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Review Article

A Review on the Cytotoxic and Antimicrobial Properties of Xanthones from *Cratoxylum cochinchinense*

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ABSTRACT

Cratoxylum cochinchinense is a perennial plant found in Southeast Asia, having diverse terminologies in various Southeast Asian countries. It has been traditionally used as medicine, tea and food spice until today. Its phytochemical analysis reveals a rich array of bioactive compounds in different parts of the plant, specifically xanthones, which are scientifically determined to be the most abundant secondary metabolites in *C. cochinchinense*. Xanthones do possess numerous beneficial properties and are actively researched to unlock its vast potential. It could be synthesized both biologically and synthetically, where the latter method is gaining much interest among researchers to improve its biological properties. Due to limited compiled resources on the biological benefits of xanthones from *C. cochinchinense*, this paper aims to review their cytotoxic properties specifically towards cancer cells, as well as their antimalarial and antibacterial effects in order to further support the medicinal use of this plant.

Keywords: Antimalarial, Antimicrobial, Antioxidant, Asian plant, Cratoxylum cochinchinense, Cytotoxicity

Introduction

Cratoxylum cochinchinense (Lour.) Blume is a polyphenol-rich plant found in Southeast Asia, and it is categorized under the Hypericaceae family [1-3]. It is an evergreen, perennial tree that can grow up to 33 meters in height [2]. The tree is widely distributed in Indochina, China, Thailand, Sulawesi, Sumatra, Malaysia, Borneo and the Philippines [2, 3]. The common name in English for *C. cochinchinense* is Yellow Cow Wood or Tree-Avens. In Malaysia it is known as Derum Selunchor, Kemutong, Kayu Arang, Gerrongang, Serungan among many [4] while in Thailand, it is called Tiu Kliang or Tu Bai Lueam or Tuegliang [5]. Vietnamese named this plant Thành Ngạnh Nam while Indonesians called them Kayu Lulus, Lelulus or Mara Jalang [6].

The *C. cochinchinense*, as shown in Figure 1 is commonly found in both primary and secondary forest. It flourishes in lowland, hills, freshwater swamp forests, and riverbanks, up to 500 m in altitude [1, 7]. The bark (Figure 1) is flaky and

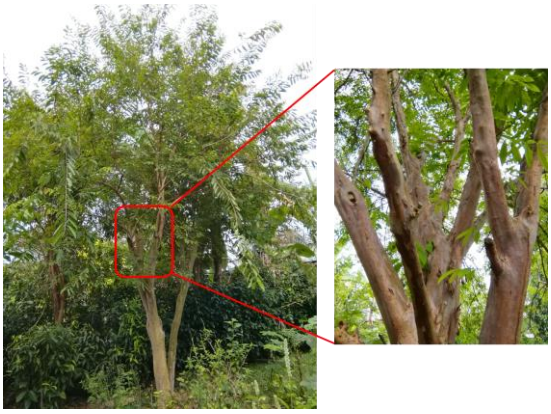

Figure 1. The tree of *C. cochinchinense* with an enlarged view of its bark.

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Figure 2. *C. cochinchinense* leaves and flowers.

smooth, ranging in color from light buff to pale brownish-yellow, and peels off in angular chunks or long strips [2, 4, 7].

Its opposing, stalked leaves (Figure 2) with a curve have fleshy to papery leaf blades that are 3–13 by 1–4.4 cm, with minute gland-dots, curved lateral veins, which unite but do not form intramarginal veins, and are oval to oblong to lance-shaped [7]. The young twigs are flattened and the leaves are simple with lateral vein and elliptical or sometimes slightly obovate [3]. Its mature leaf blades are green on top and grey-green on the undersides, with a pronounced bloom. Its leaf blades are also deep purple when young, turning pinkish-brown as they mature [2, 7].

The *C. cochinchinense* has 1.3–2.5 cm broad flowers with deep scarlet to pink to pinkish-orange petals that are faintly aromatic (Figure 2). The flowers of *C. cochinchinense* species are known by their 1–5 flowered cymules, terminal inflorescences, and flowers with recurved or cucullate staminodial scales. They are frequently seen in pairs on flowering shoots that are 5 - 15 cm long and appear at the angles of leaves or branch terminals. The fruits are capsular and ellipsoid in shape [3]. A study by Nguyen et al. [8] provides an in-depth ethnobotany description of *C. cochinchinense*, matching an earlier report by Mahabusarakam et al. [9].

