

Review

Chemical constituents and biological activities of *Garcinia cowa* Roxb.

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Abstract: *Garcinia cowa* is an abundant source of bioactive phytochemicals. Phytochemical investigations of the plant parts indicated that the fruit, twig and stem are the best source of secondary metabolites, providing flavonoids, phloroglucinols and xanthenes respectively. Seventy-eight of these compounds have been identified from the plant and several have interesting pharmacological activities.

Keywords: *Garcinia cowa*, flavonoids, xanthenes, phloroglucinols

INTRODUCTION

Many pharmaceutical drug discoveries originated from traditional folk medicine and its associated plant materials and bioactive secondary metabolites. The Genus *Garcinia*, belonging to the Family Clusiaceae which comprises about 300 species, have been widely investigated in terms of their bioactive ingredients. Native to Asia, Africa, South America and Polynesia, the plants are small to medium sized evergreen trees which may grow up to 30 m in height and are widely distributed in the tropical and temperate regions of the world [1]. Twenty-nine species have been observed in Thailand, with 20, 13, 12, 7, 6 and 3 species found in the south, middle, north, east, north-east and west of the country respectively (Figure 1).

Garcinia is a rich source of secondary metabolites, especially triterpenes [1], flavonoids [5], xanthenes [6] and phloroglucinols [7]. The latter two groups are well recognised as chemotaxonomic markers for this genus [8a-e]. Many of the isolated compounds have a wide range

of pharmacological activities including anticancer, anti-inflammatory, antibacterial, antiviral, antifungal, anti-HIV, antidepressant and antioxidant [1, 9-13].



Figure 1. Species of *Garcinia* found in different parts of Thailand [2-4]

Garcinia cowa (Figure 2a), commonly known as Cha-muang in Thai, is widely distributed throughout Malaysia, Thailand and Myanmar. The fruits and young leaves are edible with a sour taste. The bark is dark brown with a yellow latex (Figure 2b). The plant has unisex flowers: yellow orange female flowers found at the end of branches and male flowers found along the branches as clusters (Figure 2c). The leaves are glossy, deep green, oblong and up to 6-15 cm in length and 2.5-6.0 cm in width (Figure 2d). The fruits are globose (2.5-6.0 cm in size), green when young and dull

orange or yellow at maturity with 5-8 shallow grooves, at least near the top, and contain 6-8 large 3-angled seeds (Figure 2e) [14].

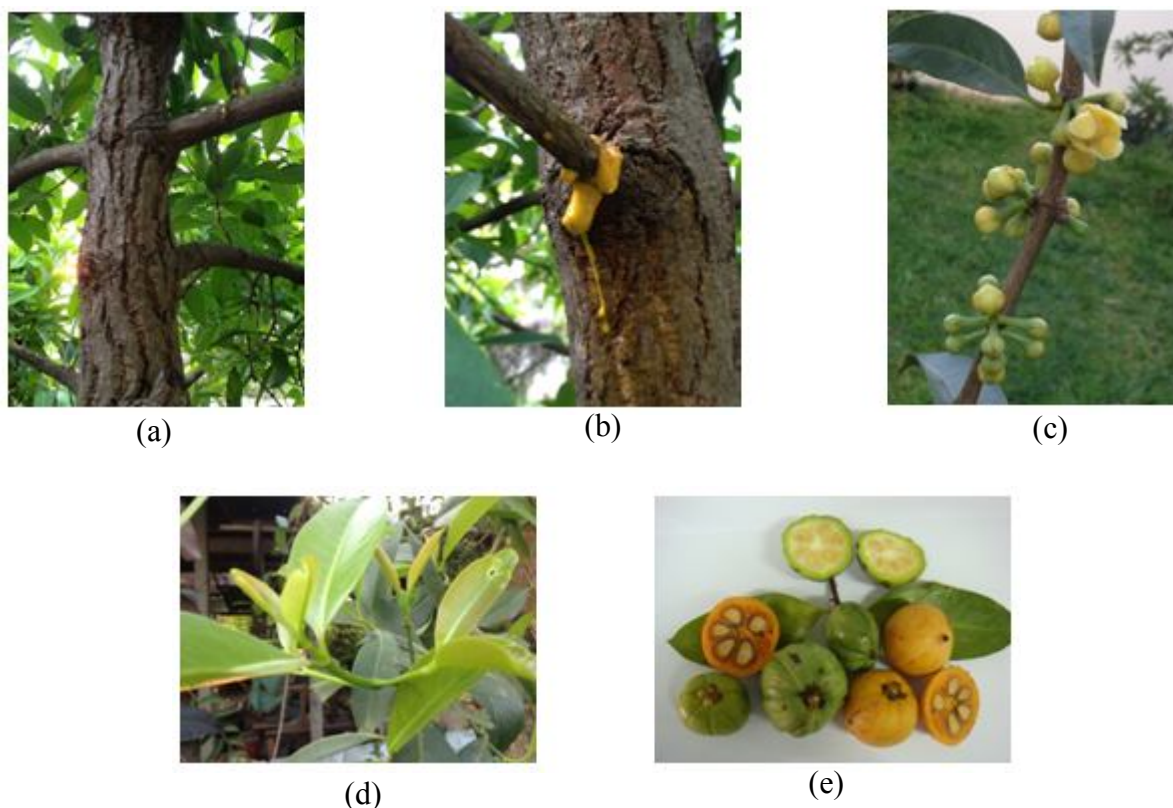


Figure 2. Parts of *G. cowa*: (a) branch, (b) bark and latex, (c) inflorescences, (d) leaves and (e) ripe and immature fruits (Photos taken by S. Laphookhieo, 2011)

Many parts of *G. cowa* have been used in traditional folk medicine. For example, the bark, latex and root have been used as an antifever agent [15, 16] while the fruit and leaves have been used for indigestion and improvement of blood circulation, and as an expectorant [16]. The chemical composition and biological activities of various parts of *G. cowa* have been investigated. The major compounds found were xanthenes and phloroglucinols. However, minor compounds, including depsidones, terpenoids, steroids and flavonoids, were also observed. Currently, 78 compounds have been isolated from the twig [17], stem [18], fruit [19, 20] and latex [15]. This review mainly focuses on the chemical structures and biological activities of the phytochemicals isolated from *G. cowa* and covers the literature up to April 2012.

DISTRIBUTION AND BIOLOGICAL ACTIVITY

The biological activities of the extracts from various parts of *G. cowa* have been investigated, including the hexane and chloroform extracts of the fruit rind and methanol extract of the leaves and twigs [21-23]. The hexane and chloroform extracts from the fruit rind of *G. cowa* were tested against four Gram-positive bacteria (*Bacillus cereus*, *B. coagulans*, *B. subtilis* and *Staphylococcus aureus*) and one Gram-negative bacterium (*Escherichia coli*). Both extracts significantly inhibited bacterial

growth of the Gram-positive bacteria (IC_{50} s 15-30 $\mu\text{g/mL}$) but not *E. coli* (IC_{50} s 250-500 $\mu\text{g/mL}$) [21]. The extracts were also found to inhibit the growth of *Aspergillus flavus* ATCC 46283, a common fungal food contaminant which produces aflatoxin B₁. The degree of inhibition of aflatoxin B₁ production (100% at a concentration of 2000 ppm) was found to be much higher than the inhibition of fungal growth (ca 40-60% at the same concentration) [22]. The methanol extracts of the leaves and twigs of *G. cowa* were evaluated for their ability to inhibit low-density lipoprotein peroxidation induced by copper ions. The twig extract had an IC_{50} value of 20.5 $\mu\text{g/mL}$ and was more potent (higher % inhibition at 1000 $\mu\text{g/mL}$) than the leaf extract (IC_{50} not measured). The twig extract was more potent than the leaf extract on platelet aggregation of human whole blood induced by arachidonic acid, adenosine diphosphate and collagen. These activities may be due to the total phenolic content of these extracts, which were 19 and 61 mg of gallic acid equivalent per g of extract for the leaf and twig extracts respectively [23]. The structural types, chemical structures and biological activities of the natural products isolated from different parts of *G. cowa* were summarised in Table 1. A summary of the number of natural product compounds first discovered in each structural class is shown in Figure 3 and from different parts of the plant is shown in Figure 4.

