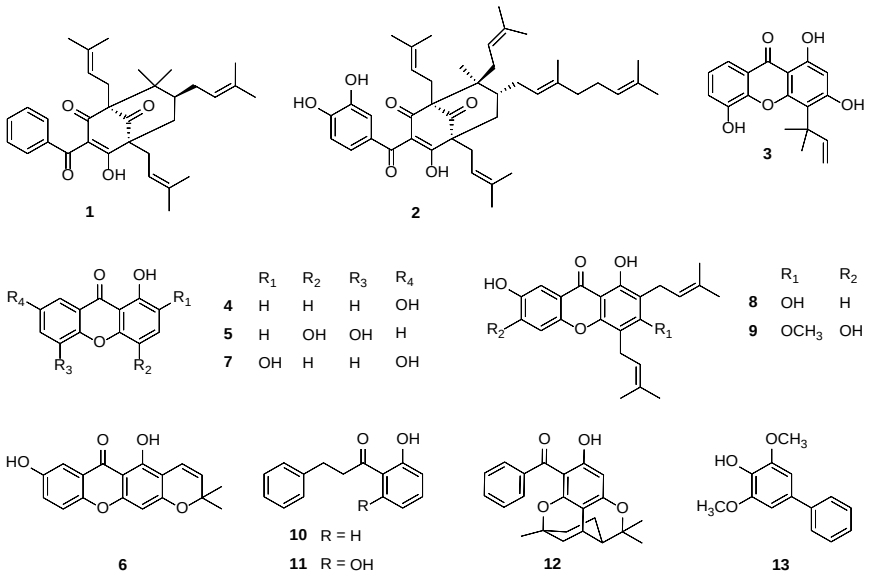


**Figure 1** Chemical constituents isolated from the branches of *G. schomburgkiana*

Chalcones **10** and **11** have been previously reported from *Peperomia obtusifolia* (Tanaka, Asai, & Iinuma, 1998) and *Flindersia brassii* (Hambley et al., 1990*)* respectively while they firstly occur in genus *Garcinia*. Besides, compound **9** was found for the first time in this genus. To the best of our knowledge, the pharmacological investigations of compounds **9**, **10**, and **11** from the plants have never been reported so far. The structure elucidations of compounds **9**, **10**, and **11** were summarized as follows.

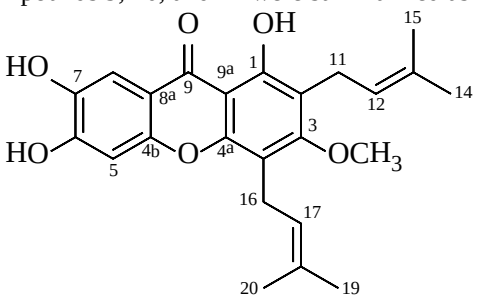

**Figure 2** The chemical structure of cudratricusxanthone K (**9**)

Cudratricusxanthone K (**9**): $^{1}$H NMR (500 MHz, acetone-$d_6$); $\delta_H$ 13.37 (1H, s, OH-1), 7.46 (1H, s, H-8), 6.89 (1H, s, H-5), 5.15 (2H, m, H-12, 17), 3.89 (3H, s, $OCH_3$-3), 3.50 (2H, d, $J$ = 7.5 Hz, H-16), 3.36 (2H, d, $J$ = 6.5 Hz, H-11), 1.80 (3H, s, $CH_3$-20); 1.70 (3H, s, $CH_3$-15), and 1.57 (6H, s, $CH_3$-14, 19); $^{13}$C NMR (126 MHz, acetone-$d_6$); $\delta_C$ 176.4 (C-9), 165.0 (C-3), 160.1 (C-1), 155.5 (C-6), 153.1 (C-4a), 152.4 (C-4b), 136.3 (C-7), 134.4 (C-13), 133.8 (C-18), 121.6 (C-12, 17), 117.6 (C-2), 111.7 (C-4, 8a), 108.3 (C-8), 104.5 (C-9a), 102.6 (C-5), 60.1 ($OCH_3$), 29.5 (C-15, 20), 25.8 (C-11, 16), 18.1 (C-14, 19) (Hwang et al., 2007).

