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Review Article

Comprehensive Review of *Cratoxylum* Genus: Ethnomedical Uses, Phytochemistry, and Pharmacological Properties

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ABSTRACT

In the past, the *Cratoxylum* genus has often been utilized as traditional medicines, culinary ingredients, health supplements, as well as manufacturing materials. This flowering plant belongs to the family Hypericaceae and is classified into six species: *Cratoxylum arborescens*, *Cratoxylum cochinchinense*, *Cratoxylum formosum*, *Cratoxylum glaucum*, *Cratoxylum maingayi*, and *Cratoxylum sumatranum*. The *Cratoxylum* genus is native to Asia as a traditional medicinal plant. It is currently being translated into conventional therapeutics as a preventive agent for diabetes mellitus and cardiovascular diseases. The phytochemical analysis and pharmacological investigations on the *Cratoxylum* species have unveiled the wide spectrum of phytoconstituents, including xanthones, triterpenoids, flavonoids, and phenolic compounds. These compounds are attributed to their significant pharmacological effects, such as antibacterial, antifungal, antioxidant, antimalarial, anti-gastric ulcer, anti-HIV-1 reverse transcriptase, antidiabetic, and anticancer activities. These research findings have strengthened the foundation

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of the *Cratoxylum* genus as a traditional medicinal plant to be further developed and applied as selective therapeutic drugs for various ailments. This paper discusses the *Cratoxylum* genus regarding its traditional uses, phytochemical compounds, and pharmacological properties.

Keywords: *Cratoxylum* genus, conventional therapeutics, ethnomedical uses, pharmacological properties, phytochemical compounds

INTRODUCTION

Cratoxylum is a genus of flowering plants categorized under the Hypericaceae family. The genus is known to be native to Southeast Asia, with six accepted species: *C. arborescens*, *C. cochinchinense*, *C. formosum*, *C. glaucum*, *C. maingayi*, and *C. sumatranum*. They are widely spread in the Southeast Asian region, including countries like Malaysia, Singapore, Indonesia, Vietnam, and Thailand. They are also found in Asian countries, such as India and China. *Cratoxylum* species have a long history in the traditional medicinal systems of these countries due to their health benefits aligned with proven pharmacological properties.

Over the years, several *Cratoxylum* species have been studied and were reported to possess various bioactivities such as antibacterial, antifungal, antioxidant, antimalarial, anti-gastric ulcer, anti-human immunodeficiency viruses (anti-HIV), antidiabetic, and anticancer effects. Furthermore, phytochemical analysis conducted on various *Cratoxylum* species elucidated a wide range of phytochemical compounds, which included flavonoids, xanthones, terpenoids, sterol, triterpenoids, benzophenone, quinone, and other phenolic compounds, which may contribute to its significant pharmacological properties. In this review, traditional medicinal uses, chemical constituents, and pharmacological characteristics of the *Cratoxylum* genus will be discussed systematically.

BACKGROUND

Cratoxylum is a genus of flowering plants that belongs to the family Hypericaceae. The genus is native to tropical Asia and distributed from India through South China to Malaysia. The name *Cratoxylum* is derived from the words '*kratos*' and '*xylon*' in Greek, which means strong wood, generally referring to its hard and durable timber (Soepadmo & Wong, 1995). To date, there are six recognized species in this genus: *C. arborescens* (Figure 1), *C. cochinchinense* (Figure 2), *C. formosum* (Figure 3), *C. glaucum* (Figure 4), *C. maingayi* (Figure 5), *C. sumatranum*; which are often integrated into traditional medicinal systems in the past (Neo et al., 2016).

Cratoxylum species are usually shrubs or small to medium-sized evergreen trees with five-petal flowers that are white, red, or pink (Neo et al., 2016). They are rare in primary forests and usually grow in the lowland areas such as gaps, forest fringes, and disturbed habitats. However, these species can also be found in well-drained soils and swampy areas (Neo et al., 2016; Soepadmo & Wong, 1995).

Figure 1. *Cratoxylum arborescens* (Ibrahim et al., 2015)

Figure 2. *Cratoxylum cochinchinense*. Photos were taken at Singapore Botanic Gardens (Photograph: Chui Yin Bok)

Figure 3. *Cratoxylum formosum*. Photos were taken at Singapore Botanic Gardens (Photograph: Chui Yin Bok)

Figure 4. *Cratoxylum glaucum*. Photos were taken at Bako National Park, Kuching, Sarawak (Photograph: Chui Yin Bok)

TRADITIONAL USES

In the past, various *Cratoxylum* species were used mainly for medicinal and manufacturing purposes. As a traditional medicine, the decoction of the bark and leaves of *C. cochinchinense* can relieve fever, while the decoction of roots can be served as a post-labor tonic for women. *Cratoxylum formosum* bark decoction and resin are used for colic and itch treatment, respectively. A pounded mixture of the bark and leaves of *C. formosum* with coconut oil is found to heal skin problems (Boo et al., 2003; Choi et al., 2012). In Thailand, leaves of *C. formosum* are used as herbal remedies as they are discovered to reduce the risk of cardiovascular diseases by preventing vascular dysfunction as well as conferring protection towards gastric

Figure 5. *Cratoxylum maingayi*. Photos taken at Singapore Botanic Gardens (Photograph: Chui Yin Bok)

mucosal to prevent the formation of gastric ulcers (Kukongviriyapan et al., 2007; Sripanidkulchai et al., 2010). The bark, roots, and leaves of *C. arborescens* are widely integrated into folk medicine to treat fever, coughs, diarrhea, itches, ulcers, and abdominal complaints (Sidahmed et al., 2013).

Apart from medicinal purposes, *Cratoxylum* species are also being consumed in daily diets. In Vietnam, *C. formosum* serves as a vegetable side dish or an ingredient in soup (Choi et al., 2012). In China, the leaves of *C. formosum* ssp. *pruniflorum* are substitutes for 'kuding tea' in Yunnan Province (Xiong et al., 2014). Furthermore, as mentioned earlier, the name *Cratoxylum* means 'strong wood' in Greek; hence the timbers are used in the manufacturing of various wood products, especially in construction and furniture production. This medium-weight hardwood is also used as charcoal and firewood as well as for carving purposes (Boo et al., 2003). A detailed summary of the ethnobotanical uses of the different species is shown in Table 1.

Table 1
Cratoxylum *species and its ethnomedical usages*

Plant	Parts	Traditional uses	References
Cratoxylum arborescens	Leaves	Treat gastric ulcer	Juanda et al. (2019)
Cratoxylum cochinchinense	Roots and stem	Function as diuretic	Juanda et al. (2019)
	Bark, root, and leaves	Treat diarrhea, itches, ulcer, abdominal complaints, fever, and coughs	Juanda et al. (2019)
	Roots	Post-labor tonic for women	Boo et al. (2003)
	Barks and leaves	Relieve fever	Boo et al. (2003)
Cratoxylum formosum	Leaves	To remedy food poisoning, internal bleeding, diarrhea, and liver cirrhosis	Juanda et al. (2019)
		Reduce the risk of cardiovascular diseases	Kukongviriyapan et al. (2007)
		Protective effects towards gastric mucosal	Sripanidkulchai et al. (2010)
	Barks and leaves	Treatment for skin problems and wound healing	Juanda et al. (2019)
	Flower	To cure coughs	Juanda et al. (2019)
	Barks	To treat colic	Boo et al. (2003)
Cratoxylum glaucum	Young stem	To decrease blood pressure Use as an ingredient in culinary	Juanda et al. (2019)
	Leaves, roots, and barks	To treat ulcers, diarrhea, itches, fever, cough, and abdominal complaints	Thaweboon et al. (2014)
Cratoxylum sumatranum	Decocted barks, leaves, and roots	To relieve cough, colds, and dysentery	Dapar (2020)
	Leaves	Relieve toothache To treat burns, scabies, and ulcers	Dapar et al. (2020)
	Leaves and stems	To relieve fever	Dapar et al. (2020)
	Barks	To treat abdominal pain	Dapar et al. (2020)

CHEMICAL CONSTITUENTS

Phytochemicals are chemical compounds synthesized naturally in plants. Based on their chemical structures and characteristics, these compounds can be categorized under six major classes: carbohydrates, lipids, terpenoids, phenolic acids, alkaloids, and other nitrogen-containing metabolites (Huang et al., 2016). These phytochemicals are also beneficial to human health. For example, they could function as antioxidant, antibacterial, antifungal, anti-inflammatory, anti-allergic, antispasmodic, chemopreventive, hepatoprotective, hypolipidemic, neuroprotective, hypotensive, immuno-modulator, and carminative agents. In addition, they were also reported to possess the ability to prevent the development of chronic diseases such as cancer, diabetes, heart disease, and osteoporosis (Thakur et al., 2020).