This plant has been used as traditional medicines to treat several diseases such as fevers, diarrhea, ulcer, itches, coughs, edema and abdominal pain [10]. Additionally, the tender leaves are used to make tea products whereas the young fruit is used as food spice [11]. In Vietnam, the bark, roots, and leaves of *C. cochinchinense* are used for treatments of fevers, coughs, scabies, stomach aches, and eczema, whereas the twigs for scabies and burns [11]. In Thailand, in addition to treating ulcers, diarrhea, and itches, the plant is also used as diuretics [5, 9]. Consequently, it is used as a detoxification medicine in China to treat fever, diarrhea, jaundice, bruises, carbuncles, common cold, edema, hoarseness and cancer [12, 13]. In Indonesia, the essence of roots, bark, and twigs of *C. cochinchinense* is traditionally used for diarrhea and as cold medicine [14]. Previous old reports by Burkill and Wray [15, 16] respectively documented the incorporation of the plant's wood tar of stem for teeth blackening as part of the culture in Southeast Asia. The extract of the roots is also used as a post-labor tonic, and its wood is utilized for building, cabinets, furniture, and interior fittings [2, 7].

C. cochinchinense is rich in chemical constituents such as xanthones, flavonoids, tocotrienols, triterpenoids and benzophenones, anthraquinones [14, 17-23]. It has been reported that xanthones are in fact the most abundant biologically active secondary metabolites in *C. cochinchinense* [14].

These bioactive compounds have demonstrated advantageous biological properties such as antimalarial, antibacterial, anti-HIV, antioxidant and cytotoxic activities [5, 18, 24, 25]. Vitamin E derivatives such as γ-tocotrienol, δ-tocotrienol and α-tocopherol, used as active ingredients in cosmetics, have also been isolated from the leaves and fruits of *C. cochinchinense*, suggesting the potential of the plant extract in the cosmetic industry [26]. While studies showed that the xanthones in *C. cochinchinense* exerted numerous beneficial properties, the compilations of information, especially on their antimalarial, antibacterial and cytotoxicity activities are still lacking. Thus, this review aims to discuss these bioactivities conferred specifically by xanthones from *C. cochinchinense*.

General structure and properties of xanthones

Xanthones are an essential group of organic compounds that are detected and isolated from several plants including Garcinia [27, 28], Hypericum [29], Callophylum [30], Cratoxylum [11], lichens [31] and other plant families [32]. Xanthones were originally isolated by a German scientist in 1855, who was conducting studies on dysentery and the compounds were named using a Greek word for yellow, Xanthos [31]. Structurally, xanthones (9H – xanthen-9-ones) are heterocyclic compounds with dibenzo-γ-pyrone scaffold (Figure 3).

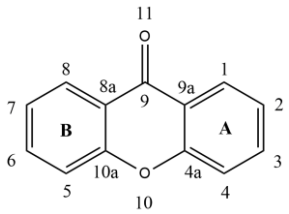

Figure 3. Structure of xanthone (9H-xanthen-9-one) [33].

There are several forms of xanthones including simple oxygenated xanthones, prenylated xanthones, xanthone glycosides, xanthonolignoids and miscellaneous xanthones, reviewed in [32]. The simple oxygenated xanthones are further subcategorised into six groups corresponding to the degree of oxygenation and can also exist as tri-oxygenated and tetra-oxygenated xanthones [32].