Table 1. Structure, distribution and biological activity of phytochemicals isolated from different parts of *G. cowa*

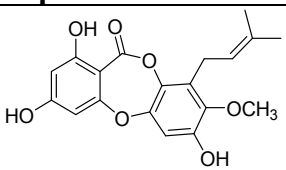
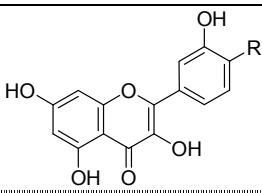
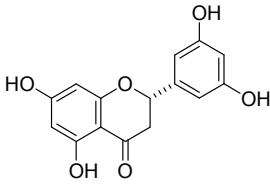
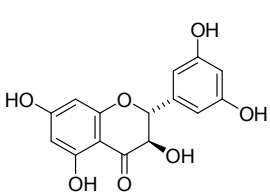
Category and structure	Name (code), source and reference	Biological activity
Depsidone		
	Cowadepsidone (1); twig [17]*	Cytotoxicity [17] NCI-H187 IC_{50} 31.47 $\mu\text{g/mL}$ MFC-7 IC_{50} 36.03 $\mu\text{g/mL}$
Flavonoid		
	R = H Kaempferol (2); branch [24]	
	R = OH Quercetin (3); stem [18]	
	2-(3,5-Dihydroxyphenyl)-2,3-dihydro-5,7-dihydroxy-3',5,5',7-tetrahydroxyflavanone (4); stem [18]	
	2-(3,5-Dihydroxyphenyl)-2,3-dihydro-3,5,7-trihydroxy-(2R,3R)-3,3',5,5',7-pentahydroxyflavanone (5); stem [18]	

Table 1. (continued)

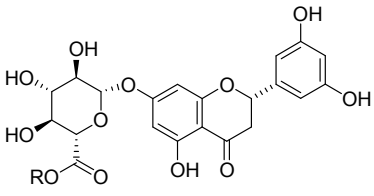
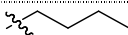
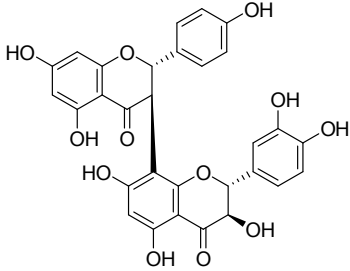
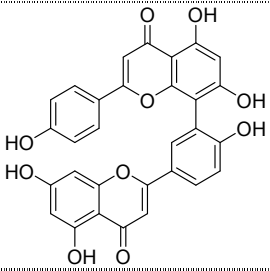
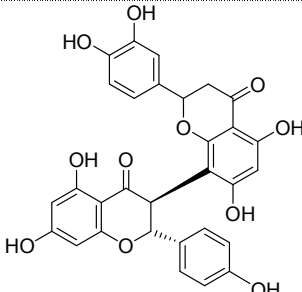
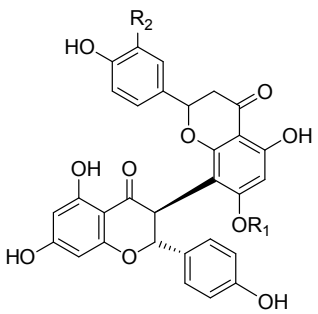
Category and structure	Name (code), source and reference	Biological activity
Flavonoid		
	R = 	
	Garccowaside A (6); stem [18]*	
	R = 	
	Garccowaside B (7); stem [18]*	
	R = CH ₃	
	Garccowaside C (8); stem [18]*	
	GB-2 (9); branch [24]	
	Amentoflavone (10); fruit [19]	
	Morelloflavone (11); fruit [19] twig [16]	Antioxidant activity [16] DPPH assay IC ₅₀ 10.01 µg/mL Hydroxyl radical scavenging assay IC ₅₀ 3.11x10 ⁻⁴ µg/mL Superoxide anion scavenging assay IC ₅₀ 1.50x10 ⁻⁴ µg/mL
	R ₁ = R ₂ = H	
	Volkensiflavone (12); twig [16]	
	R ₁ = β-glucoside; R ₂ = OH Morelloflavone-7'-O-glucoside or fukugiside (13); twig [16]	Antioxidant activity [16] DPPH assay IC ₅₀ 12.92 µg/mL Hydroxyl radical scavenging assay IC ₅₀ 5.31x10 ⁻⁴ µg/mL Superoxide anion scavenging assay IC ₅₀ 6.39x10 ⁻⁴ µg/mL

Table 1. (continued)

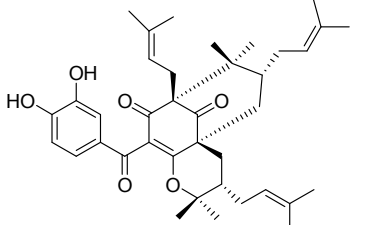
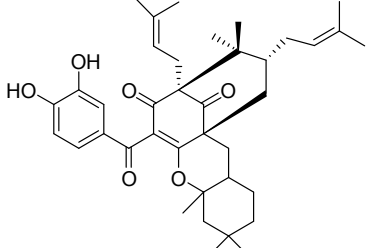
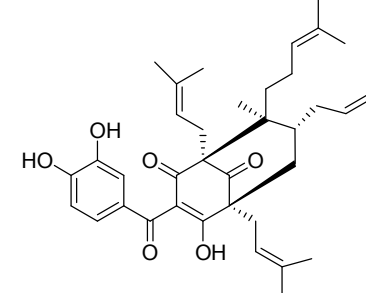
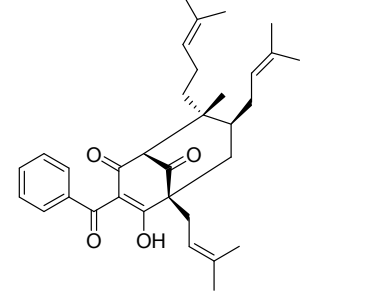
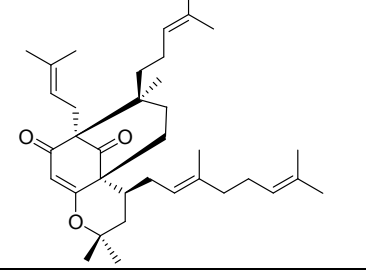
Category and structure	Name (code), source and reference	Biological activity
Phloroglucinol		
	Cambogin (14); fruit [25, 26], twig [7], stem [26]	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	Guttiferone K (15a) [#] ; fruit [26]*, stem [26]	
	Guttiferone K (15b) [#] ; twig [7]	Cytotoxicity [7] against HT-29 IC ₅₀ 3.25±0.12 µg/mL HCT-116 CCD-18Co
	Chamuangone (16); leaf [27]*	Antibacterial activity [27] <i>S. pyogenes</i> MIC 7.8 µg/mL <i>S. viridans</i> MIC 15.6 µg/mL <i>H. pylori</i> MIC 15.6 µg/mL <i>B. subtilis</i> , <i>Enterococcus sp.</i> and <i>S. aureus</i> MIC 31.2µg/mL
	Garcicowin A (17); twig [7]*	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co