The major compounds elucidated from *Cratoxylum* species are phenolic compounds, such as xanthones, flavonoids, isoflavonoids, phenolic acids, vismiones, tocotrienols, and anthraquinones. These bioactive could be detected in various parts of the plant (leaves, stems, roots, and fruits). For example, xanthones (Figure 6) isolated from *C. cochinchinense* are cratoxylumxanthone B, cratoxylumxanthone C, and cratoxylumxanthone D, while 1,3,5,6-oxygenated xanthones are detected in *C. maingayi* (Figure 7) (Laphookhieo et al., 2009; Udomchotphruet et al., 2012). Furthermore, flavonoids, such as quercetin, quercitrin, isoquercitrin, and hyperin are reported in *C. formosum* (Choi et al., 2012).

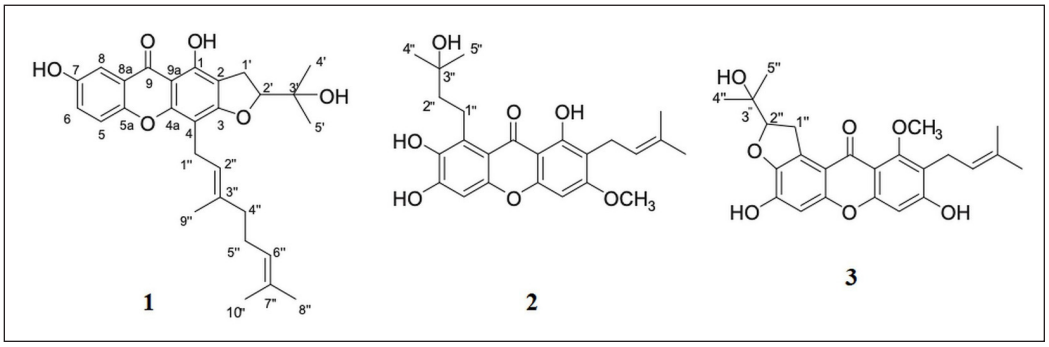

Figure 6. Xanthones isolated from *Cratoxylum cochinchinense*. (1) Cratoxylumxanthone B, (2) cratoxylumxanthone C, and (3) cratoxylumxanthone D (Udomchotphruet et al., 2012)

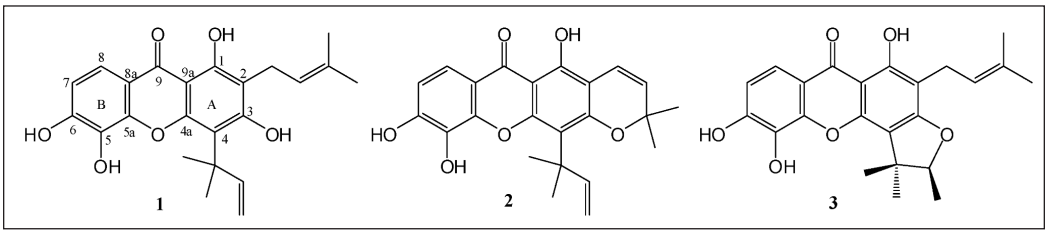

Figure 7. 1,3,5,6-oxygenated xanthones obtained from *Cratoxylum maingayi*. (1) Gerontoxanthone, (2) macluraxanthone, and (3) formoxanthone C (Laphookhieo et al., 2009)

Based on the rich phytochemical constituents present in the *Cratoxylum* genus, these compounds may have contributed to the known pharmacological activities of this genus, as illustrated in Table 2.

PHARMACOLOGICAL ACTIVITIES

Antibacterial

In the previous studies conducted on *Cratoxylum* species, it was found that

Table 2
Cratoxylum *species and its related pharmacological activities*

Plant	Parts	Pharmacological activity	Chemical constituents	References
Cratoxylum arborescens	Twigs and leaves	Anti-HIV-1 reverse transcriptase	Lup-20(29)-ene-3β,30-diol Betulinic acid Euxanthone 3β-hydroxylup-20(29)-en-30-oic acid 1,3,7-trihydroxy-6-methoxy-4,5-di(3-methylbut-2-en-yl)xanthone	Reutrakul et al. (2006)
	Stem bark	Antioxidant	Friedelin β-mangostin Vismiaquinone Fuscaxanthone C 5-demethoxycadensin 1,8-dihydoxy-3-methoxy-6-methylanthraquinonestigmasterol 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone	Thaweboon et al. (2014)
		Anti-gastric ulcer	α-mangostin	Sidahmed et al. (2013)
		Antibacterial	α-mangostin	Sidahmed et al. (2013)
Cratoxylum cochinchinense	Stem	Antioxidant	Cratoxylumxanthone A Cratoxylumxanthone C Cochinxanthone D Cochinxanthone B Dulcisxanthone B Cudratricusxanthone E α-mangostin β-mangostin 2-geranyl-1,3,7-trihydroxy-4-(3-methylbut-2-enyl)xanthone tectochrystin	Sidahmed et al. (2013)
	Stem bark	Antibacterial	α-mangostin β-mangostin Cratoxylone Garcinone B Garcinone C Pruniflorone Q Pruniflorone R	Raksat et al. (2015)

Table 2 *(continue)*

Plant	Parts	Pharmacological activity	Chemical constituents	References
			Cochinchinone A Cochinchinone M 11-hydroxy-3-*O*-methyl-1-isomangostin 1,3,7-trihydroxy-2,4-diisoprenylaxanthone 3-*O*-methylmangostenone D 5,9-dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methylbut-2-enyl)-2*H*,6*H*-pyrano[3,2-b]xanthen-6-one	
	Root	Antimalarial	5-*O*-methylcelebixanthone Celebixanthone β-mangostin Cochinchinone C	Maisuthisakul et al. (2007)
		Antibacterial	Cochinchinone A Celebixanthone methyl ether Cochinchinone L 7-geranyloxy-1,3-dihydroxyxanthone 3-geranyloxy-1,7-dihydroxyxanthone 1,3,7-trihydroxy-2,4-diisoprenylxanthone	Boonnak et al. (2009)
			Isocudraniaxanthone B Cudratricus-xanthone E Norathyriol	Mahabusarakam et al. (2008)
		Antioxidant	Cochinchinone A Cochinchinone B Cochinchinone C Cochinchinone D Cochinchinone E Cochinchinone F Caged-prenylated xanthone β-mangostin l,3,7-trihydroxy-2,4-bis(3-methyl-2-butenyl)xanthone Mangostin Macluraxanthone Garcinone B Celebixanthone Garcinone D	Mahabusarakam et al. (2008) Mahabusarakam et al. (2006)
		Cytotoxic	Cratochinone A Cratochinone B Pancixanthone-A Neriifolone A Macluraxanthone	Natrsanga et al. (2020)