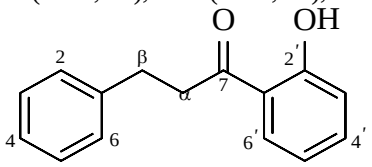

**Figure 3** The chemical structure of 2′-hydroxydihydrochalcone (**10**)

2′-hydroxydihydrochalcone (**10**): $^{1}$H NMR (500 MHz, $CDCl_3$); $\delta_H$ 12.30 (1H, s, OH-2′), 7.74 (1H, d, *J* = 8.0 Hz, H-3′), 7.46 (1H, t, *J* = 7.0 Hz, H-5′), 7.30 (2H, t, *J* = 7.5 Hz, H-3, 5), 7.24 (2H, d, *J* = 7.5 Hz, H-2, 6), 7.22 (1H, t, *J* = 7.5 Hz, H-4), 6.99 (1H, d, *J* = 8.0 Hz, H-6′), 6.88 (1H, t, *J* = 7.5 Hz, H-4′), 3.34 (2H, t, *J* = 7.5 Hz, H-$\alpha$), 3.05 (2H, t, *J* = 7.5 Hz, H-$\beta$); $^{13}$C NMR (126 MHz, $CDCl_3$); $\delta_C$ 205.0 (C-7), 162.6 (C-2′), 140.0 (C-1), 136.4 (C-5′), 129.9 (C-3′), 128.7 (C-3, 5), 128.5 (C-2, 6), 126.4 (C-4), 119.4 (C-1′) 119.0 (C-4′), 118.7 (C-6′), 40.0 (C-$\alpha$), and 30.0 (C-$\beta$) (Kostrzewa-Susłow et al., 2008).

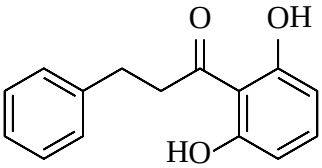


**Figure 4** The chemical structure of 1-(2′,6′-dihydroxyphenyl)-3-phenyl-1-propanone (**11**)

1-(2′,6′-dihydroxyphenyl)-3-phenyl-1-propanone (**11**): $^{1}$H NMR (500 MHz, $CDCl_3$); $\delta_H$ 9.39 (2H, s, OH-2′, 6′), 7.19 – 7.10 (5H, m, H-2, 3, 4, 5, 6), 7.20 (1H, t, *J* = 8.8 Hz, H-4′), 6.29 (2H, d, *J* = 8.8 Hz, H-3′, 5′), 3.37 (2H, t, *J* = 7.5 Hz, H-$\beta$), 2.94 (2H, t, *J* = 7.5 Hz, H-$\alpha$); $^{13}$C NMR (126 MHz, $CDCl_3$); $\delta_C$ 206.4 (C-7), 161.3 (C-2′, 6′), 141.6 (C-1), 135.9 (C-4′), 128.6 (C-2, 3, 5, 6), 12.,1 (C-4), 110.0 (C-1′), 108.6 (C-3′, 5′), 46.5 (C-$\alpha$), and 30.4 (C-$\beta$) (Hambley et al., 1990).

Furthermore, the isolated compounds were assessed for their cytotoxic properties towards Hep G2, MCF-7, HeLa S-3, KB, and HT-29 cancer cell lines and their inhibitions to the $\alpha$-glucosidase enzyme. The cytotoxic evaluation showed that the series of polyprenylated benzoylphloroglucinol provided strong to moderate cytotoxic activities. Compound **2** provides the most impressive cytotoxic properties to all tested cancer cell lines with $IC_{50}$ values ranging from 5.15 to 7.09 $\mu$M. On the other hand, compound **1** gave moderate activity towards the five cell lines with $IC_{50}$ values in the range of 10.92–21.40 $\mu$M. While, compounds **3**-**14** showed weak and inactive cytotoxicities. Results from the screening of $\alpha$-glucosidase inhibitory activity to all tested compounds mostly showed weak activities. An exception was for compound **13,** which exhibited moderate $\alpha$-glucosidase inhibitions in sucrose ($IC_{50}$ 49.23 $\mu$M) and maltose ($IC_{50}$ 98.20 $\mu$M). All data collected from the cytotoxic and $\alpha$-glucosidase inhibitory activity assay are summarized in Table 1 and Table 2, respectively.