Table 1. (continued)

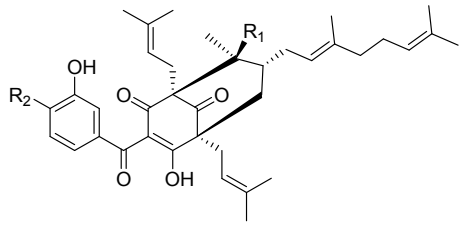
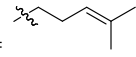
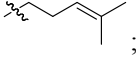
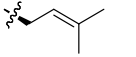
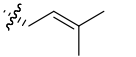
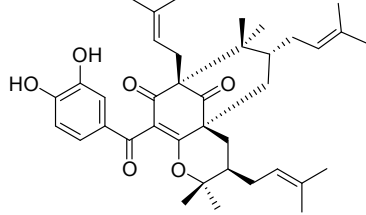
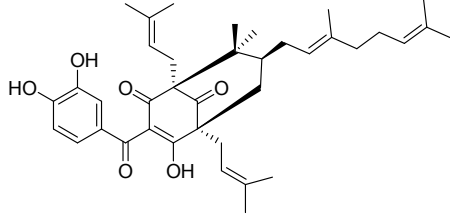
Category and structure	Name (code), source and reference	Biological activity
Phloroglucinol		
	$R_1 = $  $; R_2 = H$ Garcicowin B (18); twig [7]*	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	$R_1 = CH_3; R_2 = OH$ Oblongifolin B (19); twig [7]	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	$R_1 = $  $; R_2 = OH$ Oblongifolin C (20); twig [7]	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	$R = $  Garcicowin C (21); twig [7]*	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	$R = $  Garcicowin D (22); twig [7]*	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	30-Epicambogin (23); twig [7]	Cytotoxicity [7] against HT-29 $IC_{50} 3.07 \pm 0.06 \mu g/mL$ HCT-116 CCD-18Co
	Oblongifolin A (24); twig [7]	

Table 1. (continued)

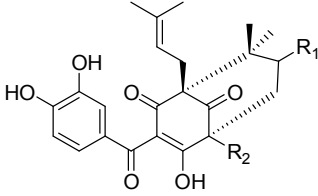
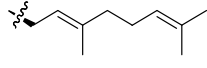
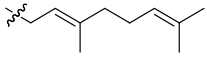
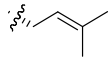
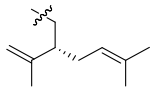
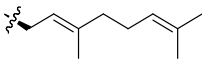
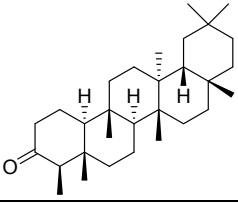
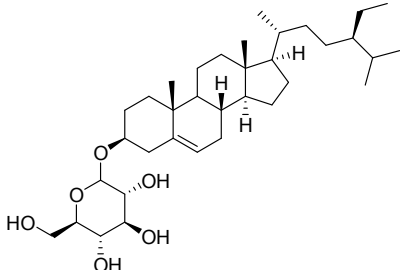
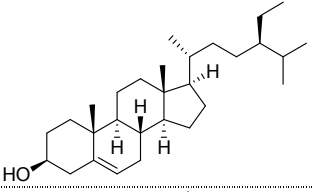
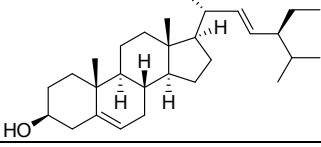
Category and structure	Name (code), source and reference	Biological activity
Phloroglucinol		
	$R_1 =$  $R_2 =$  Guttiferone B (25); twig [7]	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
	$R_1 =$  $R_2 =$  Guttiferone F (26); twig [7]	
	$R_1 = R_2 =$  Oblongifolin D (27); twig [7]	Cytotoxicity [7] against HT-29 HCT-116 CCD-18Co
Terpene and Steroid		
	Friedelin (28); branch [24]	
	Daucosterol (29); branch [24], fruit [19]	
	β-Sitosterol (30); branch [24], fruit [19]	
	Stigmasterol (31); branch [24]	

Table 1. (continued)

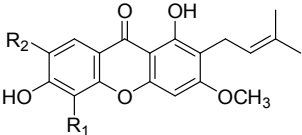
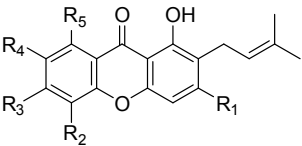
Category and structure	Name (code), source and reference	Biological activity
Xanthone		
	R ₁ = OCH ₃ ; R ₂ = H Cowaxanthone A (32); fruit [20] or cowagarcinone C; latex [15]*	Anti-inflammatory activity [16]
	R ₁ = H; R ₂ = OCH ₃ 1,6-Dihydroxy-3,7-dimethoxy-2-(3-methyl-2-butenyl)xanthone (33); fruit [20]	
	R ₁ = OH; R ₂ = H; R ₃ = R ₄ = OCH ₃ ; R ₅ = prenyl Cowaxanthone B (34); fruit [20]*	Antibacterial activity [20] <i>S. aureus</i> MIC 128 µg/mL MRSA MIC 128 µg/mL
	R ₁ = R ₃ = R ₄ = OCH ₃ ; R ₂ = H; R ₅ = prenyl Fuscaxanthone C (35); fruit [20]	Anti-inflammatory activity [16]
	R ₁ = R ₃ = OH; R ₂ = R ₅ = prenyl; R ₄ = OCH ₃ 7-O-Methylgarcinone E (36); stem [28]*, bark [29], fruit [20]	Antibacterial activity [20] <i>S. aureus</i> MIC 128 µg/mL MRSA MIC 64 µg/mL
		Antimalarial activity [29] <i>Plasmodium falciparum</i> IC ₅₀ 1.5-3.0 µg/mL
		Antimalarial activity [29] <i>Plasmodium falciparum</i> IC ₅₀ 1.5-3.0 µg/mL
	R ₁ = R ₃ = OH; R ₂ = H; R ₄ = OCH ₃ ; R ₅ = prenyl α-Mangostin (37); fruits [20], bark [29]	Antibacterial activity [20] <i>S. aureus</i> MIC 8 µg/mL MRSA MIC 8 µg/mL
		Anti-inflammatory activity [16] Antimalarial activity [29] <i>Plasmodium falciparum</i> IC ₅₀ 1.5-3.0 µg/mL
	R ₁ = R ₄ = OCH ₃ ; R ₂ = H; R ₃ = OH; R ₅ = prenyl β-Mangostin (38); fruit [20], twig [17]	Antibacterial activity [20] <i>S. aureus</i> MIC 128 µg/mL MRSA MIC 64 µg/mL

