CHAPTER 1

INTRODUCTION

1.1 Introduction

Thailand is in a tropical area and has sunlight all year round, especially in the southern part. For this reason, the varieties of plants are found including those with medicinal properties. The latter are sources of natural medicines which are neglected for a long time since the modern science occupied the livelihood of Thai people. Recently medicinal plants especially herbs have played important roles in every day life such as *Andrographis paniculata* Wall.ex Nees (**ฟ้าทะลายโจร**) reliefs the symptom of cold, *Curcuma longa* Linn (**ขมิ้นชัน**) protects and heals ulcer, as supplementary health food (*Allium sativum* Linn: **กระเทียม**, *Ganoderma licidum*: **เห็ดหลินจือ**) and ingredients in cosmetics (*Aloe barbadensis* Mill: **ว่านหางจระเข้**).

Medicinal properties of each plant depend on its chemical constituents. Anthraquinones, flavonoids, flavonoid glycosides, tocotrienols, triterpenoids, xanthones and xanthone glycosides have been isolated from *Cratoxylum* genus.

C. cochinchinense is one of a species in *Cratoxylum* genus, which gives xanthones as the major components. The roots have been previously studied in our laboratory. The crude extract of the roots showed interesting antibacterial activity but the active compounds have not been evaluated. Moreover, the chemical constituents of the twigs and fruits have not been studied. Thus the investigation of chemical constituents and the search for bioactive compounds from this plant have been ongoing project in our laboratory.

1.2 Review of Literatures

1.2.1 The Chemical Constituents of *Cratoxylum* genus (2005-2007)

Cratoxylum is in the family of Guttiferae (Clusiaceae) and distributed in several southeast Asian countries. These plants are xerophilous. They are found in Cambodia, China, India, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand and Vietnam (Blume, 1856). According to the information from SciFinder Scholar database, six species have been found in Thailand. They are *C. arborescens* (Vahl) Blume, *C. cochinchinense* (Lour.) Blume, *C. formosum* (Jack) Dyer, *C. formosum ssp. pruniflorum*, *C. maingayi* Dyer and *C. sumatranum* ssp. Neriifolium (Smitinand, T, 2001).

C. arborescens was investigated by Pattanaprateeb in 2005. Xanthones and anthraquinones were isolated from the stem bark. Later Reutrakul isolated xanthones and triterpenoids from leaves and twigs. The roots and stems of *C. cochinchinense* have been reported to contain xanthones (Mahabusarakam, *et al.*, 2006, Laphookhieo, *et al*., 2006 and Phuwapraisirisan, *et al*., 2006). Boonsri separated xanthones from the roots of *C. formosum* (Jack) Dyer whereas anthraquinones and xanthones were reported to be obtained from the bark by Boonnak, *et al*.

The chemical constituents which were isolated from this genus before 2005 were summarized in the thesis of Warraphong Nuangnaowarat (2005). The additional constituents of *Cratoxylum* genus from 2005-2007, according to the information from SciFinder were summarized in **Table 1**.

1.2.2 The Biological Activity of *Cratoxylum* genus (2005-2007)

Cratoxylum genus has been used by the local Thai people as folk medicine such as *C. cochinchinense* (Lour.) Blume has been used to treat fevers, coughs, diarrhoea, itches, ulcers and abdominal complaints (Vo, 1997) and *C. formosum* (Jack) Dyer has been used for the treatment of diarrhoea, internal bleeding and food poisoning (Anderson, 1986).

Many xanthones from *Cratoxylum* genus have been evaluated for their biological activities. Formoxanthone C, macluraxanthone, xanthone V_1 and gerontoxanthone I from *C. formosum* were reported to inhibit the growth of *Bacillus substilis*, *Staphylococus aureus*, *Steptococus faecalis* and *Salmonella typhi* with MIC values of 1.1–4.6 μg/mL. In addition, formoxanthone C and gerontoxanthone I showed strong cytotoxic activity against MCF-7, HeLa, HT-29 and KB cell lines (Boonsri, *et al*., 2006).

