Review

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Posted Date: 2 October 2024

doi: 10.20944/preprints202410.0045.v2

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 doi:10.20944/preprints202410.0045.v2

Review

Diversity and Conservation of Mangrove and Associate Species with Anticancer Properties: An Overview

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Abstract: In this article, the diversity of mangrove and associate species with anticancer properties are reviewed. Information included their scientific names, synonyms, common/vernacular names, families and life-forms. Their anticancer properties are documented with description on cancer cell types, effects and mechanisms. Mangroves are exclusive species confined to the mangrove habitat. Plants that occur in coastal areas and also in mangroves are known as associates or non-exclusive species. In this article, species with anticancer properties are 20 mangrove species belonging to 13 genera and 11 families, and 26 associate species belonging to 24 genera and 17 families. Most reported mangrove species are *Avicennia marina* and *Ceriops tagal* with five and four studies, respectively. Associate species most reported are *Talipariti tiliaceum* or *Hibiscus tiliaceus* with five studies, followed by *Anacardium occidentale*, *Artocarpus altilis*, *Ceriops manghas*, *Pluchea indica* and *Pongamia pinnata* with four studies each. In the conservation of mangrove and associate species with anticancer properties, in *in-situ* conservation, species are protected in their natural surroundings as ecosystems (e.g., virgin jungle reserves, biosphere reserves and Ramsar sites) while in *ex-situ* conservation, species are protected outside their natural habitats (e.g., arboreta and botanical gardens).

Keywords: mangrove species; associate species; diversity; *in-situ* conservation; *ex-situ* conservation; cytotoxic; antiproliferative; apoptosis

1. Introduction

Coastal plant species of tropical and sub-tropical shores can be categorized into mangroves and mangrove associates. Mangroves are exclusive plant species that are adapted to the tidal mangrove habitat, and do not extend into other coastal habitats such as sandy beaches and rocky shores. Plants that occur in all coastal habitats including mangroves are known as mangrove associates or non-exclusive species [1,2]. Mangroves are exclusive species, which are adapted to the mangrove habitat, and do not extend into other terrestrial plant communities. Plants that occur in the coastal environment and also in mangroves are mangrove associates or non-exclusive species [2].

The worldwide extent of mangroves was 147,360 km^2 with southeast Asia having the largest area of 48,200 km^2 [3]. Globally, there are 73 mangrove species in the Indo-West Pacific and Atlantic East Pacific regions with *Acrostichum aureum* occurring in both regions [4]. In Southeast Asia, a total of 52 mangrove species of trees and shrubs, and 22 species of mangrove associates have been reported [5].

The northern limit of world mangroves occurs in Okinawa and Kagoshima Prefectures in the southern part of Japan. Covering a total area of 744 ha, mangroves are found on the islands of Ishigaki, Iriomote, Okinawa and Miyako. Mangrove species include *Bruguiera gymnorhiza*, *Excoecaria agallocha*, *Heritiera littoralis*, *Kandelia obovata*, *Lumnitzera racemosa*, *Pemphis acidula* and *Rhizophora stylosa* [6]. The northernmost limit is Kamino River of Hioki City where the mangroves are pure

 doi:10.20944/preprints202410.0045.v2

stands of stunted *K. obovata*. The major use of mangroves in Japan is tourism. Each year, the number of Japanese tourists visiting Ishigaki and Iriomote is much higher than the local population of these islands. Popular tourist activities include river cruises, canoeing, forest hiking and trekking, bird-watching, snorkeling, scuba diving and recreational fishing [6].

The southern limit of the global mangroves is in New Zealand. Occurring in the northern part of North Island in the vicinity of Auckland, stunted growth of trees of *Avicennia marina* var. *australasica* are the only plant species found [7]. Trials using *A. marina* foliage as feed for dairy cattle showed that the foliage serves as both feed and salt supplement [8]. Duck hunting in New Zealand is a popular recreational activity along the mangrove waterways. During the duck hunting season, hunters use cut bushes of *A. marina* to camouflage their boats [2].

Mangrove and associate species contain bioactive compounds e.g., terpenoids, alkaloids, phenolics, saponins, flavonoids, phenolic glycosides, polysaccharides, quinones, limonoids, polyisoprenoids, tannins and steroids [9–11]. Besides anticancer activities, these metabolites also possess other pharmaceutical properties such as antioxidant, antibacterial, anti-fungal, antiviral, antimalarial, insecticidal, larvicidal, antidiabetic, anti-ulcer, anti-hypertensive, analgesic and anti-inflammatory effects [8,11,12].