Table 1. (continued)

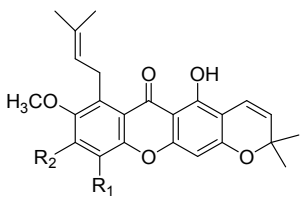
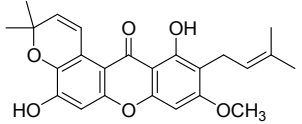
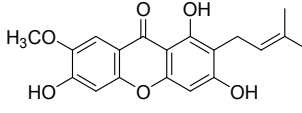
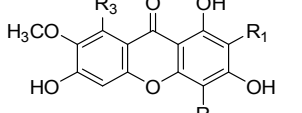
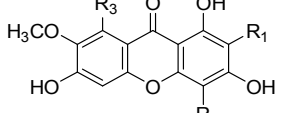
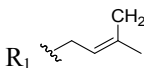
Category and structure	Name (code), source and reference	Biological activity
Xanthone		
	Antibacterial activity [20]	
	R ₁ = prenyl; R ₂ = OH	<i>S. aureus</i> MIC 128 µg/mL
	Cowaxanthone C (39); fruit [20]*	MRSA MIC 128 µg/mL
	Anti-inflammatory activity [16]	
	R ₁ = H; R ₂ = OH	Antibacterial activity [20]
	Mangostanin (40); fruit [20]	<i>S. aureus</i> MIC 4 µg/mL
	Anti-inflammatory activity [16]	
	R ₁ = H; R ₂ = OCH ₃	MRSA MIC 4 µg/mL
	6- <i>O</i> -Methylmangostanin (41); fruit [20]	
	Anti-inflammatory activity [16]	
	Cowaxanthone D (42); fruit [20]*	
	Antimalarial activity [29]	
	Cowaxanthone (43); fruit [20], latex [15, 30*], twig [17], bark [29]	<i>Plasmodium falciparum</i> IC ₅₀ 1.5-3.0 µg/mL
		Cytotoxicity [17]
	NCI-H187 IC ₅₀ 3.87 µg/mL	
		KB IC ₅₀ 15.43 µg/mL
		MFC-7 IC ₅₀ 15.45 µg/mL
	R ₁ = R ₃ = prenyl; R ₂ = CHO	
	Cowaxanthone E (44); fruit [20]*	
		Antibacterial activity [20]
	R ₁ =  ; R ₂ = H; R ₃ = geranyl	<i>S. aureus</i> MIC >128 µg/mL
	Cowanol (45); fruit [20], latex [15, 30*], twig [17], bark [29]	MRSA MIC >128 µg/mL
		Anti-inflammatory activity [16]
	Antimalarial activity [29]	
	<i>Plasmodium falciparum</i>	IC ₅₀ 1.5-3.0 µg/mL
		Cytotoxicity [17]
	NCI-H187 IC ₅₀ 37.26 µg/mL	
	KB IC ₅₀ 32.34 µg/mL	
	MFC-7 IC ₅₀ 34.62 µg/mL	

Table 1. (continued)

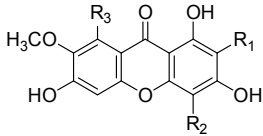
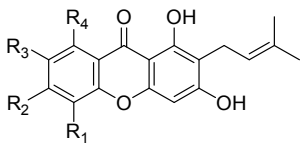
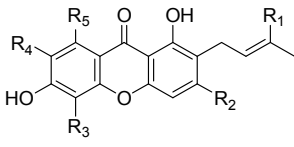
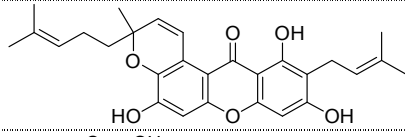
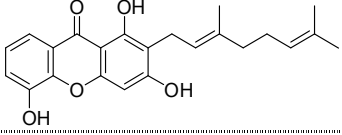
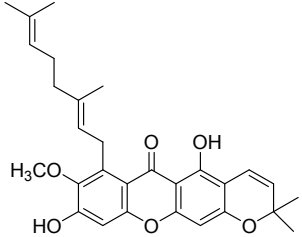
Category and structure	Name (code), source and reference	Biological activity
Xanthone		
	R ₁ = prenyl; R ₂ = H; R ₃ = geranyl Cowanin (46); fruit [20], latex [15, 30*], twig [17], bark [29]	Antibacterial activity [20] <i>S. aureus</i> MIC >128 µg/mL MRSA MIC >128 µg/mL
		Anti-inflammatory activity [16] Antimalarial activity [29] <i>Plasmodium falciparum</i> IC ₅₀ 1.5-3.0 µg/mL
	R ₁ = prenyl; R ₂ = OH; R ₃ = OCH ₃ ; R ₄ = H 1,3,6-Trihydroxy-7-methoxy-2,5-bis(3-methyl-2-butenyl)xanthone (47); latex [15, 30*] R ₁ = H; R ₂ = R ₃ = OH; R ₄ = geranyl Norcowanin (48); latex [30]*, twig [17]	Cytotoxicity [17] NCI-H187 IC ₅₀ 5.92 µg/mL KB IC ₅₀ 6.43 µg/mL MFC-7 IC ₅₀ 18.85 µg/mL
	R ₁ = CH ₃ ; R ₂ = OH; R ₃ = prenyl; R ₄ = OCH ₃ ; R ₅ = geranyl Cowagarcinone A (49); latex [15]* R ₁ = CH ₃ ; R ₂ = R ₃ = OCH ₃ ; R ₄ = R ₅ = H Cowagarcinone B (50); latex [15]* R ₁ = CH ₂ OAc; R ₂ = OH; R ₃ = H; R ₄ = OCH ₃ ; R ₅ = geranyl Cowagarcinone E (51); latex [15]*	
	Cowagarcinone D (52); latex [15]*	
	Mangostinone (53); latex [15]	
	Fuscaxanthone A (54); latex [15]	

Table 1. (continued)

Category and structure	Name (code), source and reference	Biological activity
Xanthone		
	Cowaxanthone F (55); twig [16]*	
	1,6-Dihydroxyxanthone (56); twig [16]	
	3,6-Di- <i>O</i> -methyl- γ -mangostin (57); twig [17]	Cytotoxicity [17] NCI-H187 IC ₅₀ 8.58 μ g/mL KB IC ₅₀ 6.64 μ g/mL MFC-7 IC ₅₀ 10.59 μ g/mL
	Rubraxanthone (58); stem [31, 32]	
	R ₁ = H; R ₂ = 1,5,6-Trihydroxy-3-methoxy-4-(3-hydroxy-3-methylbutyl)xanthone (59) or nigrolineaxanthone T; stem [18, 33*]	
	R ₁ = H; R ₂ = prenyl Dulxanthone A (60); stem [18, 33, 34]	Cytotoxicity [34] HepG2
	R ₁ = prenyl; R ₂ = 4-(1,1-Dimethyl-prop-2-enyl)-1,5,6-trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthen-9-(9 <i>H</i>)-one (61); stem [32]*	
	R ₁ = OCH ₃ ; R ₂ = prenyl 1,5-Dihydroxy-3-methoxy-4-(3-methylbut-2-enyl)-6',6'-dimethyl-2 <i>H</i> -pyrano(2',3':6,7) xanthone (62); stem [18, 33*]	