The biological activities of compounds from *C. cochinchinense* (Lour.) Blume have been reported such as antioxidant activity (Mahabusarakam, *et al*., 2006), antimalarial activity and cytotoxic activity (Laphookhieo, *et al*., 2006). Cochinchinone B, macluraxanthone and celebixanthone acted as strong antioxidants (Mahabusarakam, *et al*., 2006). Celebixanthone, cochinchinone A, α-mangostin, β-mangostin and cochinchinone C exhibited cytotoxic effect with IC_{50} 0.65-5.2 μg/mL whereas 5-*O*-methylcelebixanthone, celebixanthone, β-mangostin and cochinchinone C showed antimalarial activity with IC_{50} 2.6-7.2 μg/mL (Laphookhieo, *et al*., 2006).

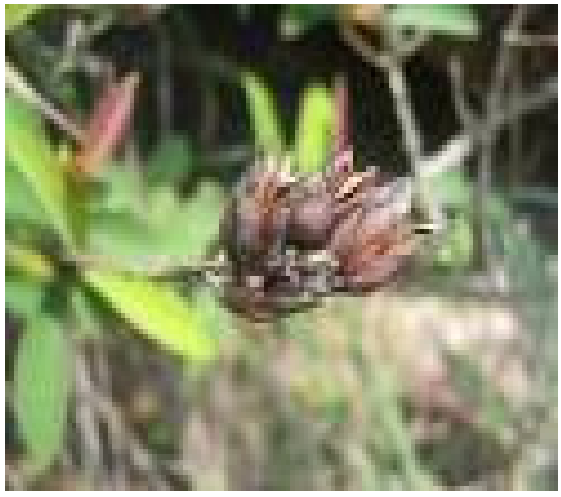


Figure 1 *Cratoxylum cochinchinense*

1.2.3 *Cratoxylum cochinchinense*

C. cochinchinense (Lour.) Blume are shrubs or trees, deciduous, 1.5-18 or 25 m tall, glabrous. Trunk is with tufted long spines on lower part. Bark is gray-yellow or gray-brown, smooth or finely straight. Twigs are somewhat compressed, glabrous and pink when young, interpetiolar scars not always continuous. Petioles are 2-3 mm, glabrous; leaf blades elliptic to oblong or lanceolate, 3-10.5 x 1-4 cm, papery, both surfaces glabrous, abaxially gray-green and with pellucid or dark glands, adaxially green, base obtuse to cuneate, apex abruptly acute or acuminate; midvein abaxially elevated, adaxially impressed; lateral veins 8-12 pairs, oblique, free; veins and veinlets reticulate, elevated on both surfaces. Cymes are axillary or extra-axillary and terminal, 1 or 2 or 3-flowered, pedunculate; peduncles 3-10 mm or longer. Pedicel 2-3 mm. Flowers are 1-1.5 cm in diameter. Sepals are oblong, 5-7 x 2-5 mm, apex rounded, with dark linear glands on entire surface, accrescent. Petals are deep crimson to pink or pinkish yellow, obovate, 5-10 x 2.5-5 mm, with dark linear gland between veins, without a petal-scale, base cuneate, apex rounded. Stamen fascicles are 4-8 mm, stalk broad to slender. Fasciclodes are oblong to obovate, cucculate, to 3 x 1-1.5 mm, apex thickened and recurved. Ovary conical, is *ca*. 3 mm, glabrous; styles linear, ca. 2 mm, divaricate from base. Cupsule is brown, ellipsoid, 0.8-1.2 cm x 4-5 mm, glabrous, to 2/3 covered by persistent calyx. Seed 5 or 6-8 in each cell, obovoid, 6-8 x 2-3 mm (Blume, 1856).

For the preliminary investigation, the crude extracts of *C. cochinchinense* (Lour.) Blume were tested against the growth of *Staphylococus aurues* ATCC25923, and methicillin-resistant strain MRSA SK1. It was found that these extracts showed interesting activity. Thus our aim is to investigate the chemical constituents and search for bioactive compounds from these extracts.