Table 2 *(continue)*

Plant	Parts	Pharmacological activity	Chemical constituents	References
			10-*O*-methyxlmacluraxanthone Pruniflorone G Pruniflorone H 6-deoxyjacareubin 9-hydroxycalabaxanthone Cratoxylumxanthone A Formoxanthone B Cochinchinone J Cochinchinone A β-mangostin 3,8-dihydroxy-1,2-dimethoxyxanthone 1,5-dihydroxy-6-methoxyxanthone 1,3,7-trihydroxyxanthone	
	Root bark	Antidiabetic	α-mangostin ɣ-mangostin Pruniflorone S Cochinechinone A Cochinchinone Q Cochinxanthone A Cratoxylone Cratoxanthone E Cratoxanthone F Cratoxanthone A 1,3,7-trihydroxy-2,4-diisoprenylxanthone 7-geranyloxy-1,3-dihydroxyxanthone	Li, Lee, et al. (2018) Li, Song, et al. (2018)
	Twigs	Antioxidant	Dulcisxanthone B β-mangostin Cudratricusxanthone E Cochinchinone B	Chailap and Nuanyai (2019)
	Fruits and leaves	Antioxidant	α-tocopherol δ-tocotrienol γ-tocotrienol Cochinchinone G Fuscaxanthone E Vismiaquinone A 7-geranyloxy-1,3-dihydroxyxanthone	Chailap et al. (2017)
	Resin extract	Antifungal	α-mangostin Macluraxanthone	Boonnak et al. (2009)
		Antibacterial	α-mangostin β-mangostin Cochinchinone A Celebixanthone methyl ether	Boonnak et al. (2009)

Table 2 *(continue)*

Plant	Parts	Pharmacological activity	Chemical constituents	References
			Dulxis-xanthone Macluraxanthone Pruniflorone G 1,3,7-trihydroxy-2,4-diisoprenylxanthone Caged-prenylated xanthone	
	Fruits	Antimalarial	Fuscaxanthone E Vismione B Vismione F Vismione E	Maisuthisakul et al. (2007)
		Antibacterial	Cochinchinone L 7-geranyloxy-1,3-dihydroxyxanthone 3-geranyloxy-1,7-dihydroxyxanthon	Boonnak et al. (2009)
	Twigs	Antibacterial	β-mangostin Cochinchinone A	Mahabusarakam et al. (2008)
Cratoxylum formosum	Stem bark	Antibacterial	Gum extract	Boonsri et al. (2006)
	Leaves	Antioxidant Anti-inflammatory	Quercetin Isoquercitin Hyperin Quercitrin	Choi et al. (2012)
	Twigs	Antioxidant	Dulcisxanthone B β-mangostin Cudratricusxanthone E Cochinchinone B	Chailap and Nuanyai (2019)
Cratoxylum glaucum	Stem bark	Antioxidant	β-mangostin 5-demethoxycadensin Friedelin Fuscaxanthone C Vismiaquinone 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone 1,8-dihydoxy-3-methoxy-6-methylanthraquinonestigmasterol	Thaweboon et al. (2014)
Cratoxylum maingayi	Stem bark	Antimalarial cytotoxic	Gerontoxanthone I Macluraxanthone Formoxanthone C	Maisuthisakul et al. (2007)
Cratoxylum sumatranum	Roots	Antibacterial	Cratosumatranone B Cratosumatranone D Pruniflorone N Pancixanthone B	Tantapakul et al. (2016)
		Antioxidant	Macluraxanthone	Tantapakul et al. (2016)

Table 2 *(continue)*

Plant	Parts	Pharmacological activity	Chemical constituents	References
	Twigs	Antibacterial	1,3,5,6-tetrahydroxyxanthone 1,3,6-trihydroxy-7-methoxyxanthone 1,5-dihydroxy-6,7-dimethoxyxanthone 1,5-dihydroxy-8-methoxyxanthone 1,7-dihydroxyxanthone 2,4,6-trimethoxybenzophenone 2,8-dihydroxy-1-methoxyxanthone 4-hydroxy-2,6-dimethoxybenzophenone Annulatomarin Cratosumatranone F Cratoxyarborenone F Trapezifolixanthone	Tantapakul et al. (2016)
		Antioxidant	1,3,5,6-tetrahydroxyxanthone	Tantapakul et al. (2016)

C. arborescens, *C. cochinchinense*, *C. formosum*, *C. maingayi*, and *C. sumatranum* possessed significant antibacterial activities towards *Bacillus cereus* (Tantapakul et al., 2016; Vu et al., 2015; Yahayu et al., 2013), *Bacillus subtilis* (Boonnak et al., 2009; Boonsri et al., 2006; Vu et al., 2015; Yahayu et al., 2013), *Escherichia coli* (Ngamsurach & Praipipat, 2021; Vu et al., 2015), *Enterococcus faecalis* (Boonnak et al., 2009), vancomycin-resistant *Enterococcus faecalis* (Boonnak et al., 2009), *Micrococcus luteus* (Tantapakul et al., 2016), *Pseudomonas aeruginosa* (Boonnak et al., 2009; Boonsri et al., 2006; Tantapakul et al., 2016; Vu et al., 2015), *Salmonella typhimurium* (Boonsri et al., 2006; Tantapakul et al., 2016; Yahayu et al., 2013), *Staphylococcus aureus* (Boonsri et al., 2006; Enggiwanto et al., 2019; Mahabusarakam et al., 2008; Ngamsurach & Praipipat, 2021; Tantapakul et al., 2016; Vu et al., 2015; Yahayu et al., 2013), methicillin-resistant *Staphylococcus aureus* (MRSA) (Boonnak et al., 2009; Mahabusarakam et al., 2008), *Staphylococcus epidermis* (Tantapakul et al., 2016), *Streptococcus mutans* (Suddhasthira et al., 2006), and *Streptococcus faecalis* (Boonsri et al., 2006).

The α-mangostin isolated from the stem bark of *C. arborescens* had shown potent reactivity against *B. cereus*, *B. subtilis*, *S. typhimurium*, and *S. aureus*, with the diameter of inhibition zones ranging from 16 to 20 mm, as compared to the standard drugs, tetracycline, and ampicillin (Yahayu et al., 2013). In the same study, β-mangostin was also isolated but demonstrated moderate antibacterial activity towards similar bacterial strains,

with the diameter of inhibition zones from 7 to 11 mm, which could be due to the loss of a hydroxyl group in its chemical structure compared to α-mangostin.

The antibacterial activities of *C. cochinchinense* were tested against Gram-positive and Gram-negative bacteria using the xanthones isolated from its green fruits and resin. The majority of the xanthones isolated possessed strong antibacterial effects against the tested Gram-positive bacteria (*B. subtilis*, *S. aureus*, *E. faecalis* TISTR 459, methicillin-resistant *S. aureus* (MRSA) ATCC 43300, vancomycin-resistant *E. faecalis* (VRE) ATCC 51299). However, among all the Gram-negative bacteria examined, xanthones, such as α-mangostin, β-mangostin, caged-prenylated xanthone, celebixanthone methyl ether, cochinchinone A, cochinchinone L, dulxisxanthone, macluraxanthone, pruniflorone G, 1,3,7-trihydroxy-2,4-diisoprenylxanthone, 3-geranyloxy-1,7-dihydroxyxanthone, and 7-geranyloxy-1,3-dihydroxyxanthone, did not show significant activities against *S. typhimurium* and *Shigella sonei* but were found to have strong antibacterial activities against *P. aeruginosa* (Boonnak et al., 2009). Interestingly, the compounds that showed inhibition towards *P. aeruginosa* were mostly 1,3,7-trihydroxy xanthones (cochinchinone A and 1,3,7-trihydroxy-2,4-diisoprenylxanthone) or 1,3,7-trioxygenated xanthones that have dihydroxyl groups and an oxygeranyl side chain either at C-3 or C-7 (7-geranyloxy-1,3-dihydroxyxanthone and 3-geranyloxy-1,7-dihydroxy- xanthone).