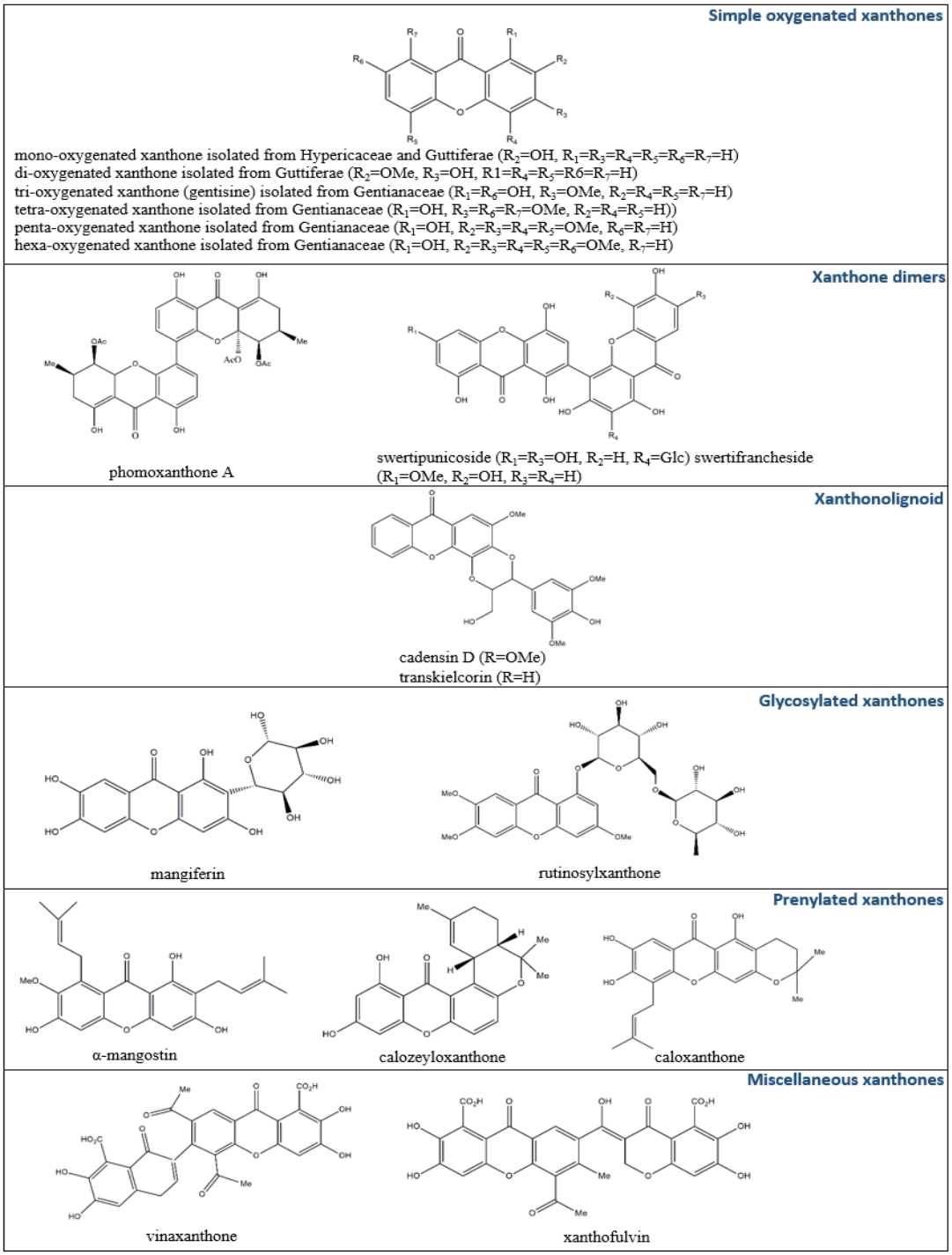

Figure 4. Classification (with examples) of xanthone derivatives [35].

Subsequently, glycosylated xanthone is separated into two subgroups: O-glycosides and C-glycosides. The glycosidic bond is established between the anomeric carbon atom of the sugar ring and the oxygen atom of the hydroxyl group found in the xanthone skeleton in O-glycosides. The C-C link connects xanthone to the glycosyl molecule in C-glycosides [34]. Figure 4 presents the most common examples of xanthone derivative for each subgroup, as compiled by Kurniawan et al. [35].

Biosynthesis of xanthones

Xanthones are polyketide derivatives generated via regioselective cyclization of benzophenone derivatives and found in numerous fungi, lichens, and higher plants [36]. In higher plants, xanthones are produced via the acetate and shikimate pathways [37]. Guttiferae, Gentianaceae, and Hypericaceae are the most prevalent xanthone families [36], in which the former is primarily composed of prenylated xanthones, whereas the latter two families are composed of oxygenated xanthone derivatives [38]. Xanthone biosynthesis, however, varies between taxa and has only been widely researched in a few mangiferin-producing plant genera, namely Hypericum, Garcinia, and Gentiana [39].

Figure 5 shows a typical pathway for plant biosynthesis as described by Masters and Bräse [31]. In this example, obtained from *Gentiana lutea* xanthone synthesis experiments [40], 3-hydroxybenzoic acid (13) in Figure 5, generated from phenylalanine, is paired with three acetate equivalents to polyketide, (14). Aromatization of

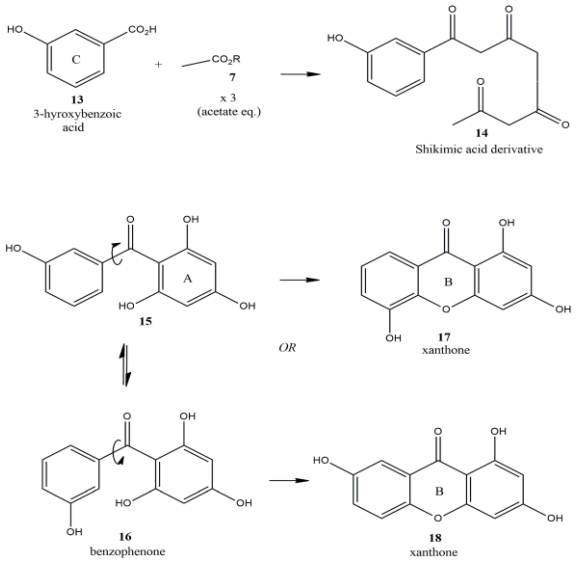

Figure 5. Xanthone biosynthesis in plants [31].

the side chain yields a freely rotating benzophenone intermediate, (15/16), which undergoes divergent oxidative phenolic coupling to yield two distinct products, 1,3,7-trihydroxyxanthone (17) and 1,3,5-trihydroxyxanthone (18). This cyclisation is catalyzed in at least some plant species, by xanthone synthase, a membrane-bound enzyme linked with cytochrome P450, a process that requires oxygen and NADPH [41]. Other schematic representations of xanthone biosynthesis pathways of different higher plants were also described in [36].