Table1 Compounds isolated from the *Cratoxylum* genus (2005-2007)

Scientific name (Investigated part)	Compounds	structures	Bibliography
C. arborescens			
(leaves and twig)	Astilbin	**1**	Reutrakul, *et al*.,
	Butulinic acid	**15**	2006
	1,7-Dihydroxy-2,8-dimethoxyxanthone	**26**	
	3,4-Dihydroxybenzoic acid	**59**	
	Eucryphin	**60**	
	Euxanthone	**18**	
	Friedelin	**13**	
	Friedelinol	**14**	
	3β-Hydroxylup-20(29)-en-30-oic acid	**17**	
	Isoastilbin	**2**	
	Lup-20(29)-ene-3β, 30-diol	**16**	
	Methoxyemodin	**8**	
	1,3,7-Trihydroxy-6-methoxy-4,5-diisoprenylxanthone	**27**	
	1,3,8-Trihydroxy-2,4-dimethoxyxanthone	**58**	
(Stem bark)	1,3-Dihydroxy-6,7-dimethoxy-2,8-diprenylxanthone	**43**	Pattanaprateeb, *et al.*, 2005
	1,7-Dihydroxyxanthone	**18**	
	Fuscaxanthone C	**30**	
	2-Geranylemodin	**9**	
	3- Geranyloxy-6-methyl-1,8-dihydroxyanthraquinone	**3**	

Table1 (continued)

Scientific name (Investigated part)	Compounds	structures	Bibliography
C. cochinchinense			
(Stem)	Cratoxylumxanthone A	**42**	Phuwapraisirisan,
	Dulcisxanthone B	**57**	*et al*., 2006
	2-Geranyl-1,3,7-trihydroxy-4-(3-methylbut-2-enyl)xanthone	**19**	
	α-Mangostin	**44**	
	β-Mangostin	**28**	
(Root)	Celebixanthone	**34**	Mahabusarakam,
	Cochinchinone A	**21**	*et al*., 2006
	Cochinchinone B	**36**	
	Cochinchinone C	**11**	
	Cochinchinone D	**12**	
	Garcinone B	**33**	
	Garcinone D	**31**	
	Mangostin	**29**	
	β-Mangostin	**28**	
	Macluraxanthone	**32**	
	1,3,7-Trihydroxy-2,4-bis (3-methyl-2-butenyl)xanthone	**20**	
	Celebixanthone	**34**	Laphookhieo, *et*
	Cochinchinone A	**21**	*al*., 2006
	Cochinchinone C	**11**	
	α- Mangostin	**44**	
	β-Mangostin	**28**	
	5-*O*-Methylcelebixanthone	**35**	

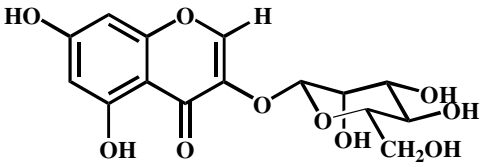
Table1 (continued)

Scientific name (Investigated part)	Compounds	structures	Bibliography
C. formosum			
(Root)	Formoxanthone A	**22**	Boonsri, *et al*.,
	Formoxanthone B	**23**	2006
	Formoxanthone C	**37**	
	Gerontoxanthone I	**39**	
	Macluraxanthone	**32**	
	Xanthone V_1	**38**	
C. formosun pruniflorum			
(Bark)	6-Deoxyjacareubin	**24**	Boonnak, *et al*.,
	3,4-Dihydrojacareubin	**41**	2006
	Emodin	**7**	
	Formoxanthone B	**23**	
	3-Geranyloxy-6-methyl-1,8-dihydroxyanthraquinone	**3**	
	Gerontoxanthone I	**39**	
	11-Hydroxy-5-methoxy-2,2,9-trimethyl-2*H*-anthra-[1,2-b]pyran-7,12-dione	**6**	
	Macluraxanthone	**32**	
	Madagascin	**4**	
	Physcion	**8**	
	Pruniflorone J	**5**	
	Vismiaquinone A	**10**	
	Xanthone V_1	**38**	

Table1 (continued)