Besides, various xanthones (isocudraniaxanthone B, cudratricusxanthone E, norathyriol, β-mangsotin, and cochinchinone A) isolated from the fruits, roots, and twigs of *C. cochinchinense* exhibited strong antibacterial activities towards *S. aureus* and methicillin-resistant *S. aureus* (MRSA SK1) with minimum inhibitory concentration (MIC) values ranging from 16 to 128 μg mL^{-1}. In this study, isocudraniaxanthone B was found to possess the strongest antibacterial activities towards *S. aureus* and MRSA SK1 with a MIC value of 16 μg mL^{-1} compared with other xanthones (Mahabusarakam et al., 2008).

Antibacterial investigations using the crude hexane extracts from the roots of *C. formosum* were also conducted against *B. substilis*, *S. aureus*, *P. aeruginosa*, *S. faecalis*, and *S. typhimurium*. It was revealed that xanthone V_1, gerontoxanthone I, formoxanthone C, and macluraxanthone isolated from the crude roots extract of *C. formosum* were able to inhibit the growth of these bacteria (Boonsri et al., 2006). Besides, the gum extract from the stem bark of *C. formosum* was reported to exhibit antibacterial activities towards *S. mutans* based on the agar diffusion method. Inhibition zones were formed with a diameter ranging from 9.5 to 11.5 mm, and MIC values were between 48 mg mL^{-1} and 97 mg mL^{-1} (Suddhasthira et al., 2006). Another study by Ngamsurach and Praipipat (2021) used similar procedures to investigate the antibacterial potential of *C. formosum* leaves extract by synthesizing it into beads using sodium alginate. The study revealed that *C. formosum* beads (CFB) possessed antibacterial properties against *S. aureus* and

E. coli. CFB demonstrated a dose-dependent antibacterial potential indicating more effective results at a higher concentration range. As a result, the diameter of the inhibition zones on *S. aureus* was between 6.0 to 8.3 mm, while the diameter of the inhibition zones on *E. coli* was between 6.1 to 8.8 mm, with the increasing concentration of CFB from 100 to 400 mg mL^{-1}. Vu et al. (2015) also investigated the antibacterial activities of the leaf extracts of *C. formosum* by using the broth microdilution method. Three Gram-positive strains (*B. cereus* ATCC 21768, *B. subtilis* ATCC 6633, and *S. aureus* ATCC 6538) and two Gram-negative bacterial strains (*E. coli* American Type Culture Collection, ATCC 25922 and *P. aeruginosa* ATCC 9027) were used to test the antibacterial activities of the leaf extracts. The extracts were a potent antibacterial agent against all five strains, with the MIC concentration ranging from 125 to 2000 µg mL^{-1} (Vu et al., 2015).

Cratoxylum glaucum was also tested for its antibacterial activity toward *S. aureus*, as reported by Enggiwanto et al. (2019). The researchers emulsified the extracts into nanoemulsion, an effective drug delivery system for bacterial cells. The agar diffusion results showed inhibition zones with diameters ranging from 14.03 to 15.22 mm when the concentration of the extracts increased from 20 to 80%.

In another research conducted by Tantapakul et al. (2016), the roots and twigs of *C. sumatranum* ssp. *neriifolium* were found to consist of chemical constituents, such as benzophenones and xanthones. These chemical constituents were believed to have contributed to the antibacterial potentials of *C. sumatranum* towards *M. luteus*, *B. cereus*, *S. epidermis*, *S. aureus*, *S. typhimurium*, and *P. aeruginosa*.

Antifungal

The gum extract of *C. formosum* was tested against *Candida albicans* using disk diffusion and broth dilution assays. It was found that the gum extract demonstrated antifungal activity with MIC values between 0.50 and 1.25 mg mL^{-1} towards reference and clinical strains of *C. albicans* (Thaweboon et al., 2014). Another study by Boonnak et al. (2009) concluded that macluraxanthone and α-mangostin isolated from the resin of *C. cochinchinense* exhibited strong antifungal activity against the same fungus with MIC values of 2.4 and 4.7 µg mL^{-1}, respectively.

Antioxidant

Many antioxidant studies have been conducted over the years on *Cratoxylum* species. Phytochemicals confer human health benefits due to their antioxidative properties (Thakur et al., 2020). *Cratoxylum arborescens*, *C. cochinchinense*, *C. formosum*, *C. glaucum*, and *C. sumatranum* were found to be effective antioxidants as they have high contents of phytochemicals, such as anthraquinones, flavonoids, polyphenols, and triterpenoids.

Sim et al. (2010) reported that *C. arborescens* and *C. glaucum* possessed antioxidant properties as they effectively scavenged DPPH (2,2-diphenyl-1-

picrylhydrazyl) free radicals. These strong radical scavenging effects could be correlated to their high phenolic contents. In addition, the presence of xanthones and triterpenoids in the stems and leaves of *C. cochinchinense* also contributed to its antioxidant properties. Four xanthones isolated from the stem possessed potent activities in both DPPH radical scavenging and lipid peroxidation inhibition assays (Udomchotphruet et al., 2012). Furthermore, the leaves of *C. cochinchinense* also demonstrated antioxidant properties in ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)] radical scavenging assay, recording the highest antioxidant activity in trolox equivalent antioxidant capacity (TEAC) values as well as total phenolic content (Tang, Whiteman, Peng, et al., 2004).

Our group evaluated the antioxidant activities of the methanolic leaf extracts of *C. cochinchinense* by using various antioxidant assays (Tan et al., 2021). The leaves were found to be antioxidant rich as they consisted of high phenolic and flavonoid contents, with the recorded values of 129.0 ± 2.55 mg GAE g^{-1} crude extract and 159.0 ± 2.15 mg QE g^{-1} crude extract, respectively. Expectedly, the leaves were reported to have strong dose-dependent radical scavenging activities towards both DPPH and ABTS free radicals. In addition, the extract also exerted its ability to reduce ferric ions with the ferric reducing antioxidant power (FRAP) value of 99.33 ± 13.28 mg Fe (II) g^{-1} crude extract, which could be due to the presence of reducing agents converting ferric ions to ferrous ions. However, the leaf extracts showed weak metal chelating activity at 31%, even though the extract concentration had been increased to 5 mg mL^{-1}.

Tea sample produced from *C. cochinchinense* was also tested using DPPH radical scavenging assay for its antioxidant activity, compared with the *Camellia* teas (green tea, pu-erh tea, and black tea) used. The tea sample possessed total phenolic content of 51.14 mg GAE g^{-1} dry weight, which was relatively lower than pu-erh tea (67.82 mg GAE g^{-1}) and green tea (80.07 mg GAE g^{-1}) but higher than black tea (39.77 mg GAE g^{-1}). In addition, the sample charted a half maximal effective concentration (EC_{50}) value of 294.73 μg mL^{-1}, which showed intermediate antioxidant activity as compared to trolox (17.67 μg mL^{-1}), green tea (44.23 μg mL^{-1}), pu-erh tea (108.10 μg mL^{-1}), and black tea (176.23 μg mL^{-1}) (Bi et al., 2016).