Synthetic synthesis of xanthones

The paper published by Fernandes et al. [42] provides an excellent review on the synthetic studies of xanthones, in which it is suggested that synthetic techniques are gaining interests among researchers since the xanthone biosynthetic route only allows the presence of certain groups in specified places of the xanthone scaffold, limiting structural variation. Hence, for structure activity relationship (SAR) research, synthetic techniques can provide structures that would not be possible with natural compounds and this modification may increase their biological properties [42]. Ongoing development to synthesize xanthone derivatives was shown to be successful. Resende et al. [43] summarized the four different synthetic techniques of xanthone which were developed and optimized including the condensation of salicylic acid with a) a phenol derivative b) an aryl aldehyde with a phenol derivative c) a o-haloarenecarboxylic acid with arynes and d) a salicylaldehyde with 1,2-dihaloarenes. These approaches of synthesizing xanthones rely on a one-step methodology from easily available building blocks, and they are still popular due to their simplicity and ability to use a variety of substitution patterns [43].

Xanthones present in C. cochinchinense

Previous investigations as tabulated in Table 1 showed that various phytochemicals were extracted from the branches and twigs, stem barks, fruits and the roots of *C. cochinchinense*.

Antimalarial activities of xanthones present in C. cochinchinense

Malaria is a fatal disease caused by the parasite, *Plasmodium falciparum*. It may lead to anemia and yellow colourisation of the skin and eyes

(jaundice) due to the loss of erythrocytes. The infections may develop to severe malaria, resulting in impaired consciousness, kidney dysfunction, shock, coma and death if not promptly treated [49]. Therefore, growth inhibition of this parasite by xanthones of *C. cochinchinense* provides a therapeutic avenue to treat malaria.

From the roots of *C. cochinchinense*, Laphookhieo *et al.* [5] extracted a new prenylated xanthone, 5-O-methylcelebixanthone, along with other known compounds: celebixanthone, cochinchinone C and beta-mangostin. The antimalarial activity of 5-O-methylcelebixanthone, celebixanthone, cochinchinone C and beta-mangostin showed strong antimicrobial activity against *P. falciparum* with IC_{50} values of 3.2 µg/ml, 4.9 µg/ml, 2.6 µg/ml, and 7.2 µg/ml, respectively. The methoxyl group bonded at C-3 of beta-mangostin was found to contribute to the high antimalarial activity against *P. falciparum* [5]. The microculture radioisotope approach, as mentioned by Desjardins et al. [49], was used to quantitatively evaluate the *in vitro* antimalarial activity.

Table 1. Xanthones found in *C. cochinchinense.*

References	Parts of plant	Type of xanthones extracted
Laphookhieo et al. [5] Mahabusarakam et al. [9]	root	• cochinchinone A • cochinchinone C • α-mangostin • β-mangostin • 5-O methylcelebixanthone • macluraxanthone • celebixanthone • garcinone B
Mahabusarakam et al. [24]	root	• cochinchinone E • cochinchinone F • isocudraniaxanthone B • cudratricusxanthone E • norathyriol • 1,3,7-trihydroxy-2,4-di(3-methylbut-2-enyl) xanthone
Laphookhieo et al. [19] Chailap et al. [26]	fruits, leaves	• 7-geranyloxy-1,3 dihydroxyxanthone • cochinchinone G • fuscaxanthone E • vismione B • vismione F • vismione E
Udomchotphruet et al. [23] Rattanaburi et al. [46]	stem	• prenylated xanthone isocudraniaxanthone B • vismiaquinone • cochinchinoxanthone • cudratricusxanthone E • cochinchinone A • cochinchinone C • cochinchinone G • 7-geranyloxy-1,3-dihydroxy xanthone • celebixanthone
Thu et al. [44]	bark	• macluraxanthone • pruniflorone N • pruniflorone M • 6-deoxyisojacareubin • xanthone V1

continue

Raksat et al. [45]	stem bark	• cochinchinone M • cochinchinone A • 1,3,7- trihydroxy-2,4-diisoprenylxanthone • pruniflorone Q • pruniflorone R • garcinone C • garcinone B • cratoxylone • 3-O-methylmangostenone D • α-mangostin • β-mangostin • 5,9-dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methyl-but-2-enyl)-2H,6H-pyrano[3,2-b] xanthen-6-one • 11-hydroxy-3-O-methyl-1-isomangostin
Boonnak et al. [47]	green fruits, resin	• cochinchinone L • cochinchinone A • 1,3,7-trihydroxy-2,4-diisoprenylxanthone • celebixanthone methyl ether • dulxisxanthone F • α-mangostin • β-mangostin • macluraxanthone
Ito et al. [48]	branches, twigs	• cratoxanthone A to D • α-mangostin • β-mangostin, • cochinchinone A • allanxanthone C • garcinone E • mangostenol