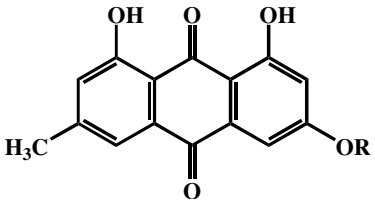
Scientific name (Investigated part)	Compounds	structures	Bibliography
(Root)	3,4-Dihydro-5,9-dihydroxy-7-(3-hydroxy-3-methylbutyl)-8-methoxy-2,2-dimethyl-2*H*,6*H*-pyrano-[3,2-b]xanthen-6-one	**45**	Boonnak, *et al*., 2006
	3,4-Dihydro-5,9-dihydroxy-8-methoxy-7-(3-methoxy-3-methylbutyl)-2,2-dimethyl-2*H*,6*H*-pyrano-[3,2-b]xanthen-6-one	**46**	
	Dulxisxanthone F	**42**	
	Formoxanthone A	**22**	
	Isocudraniaxanthone B	**40**	
	3-Isomangostin	**47**	
	α- Mangostin	**44**	
	β- Mangostin	**28**	
	10-*O*-Methylmacluraxanthone	**48**	
	Pruniflorone A	**49**	
	Pruniflorone B	**50**	
	Pruniflorone C	**51**	
	Pruniflorone D	**52**	
	Pruniflorone E	**53**	
	Pruniflorone F	**56**	
	Pruniflorone G	**54**	
	Pruniflorone H	**55**	
	Pruniflorone I	**25**	
	Pruniflorone J	**7**	

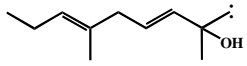
Flavonoids

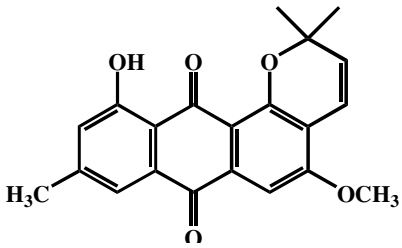


1 : 2R, 3R : Astilbin
2 : 2R, 3S : Isoastilbin

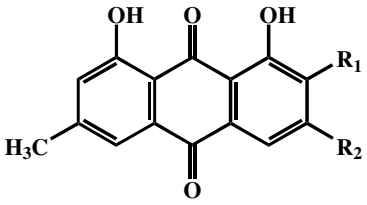
Anthraquinones



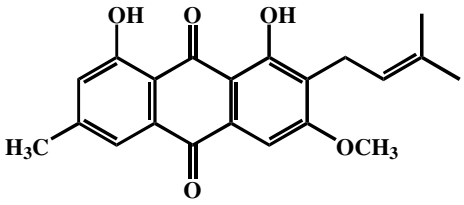
3 : R = geranyl :3-Geranyloxy-6-methyl-1,8-dihydroxyanthraquinone
4 : R = prenyl : Madagascin
5 : R =  Pruniflorone J



6 : 11-Hydroxy-5-methoxy-2,2,9-trimethyl-2*H*-anthra-[1,2-*b*] pyran-7,12-dione

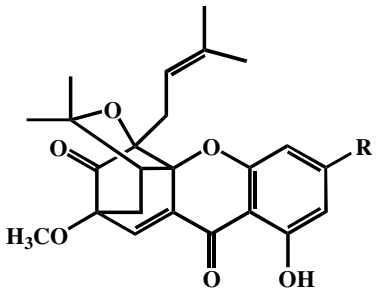


7 : R_1 = H, R_2 = OH : Emodin
8 : R_1 = H, R_2 = OCH_3 : Physcion or Methoxyemodin
9 : R_1 = geranyl, R_2 = OH : 2-Geranylemedin