Antioxidant investigations were also conducted on *C. glaucum* recently. For example, Juanda et al. (2021) reported that the leaves, stems, and cortex extracts of *C. glaucum* contained phytochemicals, such as flavonoids, quinones, phenols, tannins, saponins, and steroids/triterpenoids. Three different solvents (n-hexane, ethyl acetate, and ethanol) were used to extract the plant, revealing total phenolic contents ranging from 6.62 to 48.77 g GAE 100 g^{-1} extract and total flavonoid contents ranging from 1.54 to 25.96 g QE 100 g^{-1} extract. Ethanol extracts possessed the highest total phenolic contents, ranging from 29.51 to 48.77 g GAE 100 g^{-1} extract. For total flavonoid contents, ethyl acetate stem extract had the highest content (25.96 g QE 100 g^{-1} extract),

while ethanol cortex extract reported the lowest content (1.54 g QE 100 g^{-1} extract). The plant contained phenolic and flavonoid compounds, so the extracts could scavenge DPPH free radicals and inhibit xanthine oxidase activities.

Xanthone is an abundant secondary plant metabolite in the twigs of *C. cochinchinense* and *C. formosum*. Chailap and Nuanyai (2019) successfully isolated and identified seven xanthones present in *C. cochinchinense* and *C. formosum*, which were β-mangostin, cudratricusxanthone E, cochinchinone A, cochinchinone B, 1,3,7-trihydroxy-2,4-di-(3-methylbut-2-eyl)-xanthone, dulcisxanthone B, and 2-geranyl-1,3,7-trihydroxy-4-(3,3-dimethylallyl)-xanthone. Meanwhile, xanthones with a hydroxyl group at C-6, such as dulcisxanthone B, β-mangostin, cudratricusxanthone E, and cochinchinone B, exhibited strong free radicals scavenging activities and low potential of oxidation peaks, in DPPH radical scavenging activity assay and cyclic voltammetry, respectively. Therefore, the hydroxyl moiety at the C-6 position could be concluded to play a crucial role in the antioxidant power of xanthone (Chailap & Nuanyai, 2019).

The *C. formosum* leaf extract contained chlorogenic acid (main phenolic acid), dicaffeoylquinic acid, and two ferulic acid derivatives. Antioxidant activities of the extract were assessed using DPPH and ABTS free radical scavenging assays. It was found that chlorogenic acid and another minor compound, dicaffeoylquinic acid, contributed to the antioxidant potential of the extract by demonstrating strong scavenging activities in both assays (Maisuthisakul et al., 2007).

In the past years, very few studies have been conducted on *C. sumatranum*. However, according to Tantapakul et al. (2016), *C. sumatranum* possessed antioxidant activities. The compounds elucidated from the ethanolic extract were evaluated using DPPH radical scavenging activity assay. Among all isolated compounds, it was found that only two compounds (macluraxanthone, 1,3,5,6-tetrahy-droxyxanthone) exhibited potent antioxidant activities, while the remaining compounds showed weak activities.

Antimalarial

Several studies had been conducted on *C. cochinchinense* to test its antimalarial effects against *Plasmodium falciparum*. Roots of *C. cochinchinense* were extracted, and prenylated xanthones were isolated. Among the isolated prenylated xanthones, 5-*O*-methylcelebixanthone, celebixanthone, β-mangostin, and cochinchinone C were found to be effective in inhibiting malarial activities, with half maximal inhibitory concentration (IC_{50}) values of 3.2 μg mL^{-1}, 4.9 μg mL^{-1}, 7.2 μg mL^{-1}, and 2.6 μg mL^{-1}, respectively, while the rest of the isolated compounds were shown inactive (Laphookhieo et al., 2006). Five phenolic compounds were also detected in the fruits of *C. cochinchinense*, and their antimalarial activities were determined. Among the five phenolic compounds identified, fuscaxanthone E, vismione B, vismione

F, and vismione E showed significant antimalarial effects. Vismione B showed the strongest activity at the IC_{50} value of 0.66 µg mL^{-1}, while vismione F and E recorded IC_{50} values of 2.02 µg mL^{-1} and 3.91 µg mL^{-1}, respectively. The structural variations of the vismione derivatives influenced antimalarial properties. As reported by Laphookhieo et al. (2009), a chromene ring was seen in the structure of vismione B at C-1 and C-2 positions, while in the chemical structure of vismione E and F, hydroxyl and isoprenyl groups were present at C-1 and C-2 instead of the chromene ring.

Three 1,3,5,6-oxygenated xanthones identified as formoxanthone C, gerontoxanthone I, and macluraxanthone were isolated from *C. maingayi* stem bark. All three xanthones exhibited strong antimalarial properties against *P. falciparum* with a low IC_{50} value of below 2 µg mL^{-1}. The strong antimalarial activity was observed among these 1,3,5,6-oxygenated xanthones because of two hydroxyl groups at C-5 and C-6 positions (Laphookhieo et al., 2009).

Anti-Gastric Ulcer

Cratoxylum arborescens exhibited anti-gastric ulcer properties due to its potential as an anti-*Helicobacter pylori* agent. This plant possessed high phytochemical contents consisting of xanthones, α-mangostin, and β-mangostin (Sharifi-Rad et al., 2018). Sidahmed et al. (2013) mentioned that α-mangostin isolated from the stem bark of *C. arborescens* demonstrated antibacterial properties towards *H. pylori*. The compound α-mangostin had shown a dose-dependent activity and was certainly able to protect the gastric mucosa from bacterial infection. Furthermore, it was revealed that α-mangostin interfered with the release of nitric oxides as well as the inhibition of cyclooxygenases (COX), thus validating the gastroprotective potential of *C. arborescens* to prevent the formation of gastric ulcers. In another study by Sidahmed et al. (2016), the stem bark of *C. arborescens* was found to contain β-mangostin, demonstrating gastroprotective activity by inducing the secretion of gastro-adherent mucus in the Sprague Dawley rats against the ethanol ulcer model system. Besides, this compound also exhibited antioxidant, anti-apoptotic, and anti-*H. pylori* effects strengthening its potential as an anti-gastric ulcer agent.

Anti-HIV-1 Reverse Transcriptase

Pentacyclic triterpenoids derivatives are one of the naturally occurring triterpenoids conferring anti-HIV potential. Lupanes, such as betulinic acid and lupene derivatives, are active in the inhibition activity of HIV-1 reverse transcriptase (Cassels & Asencio, 2010; Chinsembu, 2019). The leaves and twigs of *C. arborescens* were extracted and tested using the HIV-1 reverse transcriptase assay. Among the isolated compounds, betulinic acid and the lupene derivatives (lup-20(29)-ene-3β,30-diol and 3β-hydroxylup-20(29)-en-30-oic acid) were identified, along with other compounds, which were euxanthone and 1,3,7-trihydroxy-6-methoxy-4,5-di(3-methylbut-2-en-yl) xanthone. These compounds possessed IC_{50} values ranging from 8.7 µg mL^{-1}

to 84.9 μg mL^{-1}, indicating moderate to strong activities in the inhibition of HIV-1 reverse transcriptase. The result showed that 3β-hydroxylup-20(29)-en-30-oic acid exhibited the strongest inhibition activity towards HIV-1 reverse transcriptase with an IC_{50} value of 8.7 μg mL^{-1}. The isolated compounds were also tested using the syncytium assay that utilized $^{\Delta Tat/Rev}$MC99 virus and 1A2 cell line system. It was reported that lup-20(29)-ene-3β,30-diol, betulinic acid, euxanthone, 1,3,8-trihydroxy-2,4-dimethoxyxanthone, 3,4-dihydroxybenzoic acid, and 3β-hydroxylup-20(29)-en-30-oic acid possessed anti-HIV-1 activity based on the assay with the EC_{50} values ranging from below 3.9 to 32.2 μg mL^{-1} in which betulinic acid recorded the lowest EC_{50} value lesser than 3.9 μg mL^{-1} (Reutrakul et al., 2006).