Table 1. (continued)

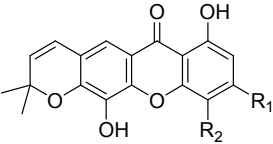
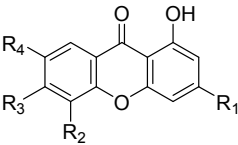
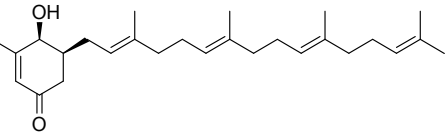
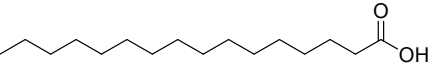
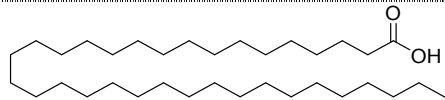
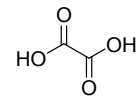
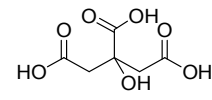
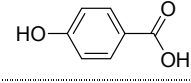
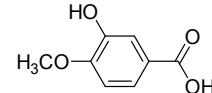
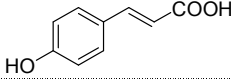
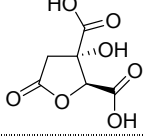
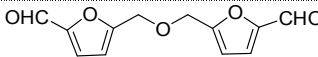
Category and structure	Name (code), source and reference	Biological activity
Xanthone		
	$R_1 = \text{OH}; R_2 = \text{H}$ 1,3,5-Trihydroxy-6',6'-dimethyl- 2 <i>H</i> -pyrano(2',3':6,7)xanthone (63); stem [18, 33]	
	$R_1 = R_3 = R_4 = \text{OH}; R_2 = \text{H}$ 1,3,6,7-Tetrahydroxyxanthone (64) or norathyriol; stem [18, 33]	
	$R_1 = R_2 = \text{OH}; R_3 = \text{OCH}_3; R_4 = \text{H}$ 1,3,5-Trihydroxy-6-methoxy- xanthone (65); stem [33]	
	$R_1 = R_4 = \text{OCH}_3; R_2 = R_3 = \text{OH}$ 1,5,6-Trihydroxy-3,7- dimethoxyxanthone (66); stem [18, 33]	
	$R_1 = R_2 = R_3 = \text{H}; R_4 = \text{OH}$ 1,7-Dihydroxyxanthone (67); stem [33]	
Miscellaneous compound		
	(2 <i>E</i> ,6 <i>E</i> ,10 <i>E</i>)-(+)-4β-Hydroxy-3- methyl-5β-(3,7,11,15- tetramethyl-hexadeca-2,6,10,14- tetraenyl)cyclo-hex-2-en-1-one (68); stem [32]*	
	Palmitic acid (69); branch [24]	
	Tetratriacontanoic acid (70); branch [24]	
	Oxalic acid (71); fruit [35], fresh leaf [35], bark [35]	
	Citric acid (72); fruit [35], fresh leaf [35], bark [35]	
	4-Hydroxybenzoic acid (73); branch [24]	
	Isovanillic acid (74); branch [24]	

Table 1. (continued)

Category and structure	Name (code), source and reference	Biological activity
Miscellaneous compound		
	<i>p</i> -Coumaric acid (75); fruit [19]	
	(-)-Hydroxycitric acid lactone (76); fruit [35], fresh leaf [35], bark [35]	
	Cirsiumaldehyde (77); fruit [19]	

Note: Biological activity: MRSA (Methicillin resistant *Staphylococcus aureus*), NCI-H187 (Human small cell lung cancer), KB (Oral cavity cancer cell), MCF-7 (Breast cancer cell), HT-29 and HCT-116 (Human colon cancer cell), CCD-18Co (Normal human colon cell), HepG2 (Human hepatocellular liver carcinoma cell)

* Firstly discovered compound (new compound)

Guttiferone K (15a, 15b) has been given two different structures in the literature [7, 26].

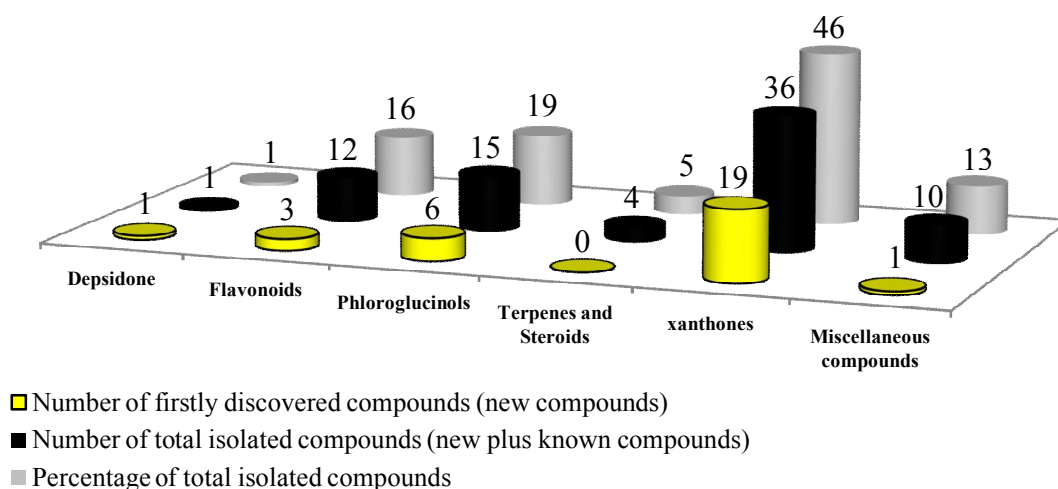


Figure 3. Classes and numbers of natural products isolated from *G. cowa*

CLASSESS OF COMPOUNDS ISOLATED FROM *G. COWA*

Depsidone

Depsidones comprise benzoic acid and phenol skeletons condensed at the *ortho*-positions through ester and ether linkages. This class of natural products is well known in the *Garcinia* species [36, 37]. However, cowadepsidone (1) was the first and only known depsidone from *G. cowa*. It was isolated from the twig extract and showed cytotoxicity against NCI-H187 and MFC-7 cancer cell lines [17].

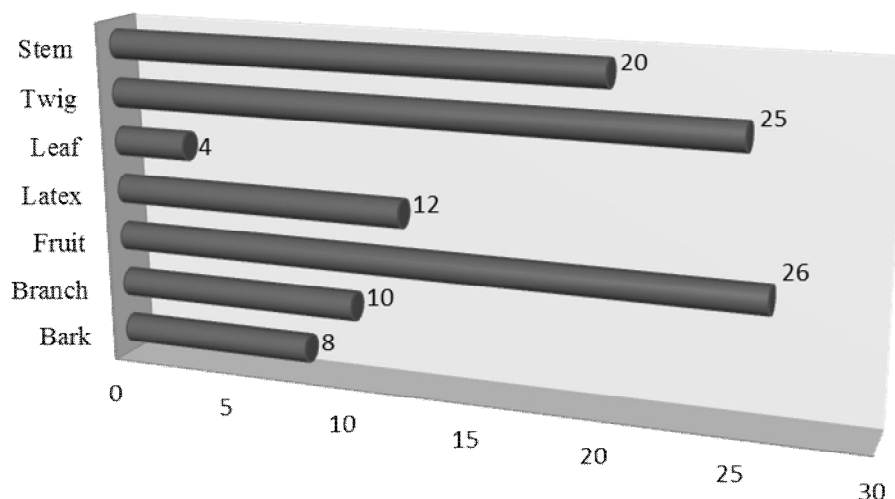


Figure 4. Numbers of natural products from different parts of *G. cowa*

Flavonoids

Twelve flavonoids (compounds **2-13** in Table 1) were isolated from *G. cowa* with garccowasides A (**6**), B (**7**) and C (**8**) being first reported as new compounds [18]. Of these compounds, only morelloflavone (**11**) and morelloflavone-7''-*O*-glucoside (**13**) showed strong antioxidant activities [16].