In this article, mangrove species and associates with anticancer properties are reviewed. Information included their species, synonyms, common/vernacular names, families, life-forms and references. Their anticancer properties are documented with description on cancer cell types, effects and mechanisms.

2. Mangrove and Associate Species with Anticancer Properties

Mangrove and associate species with anticancer properties are shown in Figures 1–3 and listed in Table 1. They include a total of 20 mangrove species and 26 associate species.

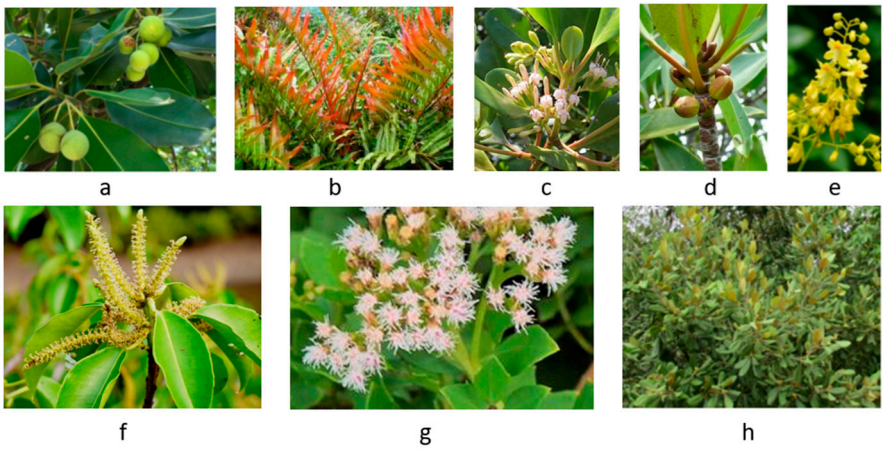

Figure 1. Calophyllum inophyllum (a), Acrostichum aureum (b), Scyphiphora hydrophyllacea (c), Rhizophora apiculata (d), Caesalpinia crista (e), Excoecaria agallocha (f), Pluchea indica (g) and Avicennia rumphiana (h).

 doi:10.20944/preprints202410.0045.v2

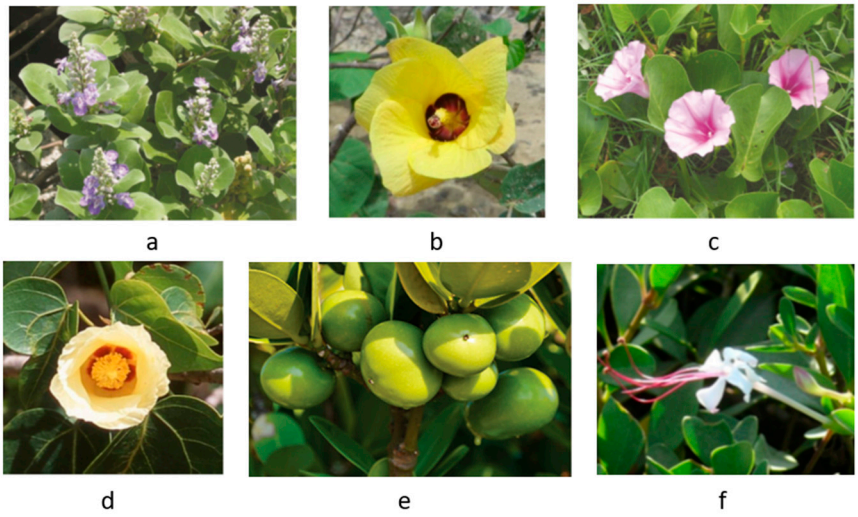

Figure 2. Vitex trifolia (a), Talipariti tiliaceum (b), Ipomoea pes-caprae (c) Thespesia populnea (d), Garcinia subelliptica (e) and Volkameria inermis (f).