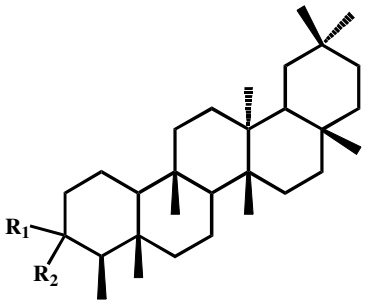
10 : Vismiaquinone A

Caged-xanthones

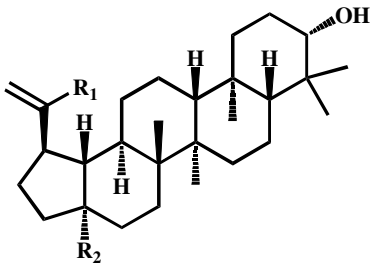


11 : R = H : Cochinchinone C
12 : R = OH : Cochinchinone D

Triterpenoids



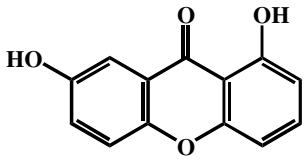
13 : R_1,R_2 = O : Friedelin
14 : R_1 = β-OH, R_2 = H : Friedelinol



15 : R_1 = CH_3, R_2 = COOH : Betulinic acid
16 : R_1 = CH_2OH, R_2 = CH_3 : Lup-20(29)-ene-3β, 30-diol
17 : R_1 = COOH, R_2 = CH_3

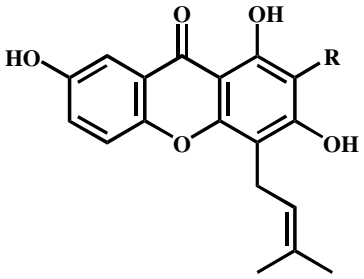
Xanthones

Dioxyxanthones



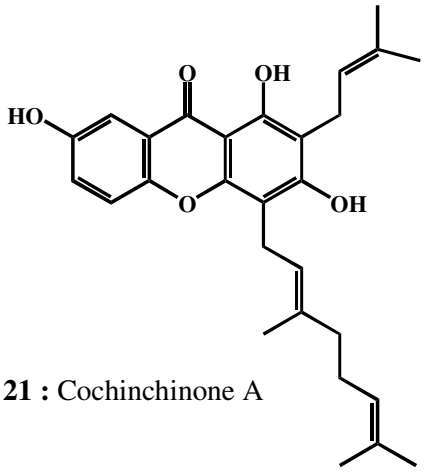
18 : 1,7-Dihydroxyxanthone (Euxanthone)

Trioxyxanthone

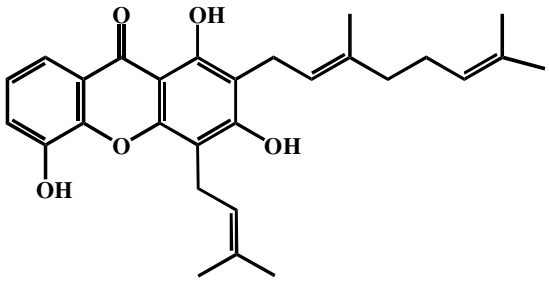


19 : R = geranyl : 2-Geranyl-1,3,7-trihydroxy-4-(3-methylbut-2-enyl)xanthone

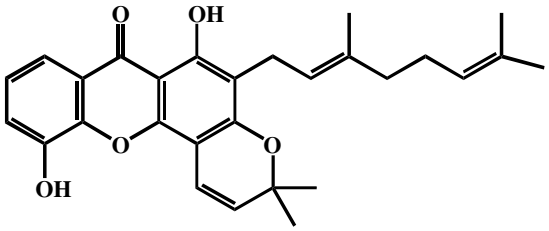
20 : R = prenyl : 1,3,7-Trihydroxy-2,4-di(3-methylbut-2-enyl)xanthone