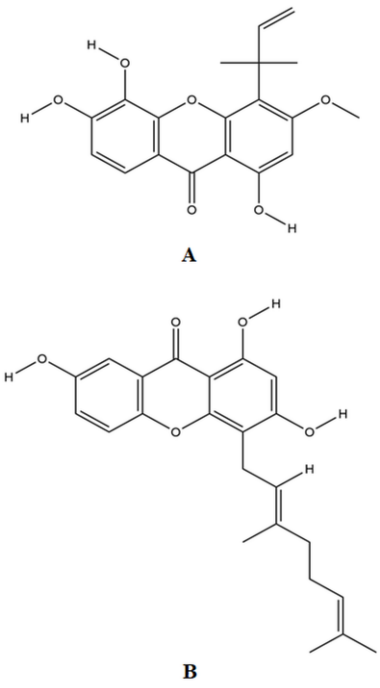

Figure 6. The chemical structures of Isocudraniaxanthone B (A) and Fuscaxanthone E (B).

The IC_{50} was described as the concentration that led to 50% depletion in parasitic development, as determined by *Plasmodium falciparum* uptake of [3H]-hypoxanthine *in vitro*. Dihydroartemisinin was the standard chemical (IC_{50}: 4.5 nM) in this assay [49].

Isocudraniaxanthone B (Figure 6A), a phytoconstituent present in the roots of *C. cochinchinense*, had also been tested for its antimalarial activity against chloroquino-resistant *P. falciparum* strains [24]. However, the compound reported was isolated from another plant, *Garcinia vieillardii*. Nevertheless, it showed strong inhibition activity towards *P. falciparum* exhibiting an IC_{50} value of 3.2 µg/ml [50].

Phytochemicals extracted from *C. cochinchinense* fruits were categorised into two groups: vismione derivatives and 1,3,7-oxygenated xanthones. Fuscaxanthone E which is a 1,3,7-oxygenated xanthone (Figure 6B), and the vismione derivatives; vismione B, vismione F, and vismione E, all showed considerable inhibitory actions against *P. falciparum* with IC_{50} values of

3.02, 0.66, 2.02, and 3.91 µg/ml, respectively [19]. With an IC_{50} of 0.66 µg/ml, vismione B possessed the strongest inhibitory activity against *P. falciparum* while vismione E was the weakest. The antimalarial drug dihydroartemisinin was employed as a control (IC_{50}: 4.0 nM). The sole structural variation between vismione B and vismione E is located at position C-1/C-2. Vismione B has a chromene ring, whereas vismione E has hydroxyl and isoprenyl groups. The antimalarial action of this chromene ring structure appeared to be of importance to this activity [19]. With the recent emergence of malarial parasite resistant against common prescribed drugs, monotherapy will no longer able to achieve maximum cure rate. Thus, a combination therapy of antimalarial drugs with active phytocompounds such as xanthones is indeed a therapeutic strategy to optimize the antimalarial effects of these drugs [50].

Antibacterial activity of xanthones from C. cochinchinense

Alpha-mangostin is one of the xanthones identified from the roots of *C. cochinchinense* [5]. In a study by Sakagami et al. [51], alpha-mangostin was discovered to possess antimicrobial activities against vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA), with MIC values of 3.13 to 6.25 µg/ml and 6.25 to 12.5 µg/ml, respectively. The MIC value is the lowest concentration of an antibiotic at which there is complete inhibition of bacterial growth. Interestingly, alpha-mangostin and gentamicin exhibited a synergistic effect against vancomycin-resistant *Enterococci*, while, alpha-mangostin and vancomycin hydrochloride showed synergy against MRSA. Further research revealed that alpha-mangostin when used along with other common antibiotics such as ampicillin and minocycline also demonstrated synergism. In view of this, antibiotics can be used in combination with xanthones to treat infections by antibiotic-resistant microbes, a current threat in nosocomial infections [51].

Beta-mangostin (β-mangostin) is a prenylated xanthone also found in *C. cochinchinense* [5]. This compound demonstrated effective antimicrobial effect towards *Mycobacterium tuberculosis* using the Microplate Alamar Blue Assay (MABA) as compared to other xanthones evaluated; γ-mangostin, garcinone D, mangostenol, tovophylin B, trapezifolixanthone, mangostanol, mangostenone A, mangostenon B, mangostinone, mangostanin demethylcalabaxanthone, trapezifolixanthone, and 1,7-dihydroxy2-(3-methylbut-2-enyl)-3-methoxyxanthone. It exhibited a low MIC value of 6.25 µg/ml indicating its potential as an antituberculosis agent. β-mangostin is a 1,3,6,7-tetraoxygenated xanthone that carries the di-C_5 units at C-2 and C-8 positions. The modifications of the C_5 units at either C-2 or C-8 positions had been reported to alter or lower the inhibitory effects of the compound [52, 53].