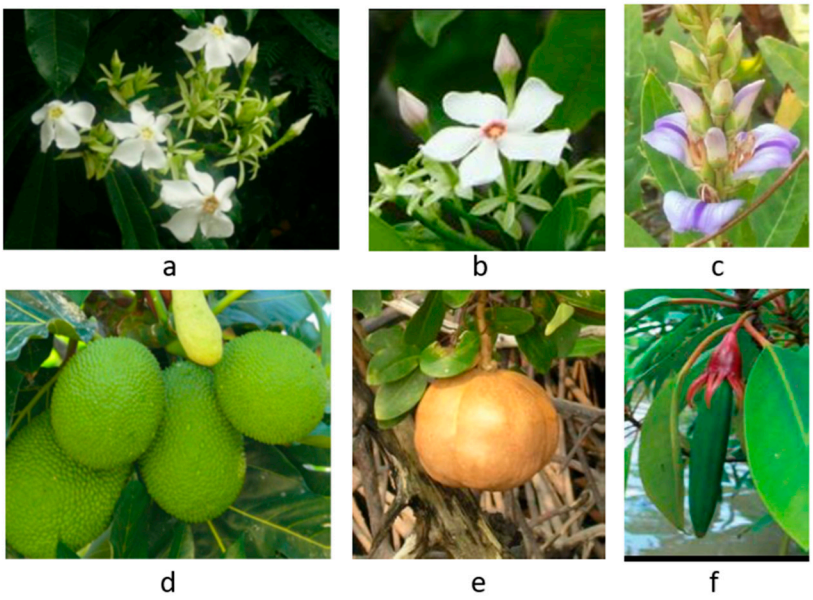

Figure 3. Cerbera odollam (a), Cerbera manghas (b), Acanthus ilicifolius (c), Artocarpus altilis (d), Xylocarpus granatum (e) and Bruguiera gymnorhiza (f).

Table 1. Mangrove and associate species with anticancer properties.

No.	Species (synonym)	Common/vernacular name	Family	Life-form	Ref.
	Mangrove species				
1	*Acanthus ebracteatus*	Sea holly, Jeruju hitam	Acanthaceae	Shrub	[5]
2	*Acanthus ilicifolius*	Mangrove holly, Jeruju putih	Acanthaceae	Shrub	[5]
3	*Acrostichum aureum*	Mangrove fern, Piai raya	Pteridaceae	Fern	[13,14]

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4	*Aegiceras corniculatum*	River mangrove, Kacang-kacang	Primulaceae	Shrub	[5]
5	*Avicennia alba*	Api-api putih	Avicenniaceae	Tree	[15]
6	*Avicennia marina*	Grey or white mangrove	Avicenniaceae	Tree	[16]
7	*Avicennia rumphiana*	Velvety mangrove, Api-api bulu	Avicenniaceae	Tree	[17]
8	*Bruguiera gymnorhiza*	Oriental mangrove, Tumu merah	Rhizophoraceae	Tree	[18]
9	*Bruguiera sexangula*	Upriver orange mangrove	Rhizophoraceae	Tree	[5]
10	*Ceriops tagal*	Indian mangrove, Tengar	Rhizophoraceae	Tree	[19]
11	*Excoecaria agallocha*	Milky mangrove, Bebuta	Euphorbiaceae	Tree	[20]
12	*Heritiera fomes*	Sundari, Sundri, Sunder	Malvaceae	Tree	[5]
13	*Lumnitzera racemosa*	Black mangrove, Terentum putih	Combretaceae	Tree	[5]
14	*Nypa fruticans*	Nipa palm, Golpata	Arecaceae	Palm	[18]
15	*Rhizophora apiculata*	Tall stilt mangrove, Bakau minyak	Rhizophoraceae	Tree	[18,21]
16	*Rhizophora mucronata*	Loop stilt mangrove, Bakau kurap	Rhizophoraceae	Tree	[18]
17	*Rhizophora stylosa*	Long-style stilt mangrove	Rhizophoraceae	Tree	[22,23]
18	*Syphiphora hydrophyllacea*	Chingam, Nilad	Rubiaceae	Shrub	[5]
19	*Xylocarpus granatum*	Cannon ball mangrove	Meliaceae	Tree	[24,25]
20	*Xylocarpus moluccensis*	Cedar mangrove, Nyireh batu	Meliaceae	Tree	[5]
	Associate species				
1	*Aglaia cucullata (Amoora cucullata)*	Pacific maple	Meliaceae	Tree	[26]
2	*Anacardium occidentale*	Cashew nut	Anacardiaceae	Tree	[27]
3	*Artocarpus altilis*	Breadfruit	Moraceae	Tree	[28]
4	*Barringtonia asiatica*	Sea poison tree, Putat laut	Lecythidaceae	Tree	[5]
5	*Barringtonia racemosa*	Powder puff tree, Common putat	Lecythidaceae	Tree	[5]
6	*Caesalpinia crista*	Squirrel's claws, Kuku tupai	Fabaceae	Tree	[29]
7	*Calophyllum inophyllum*	Beach calophyllum, Penaga laut	Clusiaceae	Tree	[30]