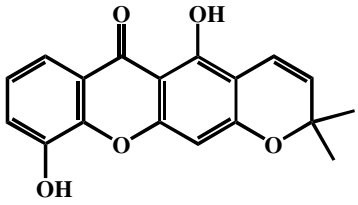
21 : Cochinchinone A



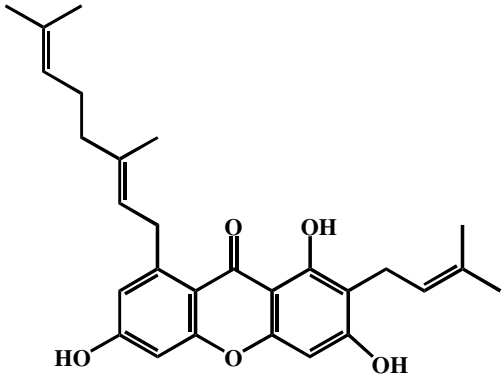
22 : Formoxanthone A



23 : Formoxanthone B

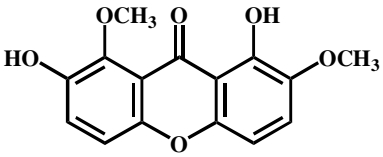


24 : 6-Deoxyjacareubin

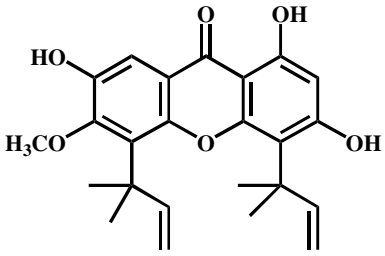


25 : Prunifiorone I

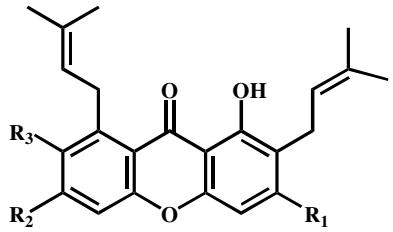
Tetraoxyxanthone



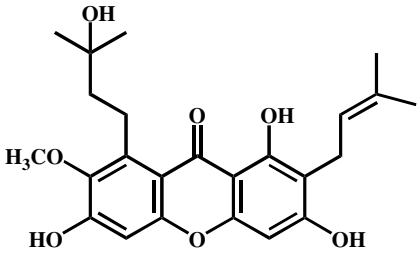
26 : 1,7-Dihydroxy-2,8-dimethoxyxanthone



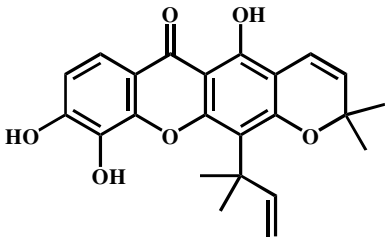
27 : 1,3,7-Trihydroxy-6-methoxy-4,5diisoprenylxanthone



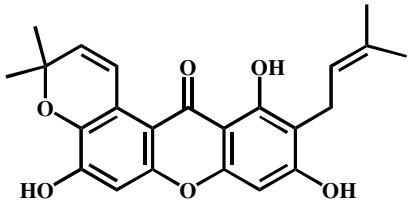
28 : $R_1 = OCH_3$, $R_2 = OH$, $R_3 = OCH_3$: β-Mangostin
29 : $R_1 = OH$, $R_2 = OH$, $R_3 = OCH_3$: Mangostin
30 : R_1, R_3, $R_4 = OCH_3$: Fuscaxanthone C