Cudratricusxanthone E (Figure 7A) is another chemical constituent often isolated from the roots of *C. cochinchinense*. This molecule was discovered to inhibit the growth of *Staphylococcus aureus* ATCC25923 and methicillin-resistant *Staphylococcus aureus* SK1 [24]. Cudratricusxanthone E showed MIC value of 128 µg/ml for *S. aureus* ATCC25923 and > 128 µg/ml for MRSA SK1 using the broth microdilution technique [24].

The antimicrobial activity of 1,3,7-trihydroxy-2,4-diisoprenylxanthone was tested against both Gram-positive (*Enterococcus faecalis* TISTR 459, *Staphylococcus aureus*, *Bacillus subtilis*, methicillin resistant *S. aureus* (MRSA) ATCC 43300, vancomycin-resistant *E.*

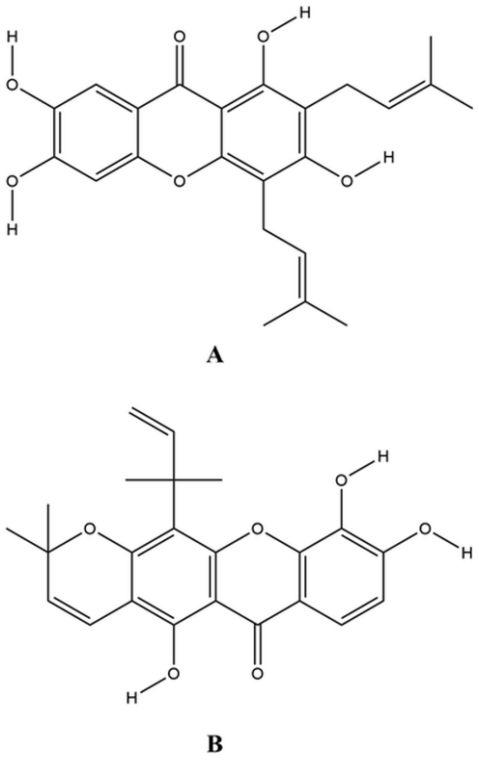

Figure 7. The chemical structures of Cudratricusxanthone E (A) and Macluraxanthone (B).

faecalis (VRE) ATCC 51299) and Gram-negative (*Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Shigella sonei*) bacteria. This xanthone demonstrated moderate inhibitory effect against all Gram-positive bacteria with MIC values ranging from 37.5-150 µg/ml whereas it displayed weak inhibitory action towards *S. typhimurium* and *S. sonei* with MIC values of >150µg/ml [47]. Nevertheless, it was an effective antibacterial agent against *P. aeruginosa* with MIC value of 4.7 µg/ml. The geranyl side chain at C-2 and C-4 of the 1,3,7-trihydroxy-2,4-diisoprenylxanthone was postulated to be the contributor for its strong activity against *P. aeruginosa* [47].

Macluraxanthone (Figure 7B) was also isolated from *C. cochinchinense* [44]. It showed significant antibacterial activity against *B. subtilis* TISTR 088 and *Bacillus cereus* TISTR 688 with MIC values ranging from 1 to 8 µg/ml. However, its inhibitory action towards Gram-negative bacteria such as *Escherichia coli* TISTR 780 and *S. typhimurium* TISTR 292 was slightly weaker (MIC value: 128 µg/ml) [54].

It was discovered that cochinchinone L could be extracted from the resin and green fruits of *C. cochinchinense* [47]. This xanthone was tested for its antibacterial properties against Gram-positive (*E. faecalis* TISTR 459, VRE ATCC 51299, MRSA ATCC 43300, *B. subtilis* and *S. aureus*) and Gram-negative (*P. aeruginosa, S. typhimurium*, *S. sonei*) bacteria [47]. The findings revealed that cochinchinone L generally possessed strong antibacterial activity. Its strongest antimicrobial activity was primarily towards *P. aeruginosa* with a MIC value of 4.7 µg/ml followed by MRSA with a MIC value of 37.5 µg/ml due to the presence of geranyl side chain at C-3 or C-7. Hence, cochinchinone L was considered as a potent anti-*P. aeruginosa* agent [47]. Nevertheless, it showed weak inhibition towards *S. aureus*, *S. typhimurium* and *S. sonei* with MIC values of >150µg/ml. Aside from that, its activity against *B. subtilis*, *E. faecalis* and VRE ATCC 51299 was at a moderate level reporting a MIC value of 150 µg/ml for all three bacteria [47].