In addition, a recent study was conducted on the stem bark of *C. formosum* ssp. *pruniflorum* for its anti-HIV-1 reverse transcriptase activity. Crude methanol extract and five fractions (CFA, CFB, CFC, CFD, and CFE) obtained from crude chloroform extract were tested. One of the chloroform fractions, CFE, exhibited effective anti-HIV-1 reverse transcriptase activity, similar to the positive control, Nevirapine, while the rest of the samples showed low inhibition (Srisombat et al., 2019).

Antidiabetic

The root bark of *C. cochinchinense* was reported to inhibit the activities of protein tyrosine phosphatase 1B (PTP1B) and α-glucosidase, which were the key target enzymes for the treatment of non-communicable chronic diseases such as obesity and diabetes mellitus. The isolated alkylated xanthones from *C. cochinchinense* demonstrated significant inhibitory activity with IC_{50} values ranging from 1.7 to 72.7 μM for α-glucosidase and 2.4 to 52.5 μM for PTP1B. Cratoxanthone A (IC_{50} = 4.8 μM), α-mangostin (IC_{50} = 5.7 μM), and ɣ-mangostin (IC_{50} = 1.7 μM) were the xanthones identified as the most active α-glucosidase inhibitors with IC_{50} values less than 10 μM. Li, Lee, et al. (2018) mentioned that subtle structural changes in the relevant compounds contributed to the α-glucosidase inhibitory potencies of xanthones. Xanthones with prenyl group on A-ring that bore free hydroxyl groups, such as cratoxanthone A, showed better inhibition towards α-glucosidase as compared to cochinchinone A. Furthermore, cratoxanthone A (IC_{50} = 2.4 μM), cochinchinone A (IC_{50} = 5.2 μM), and α-mangostin (IC_{50} = 5.5 μM) were the most active PTP1B inhibitors. Among the isolated alkylated xanthones, cratoxanthone A, and α-mangostin were the most potent inhibitors for α-glucosidase and PTP1B. In addition, two new xanthones, cratoxanthone E and F, were also identified from the *C. cochinchinense* root bark, demonstrating inhibition towards α-glucosidase and PTP1B (Li, Song, et al., 2018).

Besides, caged xanthones were also elucidated from the root bark of *C. cochinchinense*. As a result, six caged xanthones were isolated, and these compounds were studied for their

PTP1B inhibitory potentials. Among the isolated compounds, cochinchinoxanthone C, cochinchinoxanthone D, and cochinchinoxanthone recorded significant PTP1B inhibitory activities with IC_{50} values of 76.3, 46.2, and 6.6 µM, respectively. As such, cochinchinoxanthone was reported to be the most potent PTP1B inhibitor among the isolated caged xanthones (Li, Lee, et al., 2018).

Anticancer

The 1,3-dihydroxy-6,7-dimethoxy-2,8-diprenylxanthone and 2-geranylemodin were the xanthones compounds obtained from the *C. arborescens* stem bark with moderate cytotoxic effect towards NCI-H187 (lung cancer cell line) at IC_{50} values of 3.69 ± 1.27 and 3.08 ± 0.73 µg mL^{-1}, respectively (Pattanaprateeb et al., 2005). Besides, α-mangostin as the major bioactive compound in *C. arborescens*, was cytotoxic towards human cervix carcinoma cells (WRL-68) with IC_{50} value of 65 µg mL^{-1} but did not have any cytotoxic effect on normal kidney and liver cells as determined using *in vivo* mice model after 14 days of oral gavage with 100 mg kg^{-1}, 500 mg kg^{-1}, and 1000 mg kg^{-1} of compound (Ibrahim et al., 2015). Moreover, α-mangostin also showed a remarkable cytotoxic effect on the HeLa cancer cell line with an IC_{50} value of 24.53 ± 1.48 µM. However, no significant cytotoxic effects were shown towards normal human epithelial ovarian cells (SV40), where the IC_{50} value of 93.26 ± 3.92 µM was recorded after 24 hours of incubation. The proliferation and colony-forming capabilities of HeLa cells were significantly reduced and inhibited after treatment with α-mangostin isolated from *C. arborescens* in a dose and time-dependent manner. It was reported that the apoptosis in HeLa cells was induced by α-mangostin via the mitochondrial-dependent pathway. First, it disrupted the mitochondrial membrane potential with reactive oxygen species (ROS) due to high oxidative stress. It triggered the release of cytochrome C into the cytosol, which marked the early apoptosis process. Then, the free cytochrome C activated caspases (caspase-3, caspase-7, and caspase-9), which eventually led to apoptosis (El Habbash et al., 2017). In addition, Yahayu et al. (2013) showed that the α-mangostin and β-mangostin extracted from the *C. arborescens* stem bark exhibited high cytotoxicities against estrogen receptor-positive human breast adenocarcinoma cells (MCF-7) with IC_{50} values of 12.48 µg ml^{-1} and 28.42 µg ml^{-1}, respectively. The high cytotoxicity of α-mangostin towards MCF-7 cells was associated with the prenyl groups that affected the mitochondrial signal transduction pathway, which was responsible for the mitochondria permeability. In contrast, β-mangostin demonstrated a slightly lower cytotoxic effect on MCF-7 cells due to the loss of one hydroxyl group (Yahayu et al., 2013).

The cytotoxic effect of the less potent β-mangostin of *C. arborescens* isolated from stem bark was further studied by Syam et al. (2014) against the estrogen receptor-positive human breast adenocarcinoma

cells (MCF-7), estrogen receptor-negative human breast adenocarcinoma cells (MDA-MB 231), human liver hepatocellular cells (HepG2), human lung cancer cells (A-549), and human prostate cancer cells (PC3). This phytocompound exhibited a selective cytotoxic effect as the most significant cytotoxicity was observed for the two breast cancer cell lines, MCF-7 and MDA-MB-231. The MCF-7 and MDA-MB-231 cells showed prominent growth inhibition and cellular shrinkage after 24 hours post-treatment with β-mangostin. Meanwhile, animal experiments also validated that β-mangostin was non-hepatotoxic and nephrotoxic, with no significant changes in the body weight of mice models after treatment (Syam et al., 2014). Besides, β-mangostin also showed a significant antiproliferative effect on human promyelocytic leukemia cells (HL60) at a concentration of 58 µM post-treatment, with a 70% reduction in cellular viability. A similar apoptotic pathway was observed after induction with β-mangostin, which exhibited adverse effects on the mitochondrial membrane potential through the generation of an excessive amount of reactive oxygen species that led to the release of cytochrome C into the cytosol. Then, the free cytochrome C triggered the caspase-3 and caspase-9 activities, causing cell apoptosis. β-mangostin reduced the transcription of the mRNA of the apoptosis repressor genes Bcl-2 and HSP70 while upregulating the gene expression of caspase-9 as observed in quantitative real-time polymerase chain reaction (qPCR) reaction in a dose-dependent manner (Omer et al., 2017*).*

Hexane fraction of xanthones extracted from the roots of *C. cochinchinense* was significantly cytotoxic towards human lung cancer cells (NCI-H187) but demonstrated no antiproliferative effect on human mouth epidermoid carcinoma cells (KB) and breast cancer cells (BC-549). The geranyl moiety on the xanthones isolated from *C. cochinchinense* was considered responsible for its remarkable anticancer activity (Laphookhieo et al., 2006). Meanwhile, Mahabusarakam et al. (2008) reported that the dichloromethane fraction and methanolic fraction of xanthones from the roots of a similar plant consisting of 7-geranyloxy-1,3-dihydroxyxanthone and celebixanthone had strong cytotoxic effect towards MCF-7, HeLa, HT-29, and KB cancer cell lines, with IC_{50} values in the range of 0.32 to 0.45 mg mL^{-1}. The contradicting results for KB cancer cells may be due to the difference in the phytochemical contents in the various fractions tested by the researchers.