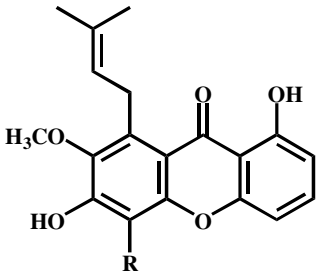
31 : Garcinone D



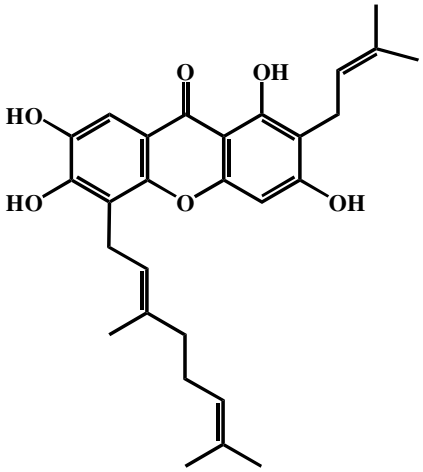
32 : Macluraxanthone



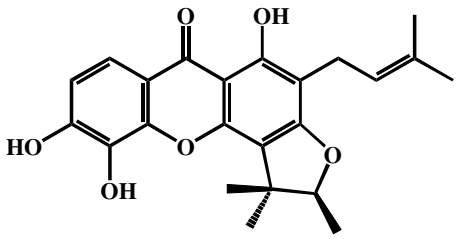
33 : Garcinone B



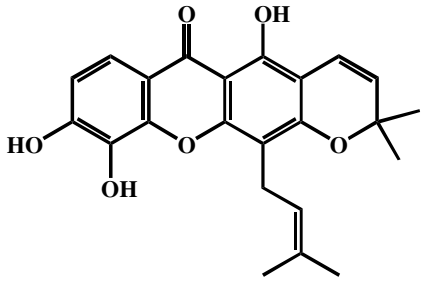
34 : R = OH : Celebixanthone
35 : R = OCH_3 : 5-*O*-Methylcelebixanthone



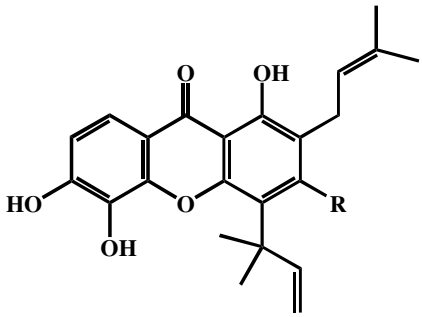
36 : Cochinchinone B



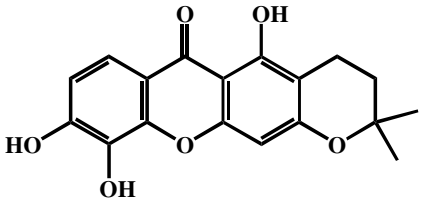
37 : Formoxanthone C



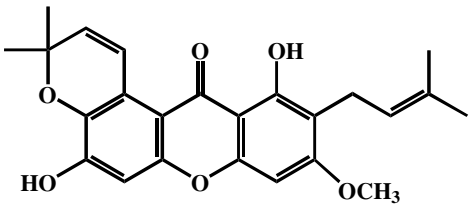
38 : Xanthone V_1



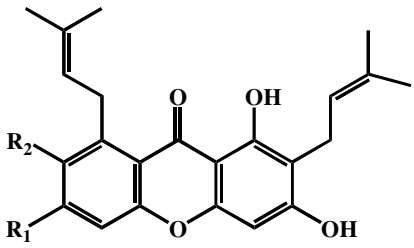
39 : R = OH : Gerontoxanthone I
40 : R = OCH_3 : Isocudraniaxanthone B



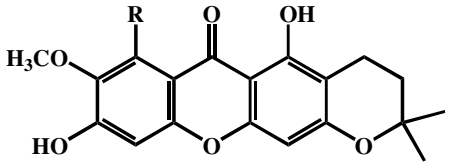
41 : 3,4-Dihydrojacareubin



42 : Dulxisxanthone F,
or Cratoxylumxanthone A



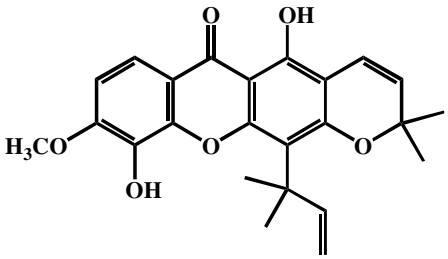
43 : R_1, R_2 = OCH_3 : 1,3-Dihydroxy-
6,7-dimethoxy-2,8- diprenylxanthone
44 : R_1, R_2 = OH: α-Mangostin



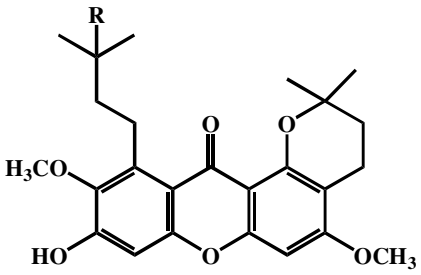
45 : R = 3-hydroxy-3-methylbutyl : 3,4-Dihydro-5,9-dihydroxy-7- (3-hydroxy-3-methylbutyl) -8-methoxy-2,2-dimethyl-2*H*,6*H*-pyrano-[3,2-*b*]xanthone-6-one