Phloroglucinols

Phloroglucinols are based on a phloroglucinol or 1,3,5-benzenetriol core skeleton or its 1,3,5-cyclohexanetrione (phloroglucin) tautomer. The phloroglucinols found in *G. cowa* have a benzoyl group and geranyl and polyprenyl units as substituent groups. So far, fifteen phloroglucinols (compounds **14-27** in Table 1) have been obtained from the twig including six new compounds: guttiferone K (**15a**), chamuangone (**16**), garcicowins A (**17**), B (**18**), C (**21**) and D (**22**) [7, 26, 27], and nine known phloroglucinols: cambogin (**14**), guttiferones K (**15b**), B (**25**) and F(**26**), oblongifolins B (**19**), C (**20**), A (**24**) and D (**27**), and 30-epicambogin (**23**). Some of them showed selective cytotoxicity against two cancer cell lines (HT-29 and HCT-116) and normal colon cells (CCD-18Co). Guttiferone K (**15**) and 30-epicambogin (**23**) exhibited highest cytotoxicity against cancer cell line HT-29 [7]. The name guttiferone K has been given to two different structures in the literature [7, 26] as shown in Table 1. Only one compound, chamuangone (**16**), was tested for its antibacterial activity and was found to be active against *S. pyogenes* (MIC = 7.8 µg/mL), *S. viridans* and *H. pylori* (MICs = 15.6 µg/mL), and *S. aureus*, *B. subtilis* and *Enterococcus* sp. (all of this bacteria shown MICs = 31.2 µg/mL) [27].

Terpenes and Steroids

Terpenes and steroids represent two large classes of natural products, although they are rare in *G. cowa*. Only four of these types of compounds (5% of the total compounds isolated) were present in *G. cowa*, viz. friedelin (**28**), daucosterol (**29**), β -sitosterol (**30**) and stigmasterol (**31**) [24]. None of these compounds were further studied for their biological activities. However, these compounds which were isolated from other plants had been investigated for their biological

activities. Friedelin (**28**) from the root bark of *Terminalia avicennioides* exhibited antibacterial activity against Bacillus Calmette-Guerin (BCG) with an MIC of 4.9 µg/mL [38]. Friedelin (**28**) and stigmasterol (**31**) isolated from the leaf of *Jatropha tanjorensis* were tested against human pathogenic microorganisms, i.e. Gram-positive bacteria: *Bacillus cereus*, *B. subtilis*, *S. aureus* and *S. epidermis*; Gram-negative bacteria: *Aeromonas hydrophila*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *P. vulgaris*, *Salmonella paratyphi*, *S. paratyphi A*, *Vibrio alcaligenes* and *V. cholera*; and fungi: *Aspergillus fumigatus*, *Candida albicans*, *Microsporum gypseum* and *Trichophyton rubrum* using the agar-well diffusion and disk diffusion methods [39]. Friedelin (**28**), at the concentration of 2 µg/mL, showed maximum activity with 37-40, 17-40 and 31-33 mm of clear zone diameter against these three types of microorganisms respectively [39], while stigmasterol (**31**) at the same concentration exhibited maximum activity with 13-15, 8-17 and 7-8 mm of clear zone diameter respectively [39]. Daucosterol (**29**) from the roots of *Astragalus membranaceus* had no growth-inhibitory effect by direct contact but possessed immunomodulatory effect against disseminated candidiasis caused by *Candida albicans* [40]. β-Sitosterol (**30**) and stigmasterol (**31**), isolated from the bark of *Grewia tiliaefolia*, at the same concentration of 1 µg/mL showed antibacterial activity against the Gram-negative bacterium *P. aeruginosa* (ATCC-20852) with 18 and 20 mm of clear zones respectively and against *Klebsiella pneumonia* (MTCC-618) with 15 and 15 mm of clear zones respectively as determined by the agar diffusion method [41].

Xanthones

Xanthones, with two aromatic rings linked via carbonyl and ether linkages, are the major components of the *Garcinia* genus [8c-e]. They are commonly found in several parts of *G. cowa*, especially in the stem, fruit and latex. Thirty six xanthones (46% of the total isolated compounds) have been isolated and nineteen of them were first isolated from *G. cowa*. They are cowagarcinone C (**32**), cowaxanthone (**43**), cowanol (**45**), cowanin (**46**), 1,3,6-trihydroxy-7-methoxy-2,5-bis(3-methyl-2-butenyl)xanthone (**47**), norcowanin (**48**), cowagarcinones A (**49**), B (**50**), E (**51**) and D (**52**) from the latex [15, 30]; cowaxanthones B (**34**), C (**39**), D (**42**) and E (**44**) from the fruit [20]; 7-*O*-methylgarcinone E (**36**), 1,5,6-trihydroxy-3-methoxy-4-(3-hydroxyl-3-methylbutyl)xanthone (**59**), 4-(1,1-dimethyl-prop-2-enyl)-1,5,6-trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthen-9(9*H*)-one (**61**) and 1,5-dihydroxy-3-methoxy-6',6'-dimethyl-2*H*-pyrano(2',3':6,7)-4-(3-methylbut-2-enyl)xanthone (**62**) from the stem [18, 33]; and cowaxanthone F (**55**) from the twig [16]. Most of these xanthones showed interesting biological activities.

Antibacterial activity

Eight xanthones from the fruit: cowaxanthones B (**34**) and C (**39**), 7-*O*-methylgarcinone E (**36**), α-mangostin (**37**), β-mangostin (**38**), mangostanin (**40**), cowanol (**45**) and cowanin (**46**) were investigated for their antibacterial activity against *S. aureus* and MRSA. α-Mangostin (**37**) and mangostanin (**40**) showed significant activity against these bacteria. α-Mangostin (**37**) had a MIC value of 8 µg/mL against both *S. aureus* and MRSA while mangostanin (**40**) had an MIC value of 4 µg/mL against both bacteria [20].

Anti-inflammatory activity

Eight xanthenes: cowaxanthenes A (32), B (34), C (39) and D (42), α -mangostin (37), mangostanin (40), cowanol (45) and cowanin (46) were tested for their anti-inflammatory activity using the ethyl phenylpropiolate induced ear edema assay. All xanthenes except cowanol were more active than the standard drug, phenylbutazone [16].

Antimalarial activity

Five xanthenes isolated from the stem bark: 7-*O*-methylgarcinone E (36), α -mangostin (37), cowaxanthone (43), cowanol (45) and cowanin (46) had significant in vitro antimalarial activity against *Plasmodium falciparum* with IC₅₀ values ranging between 1.5-3.0 μ g/mL [29].