Laphookhieo et al. (2009) isolated formoxanthone C, gerontoxanthone I, and macluraxanthone from the bark of *C. cochinchinense*; vismione E and vismione F from the fruits of *C. cochinchinense* and these compounds were found to exhibit cytotoxic effects towards NCI-H187 cancer cells. Interestingly, formoxanthone C demonstrated the highest cytotoxic effect on NCI-H187 cancer cells with an IC_{50} value of 0.22 µg mL^{-1} compared to other isolated compounds and elliticine (IC_{50} = 0.45 µg mL^{-1}), a standard drug used in the sulforhodamine B (SRB) colorimetric cytotoxicity assay. In addition, pruniflorone

M, pruniflorone N, and 6-deoxyisojacareubin had been identified from the barks of *C. cochinchinense* with their significant antiproliferative effects on human breast cancer cells (MCF-7 and SKBR3), Ishikawa endometrial adenocarcinoma, ovarian carcinoma (BG-1), mesothelioma (IST-MES1), and human liver cancer cells (HepG2) based on MTT assays (Thu et al., 2017). Furthermore, fruits and leaves of *C. cochinchinense* also contained cochinchinone G, which showed a strong cytotoxic effect on the breast (BT474), lung (ChaGO-K-1), liver (HepG2), gastric (KATO-3), and colon (SW-620) cancer cell lines in MTT [3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide] assays at IC_{50} values of 5.25 μg mL^{-1}, 5.44 μg mL^{-1}, 5.74 μg mL^{-1}, 5.32 μg mL^{-1}, and 4.64 μg mL^{-1}, respectively (Chailap et al., 2017).

On the other hand, Ren et al. (2011) identified α-mangostin as the most potent cytotoxic xanthone from the *C. cochinchinense* methanolic stem extract against the human colon cancer cell line (HT-29) with a median effective dose (ED_{50}) value of 4.1 μM. Meanwhile, the semi-synthetic derivatives of 6-*O*-benzoyl-α-mangostin and 3,6-di-*O*-acetyl-α-mangostin obtained from the chemical modification of α-mangostin were shown to be highly cytotoxic towards the HT-29 human colon cancer cells with ED_{50} values of 1.0 and 1.9 μM, respectively. This study discovered that the carboxyl group at C-18 and the prenyl groups at C-2 and C-4 were not responsible for the cytotoxicity of the xanthone compounds. The chemical modification of α-mangostin revealed that 3,6-diacetylation and 6-benzoylation could improve the cytotoxicity; at C-2 and C-3, the cyclization had retained the initial cytotoxicity, while at C-1, C-2, the cyclization, and 3,6-dimethylation would decrease the xanthone cytotoxicity. Besides, Ren et al. (2011) also found that 1,3,7-trihydroxy-2,4-diisoprenylxanthone isolated from the *C. cochinchinense* stem extracts possessed the highest inhibitory effect (IC_{50} value of 2.9 μM) on the nuclear factor-κB (NF-κB) p65. The transcriptional factor p65 plays a key role in the inflammatory responses on the NF-κB signaling pathway. Stimulation of the p65 transcriptional factor at aberrant levels would induce the canonical NF-κB signaling pathway above basal levels and indirectly trigger the development of tumors (Giridharan & Srinivasan, 2018).

In a study by Tang, Whiteman, Jenner, et al. (2004), a semipurified extract (YCT) containing at least 90% mangiferin was obtained from *C. cochinchinense*. This extract had induced a selective cytotoxic effect towards Jurkat T cells (T cell leukemia) by reducing 60% of cellular viability at 63.35 μg mL^{-1} after 48 hours of treatment but no significant effect on normal cell lines (Chang's liver cell (CL), Madin–Darby canine kidney (MDCK), human articular chondrocytes (HAC), rat pheochromocytoma cells (PC12), and human chondrosarcoma cells (HTB94)). It was postulated that YCT acted on the plasma membrane redox system (PMRS), such as cNOX (constitutive) and tNOX

(tumor-associated) plasma membrane oxidases that were active on T cell leukemia but inactive on normal lymphocytes. At first, YCT induced high oxidative stress by accumulating radical oxygen species (ROS) in the mitochondria. This action depolarized the mitochondrial membrane causing a rapid influx of calcium ions (Ca^{2+}) through the membrane's non-selective cation channel. Excessive Ca^{2+} led to a fall in mitochondria membrane potential, ultimately leading to cell death. Hepatotoxicity was observed in this experiment despite the positive effect of YCT on T cells. Human fetal liver cells (HFL) and human liver cancer cells were most susceptible to YCT, with reduced viability to 10% and 20%, respectively, after 48 hours of exposure at 63.35 μg mL^{-1} (Tang, Whiteman, Jenner, et al., 2004).

The anticancer properties of *C. cochinchinense* were mainly attributed to the xanthone compounds present in different parts of the plant. Studies have suggested that the selective cytotoxic effects of different xanthones on cancer cell lines largely depended on the molecular moiety present in the xanthones. For example, the hydroxyl moiety presents at C-5 of celebixanthone and the geranyl group at C-4 of cochinchinone A were responsible for the high cytotoxic effect towards human lung cancer cell (NCI-H187), but the opposite was observed for the methoxyl group at 5-*O*-methylcelebixanthone and prenyl group at 1,3,7-trihydroxy-2,4-di(3-methylbut-2-enyl) xanthone (Laphookhieo et al., 2006). This finding was supported by Chailap et al. (2017), who reported that cochinchinone G, which possessed two hydroxyl groups, expressed a high cytotoxic effect towards breast (BT474), lung (ChaGO-K-1), liver (HepG2), gastric (KATO-3), and colon (SW-620) cancer cell lines. Meanwhile, α,α,β-trimethylfuran ring on C-3/C-4 of formoxanthone C also contributed to the high cytotoxic effect towards NCI-H187. On the other hand, at C-4, the 1,1-dimethyl-2-propenyl moiety of gerontoxanthone I and macluraxanthone were reported to reduce the cytotoxic effect on NCI-H187 (Laphookhieo et al., 2009). Xanthone with an additional oxygenated heterocyclic ring fused with the xanthone nucleus at C-3/C-4 showed a high cytotoxic effect towards human breast cancer cells (MCF-7 and SKBR3), Ishikawa endometrial adenocarcinoma, ovarian carcinoma (BG-1), mesothelioma (IST-MES1), and human liver cancer cells (HepG2). However, an isoprenyl moiety in xanthone V_1 and macluraxanthone reduced the cytotoxic effect (Takamatsu et al., 2003). Chemical modifications, such as 3,6-diacetylation and 6-benzoylation, were reported to have improved the cytotoxicity towards cancer cell lines while cyclization at C-2 and C-3 on α-mangostin retained the initial cytotoxicity and cyclization at C-1 and C-2 and 3,6-dimethylation greatly reduced the cytotoxicity (Ren et al., 2011).