Compounds extracted from *C. cochinchinense* stem bark were tested for their antibacterial properties against Gram-positive (*B. cereus* TISTR 688, *Micrococcus luteus* TISTR 884, *B. subtilis* TISTR 008, *Staphylococcus epidermidis* ATCC 12228, *S. aureus* TISTR 1466) and Gram-negative (*E. coli* TISTR 780, *P. aeruginosa* TISTR 781 and *S. typhimurium* TISTR 292) bacteria [45]. Garcinone C, one of the isolated compounds exhibited good activity with MIC values of less than 8 µg/ml against *M. luteus*, *B. cereus* and *S. epidermidis*. Moderate antimicrobial activity was demonstrated by this compound towards the Gram-negative bacteria tested in this study (*E. coli*, *S. typhimurium* and *P. aeruginosa*) with similar MIC value of 64 µg/ml. However, it displayed a weaker inhibitory effect towards *B. subtilis* at MIC value of 128 µg/ml [45].

The acetone extract of *C. cochinchinense* stem bark was exposed to silica gel column chromatography to isolate the molecule, cochinchinone M (in the form of a yellow amorphous powder) [45]. This compound was found to be highly effective in the growth inhibition of *M. luteus, B. cereus, S. epidermidis* and *P. aeruginosa* with the MIC value of 2 µg/ml. Aside from that, cochinchinone M also demonstrated moderate antimicrobial action against *B. subtilis*, *S. aureus, E. coli* and *S. typhimurium* with MIC value of 64 µg/ml [45].

Cratoxylone extracted from the stem bark of *C. cochinchinense* showed strong activity against the Gram-positive bacteria including *M. luteus, B. cereus*, and *S. epidermidis* with MIC value of 8 µg/ml for all three but exhibited a slightly weaker activity for *B. subtilis* with MIC value of 64 µg/ml. This compound also exhibited moderate antimicrobial action against the Gram-negative bacteria tested such as *E. coli*, *S. typhimurium* and *P. aeruginosa* with the MIC values in the range of 64-128 µg/ml [45].

Antioxidant and cytotoxic activities of xanthones present in C. cochinchinense

Xanthones are also found to exert biological functions such as antioxidative, and anti-cancer effects [45]. They are able to scavenge free radicals either through a single electron transfer (SET) or hydrogen atom transfer (HAT) mechanisms. Free radicals are unstable compounds that can be harmful if their levels become too high leading to cellular death. They are indirectly linked to several illnesses such as heart disease, diabetes and cancer, inflammation, rheumatoid arthritis, Alzheimer's disease and aging. Thus, the antioxidant activities of xanthones present in *C. cochinchinense* are crucial to prevent the onset of health disorders caused by the free radicals present in the body. Celebixanthone, alpha-mangostin,

cudratricusxanthone E, norathyriol, isocudraniaxanthone, macluraxanthone, and mangiferin were all reported to have antioxidant properties [55].

At the concentration of 50 µM, celebixanthone and macluraxanthone exhibited strong DPPH radical scavenging activity with IC_{50} values of 12.3 and 19.0 µM, respectively. Furthermore, these compounds possessed the ortho-dihydroxy groups which will give higher stability to their radical forms when donating the hydrogen radicals [9]. Cudratricusxanthone E also showed high DPPH radical scavenging activity with IC_{50} value of 179.7 µM owing to the occurrence of similar ortho-dihydroxy groups at C-6 and C-7 on ring B of its structure [23].

A xanthone aglycone, norathyriol demonstrated higher inhibition of DPPH radical as compared to isoathyriol due to the substitution of the free hydroxyl group at C-6 with methoxy group [56]. In addition, mangiferin was reported to have potent superoxide ($O_2 \cdot^-$) scavenging ability with an IC_{50} of 14.95 ± 2.95 µg/ml [57]. According to Jo et al. [57], isocudraniaxanthone B displayed superior antioxidant property than other alkoxylated xanthones due to the presence of catechol components.

Xanthones present in *C. cochinchinense* was also found to have anticancer functions. They possessed cytotoxic activities against various human cancer cell lines. The xanthones antiproliferative activities against the human tumor cell lines was assessed by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay based on the transformation of MTT to MTT-formazan by mitochondrial enzyme in viable cells. Pruniflorone N exhibited a distinct cytotoxic effect against SkBr3 and MCF7 breast, hepatocellular HepG2, IST-MES1 mesothelioma, BG-1 ovarian, and Ishikawa endometrial cancer cells with IC_{50} values in the range of 3-9 µM while xanthone V1 showed a moderate effect on all cells with IC_{50} values in the range of 18-25 µM [44]. The decrease in cytotoxicity of xanthone V1 may be due to the presence of an isoprenyl portion [44]. Besides that, both pruniflorone M as well as 6-deoxyisojacareubin exhibited high anti-proliferative activity against several specific cell lines such as BG-1 ovarian cancer cells with IC_{50} values ranging from 6 to 7 µM. The reason behind the high anti-proliferative activity exhibited by pruniflorone N, pruniflorone M and 6-deoxyisojacareubin could be due to the presence of supplementary oxygenated heterocyclic ring bonded to the central xanthone at C-3 or C-4 [44].