Anticancer activity

Six xanthenes: cowaxanthone (43), cowanol (45), cowanin (46), norcowanin (48), 3,6-di-*O*-methyl- γ -mangostin (57) and dulxanthone A (60) isolated from twig were evaluated for their cytotoxicity against NCI-H187, KB, MFC-7 and/or HepG2 cell lines. Cowaxanthone (43), cowanin (46), norcowanin (48) and 3,6-di-*O*-methyl- γ -mangostin (57) exhibited significant cytotoxicity against the NCI-H187 cell line with IC₅₀ values ranging between 3.87-8.58 μ g/mL, and moderately inhibited KB and MCF-7 cancer cell lines with IC₅₀ values ranging between 6.43-15.43 and 10.59-21.38 μ g/mL respectively [17]. Dulxanthone A (60) was found to be cytotoxic against the HepG2 cell line [34].

Miscellaneous Compounds

Ten (13% of the total isolated compounds) of the miscellaneous class of compounds have been isolated, including a new discovery: (2*E*,6*E*,10*E*)-(+)-4 β -hydroxy-3-methyl-5 β -(3,7,11,15-tetramethyl-hexadeca-2,6,10,14-tetraenyl)cyclohex-2-en-1-one (68) [32]. None of the isolated compounds from this class were tested for their biological activities.

CONCLUSIONS

G. cowa is an important source of bioactive compounds. Among the parts of this tree, the fruit, twig and stem are the best source of metabolites, thirty of which have been isolated, i.e. one depsidone, one α,β -unsaturated cyclohexenone, three flavonoids, six phloroglucinols and nineteen xanthenes. Some of these compounds show interesting pharmacological activities. α -Mangostin (37), cowanol (45) and cowanin (46) are commonly found in all parts of *G. cowa* and they can be used as chemotaxonomic markers of this species. The plant is still under investigation by our research group with the prospect of identifying new bioactive compounds in the near future.

ACKNOWLEDGMENT

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REFERENCES

1. A. Kijjoa and L. M. M. Vieira, "Triterpenes from the plants of the Family Clusiaceae (Guttiferae): Chemistry and biological activities", in "Natural Products: Chemistry, Biochemistry and Pharmacology", (Ed. G. Brahmachari), Alpha Science International Ltd., Oxford, 2009, Ch. 13.

2. T. Smitinand, "Thai Plant Names", The Forest Herbarium Royal Forest Department, Bangkok, **2001**, pp.246-248.
3. (a) J. F. Maxwell, "Vegetation of Doi Tung, Chiang Rai province, northern Thailand", *Maejo Int. J. Sci. Technol.*, **2007**, 1, 10-63; (b) J. F. Maxwell, "Addendum to vegetation of Doi Tung, Chiang Rai province, northern Thailand", *Maejo Int. J. Sci. Technol.*, **2008**, 2, 37-139.
4. S. Klaiklay, Y. Sukpondma, V. Rukachaisirikul and S. Phongpaichit, "Friedolanostanes and xanthenes from the twigs of *Garcinia hombroniana*", *Phytochem.*, **2013**, 85, 161-166.
5. W. H. Ansari, W. Rahman, D. Barraclough, R. Maynard and F. Scheinmann, "Biflavanoids and a flavanone-chromone from the leaves of *Garcinia dulcis* (Roxb.) Kurz", *J. Chem. Soc., Perkin Trans. I*, **1976**, 13, 1458-1463.
6. V. Rukachaisirikul, T. Ritthiwigrom, A. Pinsa, P. Sawangchote and W. C. Taylor, "Xanthenes from the stem bark of *Garcinia nigrolineata*", *Phytochem.*, **2003**, 64, 1149-1156.
7. G. Xu, W. L. T. Kan, Y. Zhou, J.-Z. Song, Q.-B. Han, C.-F. Qiao, C.-H. Cho, J. A. Rudd, G. Lin and H.-X. Xu, "Cytotoxic acylphloroglucinol derivatives from the twigs of *Garcinia cowa*", *J. Nat. Prod.*, **2010**, 73, 104-108.
8. (a) H.-D. Nguyen, B. T.-D. Trinh and L.-H. D. Nguyen, "Guttiferones Q-S, cytotoxic polyisoprenylated benzophenones from the pericarp of *Garcinia cochinchinensis*", *Phytochem. Lett.*, **2011**, 4, 129-133; (b) S.-C. Chien, C.-F. Chyu, I.-S. Chang, H.-L. Chiu and Y.-H. Kuo, "A novel polyprenylated phloroglucinol, garcinialone, from the roots of *Garcinia multiflora*", *Tetrahedron Lett.*, **2008**, 49, 5276-5278; (c) Q.-B. Han, N.-Y. Yang, H.-L. Tian, C.-F. Qiao, J.-Z. Song, D. C. Chang, S.-L. Chen, K. Q. Luo and H.-X. Xu, "Xanthenes with growth inhibition against HeLa cells from *Garcinia xipshuanbannaensis*", *Phytochem.*, **2008**, 69, 2187-2192; (d) L.-H. D. Nguyen, H. T. Vo, H. D. Pham, J. D. Connolly and L. J. Harrison, "Xanthenes from the bark of *Garcinia merguensis*", *Phytochem.*, **2003**, 63, 467-470; (e) L.-H. D. Nguyen and L. J. Harrison, "Xanthenes and triterpenoids from the bark of *Garcinia vilersiana*", *Phytochem.*, **2000**, 53, 111-114.
9. M. Hemshekhar, K. Sunitha, M. S. Santhosh, S. Devaraja, K. Kemparaju, B. S. Vishwanath, S. R. Niranjana and K. S. Girish, "An overview on genus *Garcinia*: Phytochemical and therapeutical aspects", *Phytochem. Rev.*, **2011**, 10, 325-351.
10. Y. Ren, D. D. Lantvit, E. J. Carcache de Blanco, L. B. S. Kardono, S. Riswan, H. Chai, C. E. Cottrell, N. R. Farnsworth, S. M. Swanson, Y. Ding, X.-C. Li, J. P. J. Marais, D. Ferreira and A. D. Kinghorn, "Proteasome-inhibitory and cytotoxic constituents of *Garcinia lateriflora*: Absolute configuration of caged xanthenes", *Tetrahedron*, **2010**, 66, 5311-5320.
11. Y. Sukpondma, V. Rukachaisirikul and S. Phongpaichit, "Xanthone and sesquiterpene derivatives from the fruits of *Garcinia scortechnikii*", *J. Nat. Prod.*, **2005**, 68, 1010-1017.
12. H. W. Ryu, M. J. Curtis-Long, S. Jung, Y. M. Jin, J. K. Cho, Y. B. Ryu, W. S. Lee and K. H. Park, "Xanthenes with neuraminidase inhibitory activity from the seedcases of *Garcinia mangostana*", *Bioorg. Med. Chem.*, **2010**, 18, 6258-6264.
13. I. O. Pereira, M. J. Marques, A. L. R. Pavan, B. S. Codonho, C. L. Barbieri, L. A. Beijo, A. C. Doriguetto, E. C. D'Martin and M. H. dos Santos, "Leishmanicidal activity of benzophenones and extracts from *Garcinia brasiliensis* Mart. fruits", *Phytomed.*, **2010**, 17, 339-345.
14. T. K. Lim, "Edible Medicinal and Non-Medicinal Plants, Vol. 2: Fruits", Springer Science and Business Media B.V., London, **2012**, pp.29-34.