The crude methanol extracts (CME) of *C. formosum* ssp. *pruniflorum* (Teawdang) edible parts were found to be cytotoxic towards several cervical cancer cell lines, including HeLa (adenocarcinoma with HPV 18 positive), SiHa (squamous cell carcinoma grade II with HPV 16 positive),

and C-33A (carcinoma with non-HPV infection) cell lines, with IC_{50} of 208.32, 338.06, and 107.74 µg mL^{-1}, respectively. The crude methanol extract was reported to have phenolic contents, such as gallic acid, caffeine, caffeic acid, ferulic acid, quercetin, and resveratrol. Gallic acid was already proven to be cytotoxic to the hepatitis B virus as well as liver cancer cell lines (Promraksa et al., 2015; Waiyaput et al., 2012). Besides, the growth of HepG2 cancer cells was inhibited by 50% hydroethanolic extracts of *C. formosum* ssp. *pruniflorum* with the phytoconstituent of xanthones, terpenoids, tannin, saponin, alkaloids, and reducing sugars (IC_{50} value = 55.9 ± 10.6 µg mL^{-1}), as compared to non-cancerous vero cells (IC_{50} value more than 500 µg mL^{-1}) (Nonpunya et al., 2018). The cellular effect of *C. formosum* ssp. *pruniflorum* extracts towards HepG2 was apoptosis by activating caspase enzymes (Nonpunya et al., 2018).

In a study conducted by Senggunprai et al. (2016), the cytotoxic effect of the aqueous and ethanolic leaf extracts of *C. formosum* (Jack) Dyer towards human cholangiocarcinoma (KKU-M156) cells was shown in a concentration-dependent manner with the IC_{50} values ranging from 11.3 to 12.1 mg mL^{-1}. Apoptosis was observed in most cells, and necrosis was also seen in a small proportion of the cells after 24 hours of treatment. The percentage of apoptotic and necrotic cells increased dose-dependent for both aqueous and ethanolic extracts. In addition, the cells were arrested at the G2/M phase of the cell cycle, and the expression of cyclin A and Cdc25A, which were responsible for cell cycle regulation, were down-regulated. In another study by Putthawan et al. (2018), ethanolic leaf extracts of *C. formosum* exhibited a significant cytotoxic activity on human colorectal adenocarcinoma cell line (HT-29) and human liver cancer cell line (HepG2 cells) at 35.25 ± 5.95% and 17.13 ± 0.58%, at the concentration of 2000 µg mL^{-1}, respectively.

The ethanolic leaf extract of *C. formosum* (collected at Udon Thani province) showed significant cytotoxic effects on human breast cancer cells MCF-7 cells, as reported by Buranrat et al. (2017). The extract decreased the MCF-7 cell viability dose-dependently without altering the cellular morphology (IC_{50} values of 85.70 ± 4.52 mg mL^{-1} at 24 h and 53.74 ± 3.02 mg mL^{-1} at 48 h). Besides, this extract also lowered the colony-forming ability of the MCF-7 cell line with concentration (IC_{50} values of 36.37 ± 1.80 mg mL^{-1}) by reducing its cyclin D1 (cell cycle protein) expression. Furthermore, it potentiated the activity of anticancer drugs [5-fluorouracil (5-FU), cisplatin, doxorubicin, and gemcitabine] inducing MCF-7 cell death as compared to treatment groups with ethanolic leaf extract or anticancer drugs alone. Furthermore, the *C. formosum* ethanolic leaf extract significantly increased the intracellular ROS formation and caspase-3 activity, which led to mitochondrial membrane dysfunction, resulting in the apoptosis of cancer cells. It was found that 100 mg mL^{-1} of the leaf extract could reduce the mitochondrial function of MCF-7 cancer cells by 80% compared to

the untreated cell groups. In addition, this extract inhibited the MCF-7 cell migration by reducing the protein expression of matrix metalloproteinases MMP-2 and MMP-9, major proteins involved in the metastasis, migration, and invasion processes in tumor cells. It also interfered with the mevalonate pathway (cancer cell proliferation pathway) by significantly downregulating the gene expression of Rac1 and cdk6, which were responsible for breast cancer cell proliferation.

Ahn et al. (2019) synthesized *C. formosum* silver nanoparticles (AgNPs) with 0.25 mM silver nitrate and 0.02% of *C. formosum* ethanolic leaf extract. The result demonstrated high cytotoxicity against the human lung cancer cells (A549) compared to the *C. formosum* ethanolic leaf extracts alone. However, the cytotoxicity of *C. formosum* AgNPs towards the A549 cancer cell line was found to be greatly affected by the presence of fetal bovine serum (FBS). The viability of cancer cells treated by AgNPs was 49.9% in the presence of FBS, whereas, in the absence of FBS, it was 65.4%. Furthermore, the annexin V/ propidium iodide staining method used in the study suggested that the *C. formosum* AgNPs was a potential anticancer agent by inducing early apoptosis (21.36%) in A549 human lung cancer cells (Ahn et al., 2019).

Formoxanthone C was one of the bioactive compounds isolated and identified from the roots of *C. formosum* ssp. *pruniflorum* (Jack) Dyer. It exhibited a significant cytotoxic effect towards MCF-7, HeLa, HT-29, and KB cancer cell lines at IC_{50} values of 4.9, 3.7, 5.3, and 3.3 μg mL^{-1}, respectively. Meanwhile, it was determined that the catechol unit in the xanthone increased the cytotoxic effect (Boonsri et al., 2006).

Laphookhieo et al. (2009) characterized the three 1,3,5,6-oxygenated xanthones from the stem barks of *C. maingayi* as gerontoxanthone I, macluraxanthone, and formoxanthone C, as well as their cytotoxicities against NCI-H187, small cell lung carcinoma. It was found that all three 1,3,5,6-oxygenated xanthones exhibited a significant cytotoxic effect towards NCI-H187 at IC_{50} values of 6.63 μg mL^{-1} (gerontoxanthone I), 3.42 μg mL^{-1} (macluraxanthone), and 0.22 μg mL^{-1} (formoxanthone C). The highest cytotoxic effect of formoxanthone C was found to be associated with the α,α,β-trimethylfuran ring on C-3/C-4 as compared to the less potent gerontoxanthone I, which had only isoprenyl and hydroxyl groups at C-1 and C-2, respectively (Chailap et al., 2017).

New xanthones of cratoxyarborenones A-F and the four known compounds, vismione B, 2,4,6-trihydroxybenzophenone 4-*O*-geranyl ether, betulinic acid, and δ-tocotrienol as well as two novel anthraquinobenzophenones, cratoxyarborequinones A and B were found in the leaves, stem bark, and twigs of *C. sumatranum* using bioassay directed fractionation. Their cytotoxic effects were evaluated against the human oral epidermoid carcinoma (KB) cell line. The new xanthones of cratoxyarborenones A-F were all cytotoxic towards the KB

cell, with the highest being observed for cratoxyarborenones B at EC_{50} of 1.0 ± 0.1 µg mL^{-1} in comparison to vismione B (EC_{50} = 1.3 ± 0.1 µg mL^{-1}). In contrast, the two novel anthraquinobenzophenones, cratoxyarborequinones A and B, were inactive against the KB cell (Seo et al., 2002).

CONCLUSION

This review highlighted the vast bioactivities of the flowering plant, *Cratoxylum* genus, especially in the traditional medicinal system and as proven scientifically in many studies. Various parts of the plants are found to contain distinctive phytochemical compounds which may contribute to their observed pharmacological activities, such as antibacterial, antifungal, antioxidant, antimalarial, antiulcer, anti-HIV, antidiabetic, and anticancer effects. Nonetheless, there are still other novel bioactive molecules yet to be discovered from this plant species, thus, warrants further investigation. Furthermore, more in-depth research on the mechanistic actions of the plant extracts or their specific phytoconstituents towards the reported pharmacological actions should also be carried out to provide a better perspective on their bioactivities. In addition, *in vivo* model systems are highly recommended to be integrated into biological testing to validate results from *in vitro* studies. Pre-clinical and clinical trials are vital to further develop *Cratoxylum* species as a potent therapeutic agent for many ailments.

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