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8	*Cerbera manghas*	Sea mango, Bintaro	Apocynaceae	Tree	[31]
9	*Cerbera odollam*	Pong-pong, Suicide tree	Apocynaceae	Tree	[31]
10	*Cynometra ramiflora*	Wrinkle pod mangrove	Fabaceae	Tree	[5]
11	*Ficus microcarpa*	Chinese banyan, Curtain fig	Moraceae	Tree	[32]
12	*Garcinia subelliptica*	Happiness tree, Fukugi	Clusiaceae	Tree	[33]
13	*Ipomoea pes-caprae*	Beach morning glory, Goat's foot	Convolvulaceae	Creeper	[34]
14	*Morinda citrifolia*	Indian mulberry, Mengkudu	Rubiaceae	Tree	[5]
15	*Phoenix paludosa*	Mangrove date palm	Arecaceae	Tree	[35]
16	*Planchonella obovata*	Sea gutta, Menasi	Sapotaceae	Tree	[5]
17	*Pluchea indica*	Marsh fleabane, Camphorweed	Asteraceae	Shrub	[36]
18	*Pongamia pinnata* (*Derris indica*)	Pongam, Indian beech	Fabaceae	Tree	[5]
19	*Sphagneticola triloba* (*Wedelia triloba*)	Yellow creeping daisy	Asteraceae	Herb	[37]
20	*Spinifex littoreus*	Hairy spinifex, Beach spinifex	Poaceae	Grass	[38]
21	*Talipariti tiliaceum* (*Hibiscus tiliaceus*)	Sea hibiscus, Chinese hibiscus	Malvaceae	Tree	[39,40]
22	*Terminalia catappa*	Sea almond, Ketapang	Combretaceae	Tree	[18]
23	*Thespesia populnea*	Portia tree, Milo, Bebaru	Malvaceae	Tree	[30]
24	*Vitex trifolia* (*V. ovata*, *V. rotundifolia*)	Common blue vitex, Legundi	Lamiaceae	Shrub	[34,41]
25	*Volkameria inermis* (*Clerodendrum inerme*)	Wild jasmine, Bengali	Lamiaceae	Shrub	[42]
26	*Ximenia americana*	Sea lime, Sea lemon	Olacaceae	Shrub	[5]

3. Anticancer Effects and Mechanisms of Mangrove Species

In this review article, a total of 20 mangrove plant species belonging to 13 genera and 11 families possess anticancer properties (Table 2). They include three species of *Rhizophora* (*R. apiculata*, *R. mucronata* and *R. stylosa*), three species of *Avicennia* (*A. alba*, *A. marina* and *A. rumphiana*), and two species of *Xylocarpus* (*X. granatum* and *X. moluccensis*). Most often reported mangrove species are *A. marina* and *C. tagal* with five and four studies, respectively. Cancer cells most commonly studied are

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WiDr colon cancer cells reported in *A. corniculatum*, *A. alba*, *A. marina*, *A. rumphiana*, *C. tagal*, *N. fruticans* and *R. mucronata*.

Effects and mechanisms of anticancer properties reported in mangrove species include induction of oxidative stress and mitochondrial dysfunction, reduced production of reactive oxygen species and tumor, cytotoxicity, genotoxicity, cell cycle arrest, apoptosis, autophagy, anti-proliferative effects, anti-inflammation and antimetastatic activities [43].

Table 2. Anticancer effects and mechanisms of extracts and bioactive compounds of mangrove species.

No.	Species	Effect and mechanism	Ref.
1	*Acanthus ebracteatus*	The ethyl acetate leaf extract displayed cytotoxicity and antiproliferative activity and induced apoptosis against HeLa cervical cancer cells with an IC_{50} value of 34.4 μg/mL.	[44]
2	*Acanthus ilicifolius*	Administration of the ethanol leaf extract (500 mg/kg) was found to reduce EAT in mice. The maximum increase in life span of EAT mice was 75%.	[45]
		Alkaloids (acanthosides A–D) from the ethanol root extract were cytotoxic to HepG2 liver, HeLa cervical and A549 lung cancer cells. Acanthosides A and B were the most cytotoxic to HepG2 liver cancer cells with IC_{50} values of 7.8 and 9.6 μM, respectively.	[46]
		The aqueous root extract inhibited the growth and induced apoptosis of HepG2 liver cancer cells with an IC_{50} value of 39.8 μg/mL.	[47]
3	*Acrostichum aureum*	The ethyl acetate leaf extract displayed cytotoxic and antiproliferative activity against HeLa cervical cancer cells with an IC_{50} value of 6.3 μg/mL.	[48]
		The methanol root extract exhibited cytotoxicity against AGS gastric cancer cells with an IC_{50} value of 1.0 mg/mL.	[49]
		Pterosin C, a sulphated sesquiterpene from the methanol leaf extract, was cytotoxic to AGS gastric cancer cells with an IC_{50} value of 23.9 μM.	[50]
4	*Aegiceras corniculatum*	The methanol bark extract showed cytotoxicity against HT29 colon and MDA-MB-435 breast cancer cells with IC_{50} values were 0.33 and 0.66 mg/mL, respectively.	[49]
		Five alkylated benzoquinones from the petroleum ether extract of stem and twig displayed cytotoxic activity towards HepG2 liver, BGC-823 gastric and A2780 ovarian cancer cells, and HL-60 leukemia cells. Strongest cytotoxicity was 5-*O*-methylrapanone with an IC_{50} value of 7.6 μM against HL-60 cells.	[51]
		The methanol leaf extract inhibited HeLa cervical, T47D breast and WiDr colon cancer cells with IC_{50} values of 49.4, 78.1 and 45.6 μg/mL.	[52]