46 : R = 3-methoxy-3-methylbutyl : 3,4-Dihydro-5,9-dihydroxy-8-methoxy-7-(3-methoxy-3-methylbutyl)-2,2-dimethyl-2*H*,6*H*-pyrano-[3,2-*b*]xanthone-6-one

47 : R = prenyl : Isomangostin

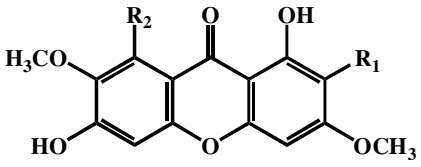


48 : 10-*O*-Methylmacluraxanthone



49 : R = OH : PruniforoneA

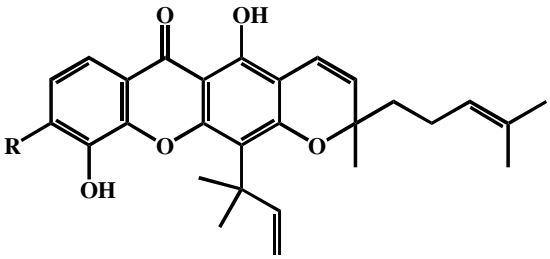
50 : R = OCH_3 : Pruniflorone B



51 : R_1 = prenyl, R_2 = 3-hydroxy-3-methylbutyl : PruniforoneC

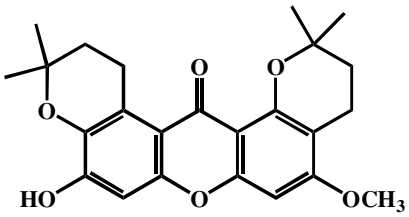
52 : R_1 = prenyl, R_2 = 3-methoxy-3-methylbutyl : Pruniflorone D

53 : R_1 = 3-hydroxy-3-methylbutyl, R_2 = prenyl : Pruniflorone E

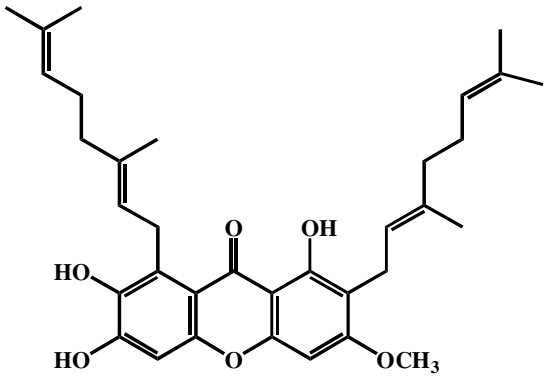


54 : R = OH : PruniforoneG

55 : R = OCH_3 : Pruniflorone H

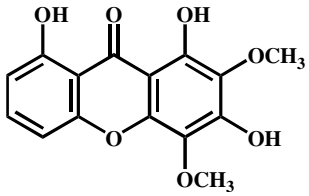


56 : Pruniflorone F



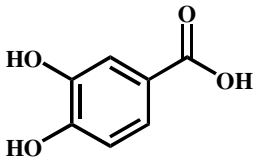
57 : Dulcisxanthone B

Pentaoxyxanthone

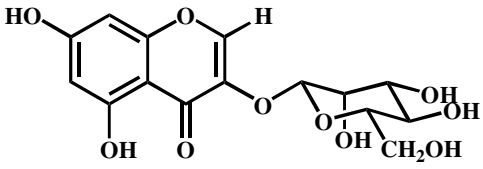


58 : 1,3,8-Trihydroxy-2,4-dimethoxyxanthone

Miscellaneous



59 : 3,4-Dihydroxybenzoic acid



60 : Eucryphin

1.3 Objective

The objectives of this work were to investigate the chemical constituents from the twigs, fruits and minor fractions from the earlier study of the roots of *C. cochinchinense*.