15. W. Mahabusarakam, P. Chairerk and W. C. Taylor, "Xanthonenes from *Garcinia cowa* Roxb. latex", *Phytochem.*, **2005**, 66, 1148-1153.
16. K. Panthong, N. Hutadilok-Towatana and A. Panthong, "Cowaxanthone F, a new tetraoxygenated xanthone, and other anti-inflammatory and antioxidant compounds from *Garcinia cowa*", *Can. J. Chem.*, **2009**, 87, 1636-1640.
17. S. Cheenpracha, W. Phakhodee, T. Ritthiwigrom, U. Prawat and S. Laphookhieo, "A new depsidone from the twigs of *Garcinia cowa*", *Heterocycles*, **2011**, 83, 1139-1144.
18. J. Shen, Z. Tian and J.-s. Yang, "The constituents from the stems of *Garcinia cowa* Roxb. and their cytotoxic activities", *Pharmazie*, **2007**, 62, 549-551.
19. J. Shen and J.-s. Yang, "Chemical constituents from fruit of *Garcinia cowa*", *Zhongguo Yaoxue Zazhi*, **2006**, 41, 660-661.
20. K. Panthong, W. Pongcharoen, S. Phongpaichit and W. C. Taylor, "Tetraoxygenated xanthonenes from the fruits of *Garcinia cowa*", *Phytochem.*, **2006**, 67, 999-1004.
21. P. S. Negi, G. K. Jayaprakasha and B. S. Jena, "Antibacterial activity of the extracts from the fruit rinds of *Garcinia cowa* and *Garcinia pedunculata* against food borne pathogens and spoilage bacteria", *LWT-Food Sci. Technol.*, **2008**, 41, 1857-1861.
22. G. S. Joseph, G. K. Jayaprakasha, A. T. Selvi, B. S. Jena and K. K. Sakariah, "Antiaflatoxic and antioxidant activities of *Garcinia* extracts", *Int. J. Food Microbiol.*, **2005**, 101, 153-160.
23. I. Jantan, F. A. Jumuddin, F. C. Saputri and K. Rahman, "Inhibitory effects of the extracts of *Garcinia* species on human low-density lipoprotein peroxidation and platelet aggregation in relation to their total phenolic contents", *J. Med. Plants Res.*, **2011**, 5, 2699-2709.
24. J. Shen and J. Yang, "Chemical constituents of branch of *Garcinia cowa* Roxb", *Zhongcaoyao*, **2007**, 38, 993-994.
25. G. K. Jayaprakasha, B. S. Jena, L. J. M. Rao and M. C. Varadaraj, "A process for the isolation of cambogin from *Garcinia cowa*", *Indian Pat.*, No. 242799 (**2010**).
26. J. Shen and J.-S. Yang, "A novel benzophenone from *Garcinia cowa*", *Acta Chim. Sinica*, **2007**, 65, 1675-1678.
27. A. Sakunpak and P. Panichayupakaranant, "Antibacterial activity of Thai edible plants against gastrointestinal pathogenic bacteria and isolation of a new broad spectrum antibacterial polyisoprenylated benzophenone, chamuangone", *Food Chem.*, **2012**, 130, 826-831.
28. K. Lihitwitayawuid, T. Phadungcharoen, C. Mahidol and S. Ruchirawat, "7-O-Methylgarcinone from *Garcinia cowa*", *Phytochem.*, **1997**, 45, 1299-1301.
29. K. Lihitwitayawuid, T. Phadungcharoen and J. Krungkrai, "Antimalarial xanthonenes from *Garcinia cowa*", *Planta Med.*, **1998**, 64, 70-72.
30. P. na Pattalung, W. Thongtheeraparp, P. Wiriyachitra and W. C. Taylor, "Xanthonenes of *Garcinia cowa*", *Planta Med.*, **1994**, 60, 365-368.
31. H.-H. Lee and H.-K. Chan, "1,3,6-Trihydroxy-7-methoxy-8-(3,7-dimethyl-2,6-octadienyl) xanthone from *Garcinia cowa*", *Phytochem.*, **1977**, 16, 2038-2040.
32. F. S. Wahyuni, L. T. Byrne, Dachriyanus, R. Dianita, J. Jubahar, N. H. Lajis and M. V. Sargent, "A new ring-reduced tetraprenyltoluquinone and a prenylated xanthone from *Garcinia cowa*", *Aust. J. Chem.*, **2004**, 57, 223-226.
33. J. Shen and J.-S. Yang, "Two new xanthonenes from the stems of *Garcinia cowa*", *Chem. Pharm. Bull.*, **2006**, 54, 126-128.

34. Z. Tian, J. Shen, A. P. Moseman, Q. Yang, J. Yang, P. Xiao, E. Wu and I. S. Kohane, "Dulxanthone A induces cell cycle arrest and apoptosis *via* up-regulation of p53 through mitochondrial pathway in HepG2 cells", *Int. J. Cancer*, **2008**, 122, 31-38.
35. B. S. Jena, G. K. Jayaprakasha and K. K. Sakariah, "Organic acids from leaves, fruits, and rinds of *Garcinia cowa*", *J. Agric. Food Chem.*, **2002**, 50, 3431-3434.
36. V. Rukachaisirikul, W. Naklue, S. Phongpaichit, N. H. Towatana and K. Maneenoon, "Phloroglucinols, depsidones and xanthenes from the twigs of *Garcinia parvifolia*", *Tetrahedron*, **2006**, 62, 8578-8585.
37. L. D. Ha, P. E. Hansen, F. Duus, H. D. Pham and L.-H. D. Nguyen, "Oliveridepsidones A-D, antioxidant depsidones from *Garcinia oliveri*", *Magn. Reson. Chem.*, **2012**, 50, 242-245.
38. A. Mann, K. Ibrahim, A. O. Oyewale, J. O. Amupitan, M. O. Fatope and J. I. Okogun, "Antimycobacterial friedelane-terpenoid from the root bark of *Terminalia avicennioides*", *Amer. J. Chem.*, **2011**, 1, 52-55.
39. M. B. Viswanathan, J. D. J. Ananthi and P. S. Kumar, "Antimicrobial activity of bioactive compounds and leaf extracts in *Jatropha tanjorensis*", *Fitoterapia*, **2012**, 83, 1153-1159.
40. J.-H. Lee, J. Y. Lee, J. H. Park, H. S. Jung, J. S. Kim, S. S. Kang, Y. S. Kim and Y. Han, "Immunoregulatory activity by daucosterol, a β -sitosterol glycoside, induces protective Th1 immune response against disseminated Candidiasis in mice", *Vaccine*, **2007**, 25, 3834-3840.
41. B. M. K. Ahamed, V. Krishna, H. B. Gowdru, H. Rajanaika, H. M. Kumaraswamy, S. Rajshekarappa, C. J. Dandin and K. M. Mahadevan, "Isolation of bactericidal constituents from the stem bark extract of *Grewia tiliaefolia* Vahl", *Res. J. Med. Plant*, **2007**, 1, 72-82.