According to Jia et al. [11], both cochinchinone A and pruniflorone Q carrying one prenyl and one geranyl moieties, cudratricusxanthone E and 1,3,7-trihydroxy-2,4-diisoprenylxanthone possessing two prenyl groups, pruniflorone N bearing a pyran ring with 1-hydroxy-4,4-dimethyl and xanthone V1 exhibited significant anti-proliferative activity towards HL-60 leukemia cells with IC_{50} values ranging from 1.0 µM to 9.64 µM. These compounds also displayed cytotoxicity on PC-3 prostate cancer cells with IC_{50} values ranging from 11.77 µM to 22.94 µM and MDA-MB-231 breast carcinoma cell lines with IC_{50} values ranging from 9.4 µM to 16.37 µM. The results revealed that prenylated xanthones groups had higher activity against human cancer cell lines than those without prenyl unit [11].

Furthermore, Ito et al. [48] reported that cratoxanthone B and garcinone E demonstrated a strong inhibitory effect on cell proliferation in human acute lymphoblastic leukemia B cell line (NALM-6) with IC_{50} values of 8.27 µM and 8.67 µM, respectively. This could be due to the presence of 6,7-dihydroxy and 5-prenyl substitutions on the B-ring of both compounds. However, cratoxanthone A and cochinchinone A displayed weak anti-proliferative effect on NALM-6 cells with IC_{50} values of 17.78 µM and 14.08 µM, respectively. Garcinone E and alpha-mangostin moderately inhibited the growth of KB epidermoid carcinoma cell line with IC_{50} values of 24.24 µM and 19.86 µM respectively [48]. The study also revealed that cratoxanthone A and B, alpha-mangostin, β-mangostin, cochinchinone A, garcinone E, allanxanthone C, and mangostenol possessed poor anti-proliferative activity in human colorectal carcinoma cell line (Colo205) [48].

Cochinchinone G had high cytotoxicity against lung (ChaGO-K-1), breast (BT474), gastric (KATO-3), liver (HepG2), and colon (SW-620) cancer cell lines with an IC_{50} of 5.44, 5.25, 5.32, 5.74, and 4.64 µg/ml, respectively [26]. 7-geranyloxy-1,3-dihydroxyxanthone exhibited moderate cytotoxic effect against these five human cancer cell lines whereas fuscaxanthone E showed weak cytotoxicity activities on all tested cell lines with IC_{50} values above 7.09 µg/ml. These results indirectly suggested that the hydrophobi-

city of xanthones played substantial role in the cytotoxic activity. Fuscaxanthone E which contained three hydroxyl groups displayed less cytotoxicity than 7-geranyloxy-1,3-dihydroxyxanthone and cochinchinone G which only consisted of two hydroxyl groups [26].

β-mangostin, cochinchinone C, isocudraniaxanthone B and celebixanthone suppressed the growth of human epidermoid carcinoma cell lines (A431) with IC_{50} values of 10.33, 2.01, 10.56 and 3.26 µg/ml, respectively. They also inhibited the growth of SkBr3 with IC_{50} values ranging from 1.54 to 12.24 µg/ml [46]. 7-geranyloxy-1,3-dihydroxyxanthone and celebixanthone had strong inhibition on the growth of MCF-7, HeLa, colon (HT-29) and KB cell lines with IC_{50} values in the range of 0.2-0.45 µg/ml. Isocudraniaxanthone B, cudratricusxanthone E and norathyriol were found to effectively suppress the growth of MCF-7, HeLa and HT-29 cancer cell lines [24]. Last but not least, cochinchinoxanthone demonstrated cytotoxicity against HT-29, A431 and SkBr3 with low IC_{50} values [58].

Conclusion

Cratoxylum cochinchinense is a perennial plant that contains a wide variety of bioactive molecules such as xanthones. Xanthones are the most abundant biologically active secondary metabolites detected in various parts of *C. cochinchinense*. Their unique structural skeleton confers them the function of growth inhibition against pathogenic microbes, free radical scavenging ability and antiproliferative properties towards various human cancer cell lines.

This review has presented a comprehensive perspective on the phytochemistry and pharmacological effects of xanthones identified in *C. cochinchinense*. The various xanthones identified and isolated from this plant may be utilized as new therapies for bacterial infection caused by antibiotic resistant species. Furthermore, the anti-cancer effect of these phytocompounds is an important research avenue to explore in order to develop efficacious treatment for this dilapidating disease.

Also, synthetic modifications of the structure of natural xanthones will certainly accelerate the discovery of more potent xanthonic drugs for medical use. Nonetheless, in-depth research on the mechanistic action of this phytocompound towards the reported bioactivities is still limited and warrants further investigation. Future work should include *in vivo* and clinical studies to further validate the bioactivities of xanthones as well as its safety profile.

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