**Table 1** Cytotoxic evaluation of the tested compounds

| Samples | $IC_{50}$ values ($\mu$M) | | | | |
|---|---|---|---|---|---|
| | **Hep G2** | **MCF-7** | **HeLa S-3** | **KB** | **HT-29** |
| **1** | 14.38±1.63 | 10.92±0.78 | 21.40±1.80 | 12.72±0.54 | 20.40±1.69 |
| **2** | 6.27±0.95 | 5.24±1.19 | 5.25±0.08 | 5.15±0.23 | 7.09±0.94 |
| **3** | >100 | >100 | 45.81±3.22 | 42.29±2.47 | >100 |
| **4** | >100 | >100 | >100 | >100 | >100 |
| **5** | >100 | >100 | >100 | 82.57±4.68 | >100 |
| **6** | >100 | >100 | >100 | 96.61±2.03 | >100 |
| **7** | >100 | >100 | >100 | >100 | >100 |
| **8** | 50.60±3.06 | 35.03±2.84 | 69.98±2.37 | 76.61±3.09 | 51.43±4.70 |
| **9** | 75.69±5.36 | >100 | 43.14±4.65 | 51.60±1.59 | 45.75±3.00 |
| **10** | >100 | >100 | >100 | >100 | >100 |
| **11** | >100 | >100 | 85.29±0.91 | 55.60±6.40 | >100 |
| **12** | >100 | >100 | >100 | >100 | >100 |
| **13** | >100 | >100 | >100 | >100 | >100 |
| Doxorubicin | 0.24±0.08 | 0.13±0.01 | 0.04±0.01 | 0.16±0.01 | 0.40±0.02 |

Note: $IC_{50} \leq 10$ $\mu$M = strong; 10 $\mu$M < $IC_{50} \leq 30$ $\mu$M = moderate; 30 $\mu$M < $IC_{50} \leq 100$ $\mu$M = weak; $IC_{50} > 100$ $\mu$M = not active

**Table 2** $\alpha$-glucosidase inhibitory activity of the tested compounds

| Samples | $IC_{50}$ values ($\mu$M) | |
|---|---|---|
| | **Maltose** | **Sucrose** |
| **1** | >100 | >100 |
| **2** | >100 | >100 |
| **3** | >100 | >100 |
| **4** | >100 | >100 |
| **5** | >100 | >100 |
| **7** | >100 | >100 |
| **8** | >100 | >100 |
| **9** | >100 | >100 |
| **10** | >100 | >100 |
| **11** | >100 | >100 |
| **12** | >100 | >100 |
| **13** | 98.20±1.97 | 49.23±0.54 |
| Acarbose | 0.16±0.95 | 3.51±4.53 |

Note: $IC_{50} \leq 10$ $\mu$M = strong; 10 $\mu$M < $IC_{50} \leq 100$ $\mu$M = moderate; $IC_{50} > 100$ $\mu$M = weak

The bioactivities results within this study lead to the preliminary structure-activity relationship (SAR) analysis. Phytochemicals that contain polyprenylated benzoylphloroglucinol moiety resulted in the most significant cytotoxicity. In comparison between oblongifolin C (**2**) and 7-epiclusianone (**1**), the SAR study suggested that hydroxy and prenyl groups' presence might enhance their cytotoxicity. The prenyl units affect the compounds' hydrophobicity, thus increasing the activities (Dhameja & Gupta, 2019). Meanwhile, the SAR in the xanthone compounds, as the dominant group isolated from *G. schomburgkiana* branches, showed that the cyclization of prenyl to pyran units could decrease the cytotoxic properties (**6**, **8**, and **9**) (Zhang et al., 2019).

## 5. Conclusion

Two polyprenylated benzoylphloroglucinols (**1** and **2**), seven xanthones (**3**–**9**), two chalcones (**10** and **11**), one benzophenone (**12**), and one biphenyl (**13**) were isolated from the branches of *G. schomburgkiana*. Moreover, cudratricusxanthone K (**9**), 2′-hydroxydihydrochalcone (**10**), and 1-(2′,6′-dihydroxyphenyl)-3-phenyl-1-propanone (**11**) were firstly reported from the genus *Garcinia*. Hence, those compounds might be used to differentiate the phytochemicals from *G. schomburgkaina* with other species. Oblongifolin C (**2**) exhibited strong cytotoxicity ($IC_{50}$<10 $\mu$M) against Hep G2, MCF-7, HeLa S-3, KB, and HT-29 cell lines. Aucuparin (**13**) inhibited $\alpha$-glucosidase enzyme activity with an $IC_{50}$ value of lower than 100 $\mu$M in both maltose and sucrose substrates. Further works from this study might involve evaluating the most potent bioactive compounds for an *in vivo* assay. These results might also provide knowledge to propose a chemical modification of natural product-derived compounds to synthesize a remarkable drug candidate.

## 6. Acknowledgements

The authors are grateful to the Graduate School of Chulalongkorn University for the Master Scholarship Program for ASEAN countries. We also thank Dr. Suttira Khumkratok from Walai Rukhavej Botanical Research Institute, Mahasarakham University, Thailand, for identifying and deposition the plant material.

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