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5	*Avicennia alba*	The methanol leaf extract inhibited HeLa cervical, T47D breast and WiDr colon cancer cells with IC_{50} values of 74.7, 50.8 and 73.2 µg/mL.	[52]
		Against MCF-7 breast cancer cells, the diethyl ether leaf extract displayed the strongest cytotoxicity, followed by butanol and methanol leaf extracts with IC_{50} values of 25.1, 27.1 and 28.9 µg/mL, respectively.	[53]
6	*Avicennia marina*	Stenocarpoquinone B and avicequinone C from the methanol twig extract showed strong antiproliferative activities against HeLa cervical cancer cells (4.3 and 0.2 µg/mL) and K562 leukemia cells (3.2 and 1.1. µg/mL), respectively.	[54]
		The ethanol leaf extract exhibited weak cytotoxicity in HL-60 leukemia cells with IC_{50} values of 600, 400 and 280 µg/mL after 24, 48 and 72 h, respectively.	[55]
		The ethyl acetate leaf extract induced apoptosis and inhibited migration of breast (AU565, MDA-MB-231 and BT483) and liver (HepG2 and Huh7) cancer cells. Antitumor activity was also observed in a xenograft mouse model of MDA-MB-231.	[56]
		From the chloroform : methanol (2:1) leaf extract, isolated PIP exhibited weak anticancer activity against WiDr cells with an IC_{50} value of 155 µg/mL. Mechanisms of the anticancer activity involved inhibition of cell cycle and induction of apoptosis.	[57]
		Lupeol, a pentacyclic triterpene, isolated from the hexane stem extract suppressed the growth of Hep3B liver cancer cells *via* induction of apoptosis, triggering the apoptotic pathway and down-regulating of BCL-2 expression.	[58]
7	*Avicennia rumphiana*	PIP isolated from the chloroform : methanol (2:1) leaf extract exhibited anticancer activity against WiDr cells with an IC_{50} value of 306 µg/mL. Mechanisms of the anticancer activity involved inhibition of cell cycle and induction of apoptosis.	[57]
8	*Bruguiera gymnorhiza*	Butanol, diethyl ether and methanol leaf extracts exhibited cytotoxicity against the MCF-7 breast cancer cells with IC_{50} values of 3.4, 16.2 and 37.1 µg/mL. Mechanisms included the induction of apoptosis and up-regulation of caspases.	[59]
9	*Bruguiera sexangula*	From the ethanol and chloroform stem and bark extracts, brugine, a sulphur-containing alkaloid, exerted anticancer activity against effects against sarcoma 180 and Lewis lung carcinoma cell *via* the calcium, cAMP and PI3K-Akt signaling pathways.	[60]
10	*Ceriops tagal*	From the ethanol extract of the embryo, betulin and 3-*epi*-betulinic acid acetate inhibited H-7402 liver and HeLa cervical cancer cells	[61]

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		with IC_{50} values of 14.4 and 11.8 μg/mL, and 10.0 and 11.3 μg/mL, respectively.	
		Dolabrane-type diterpenes tagalenes A–F isolated from the ethanol extract of twig and leaf exhibited potent inhibition against a panel of tumor cell lines. Tagalene C was most potent with IC_{50} values of 3.7, 6.3 and 5.5 μM against HCT-8 colon, Bel-7402 liver and A2780 ovarian cancer cells, respectively.	[62]
		PIP from the chloroform : methanol (2:1) leaf extract exhibited weak cytotoxicity against WiDr colon cancer cells with IC_{50} value of 276 μg/mL. Mechanisms involved apoptosis, cell cycle arrest, and decreased expression of Bcl-2 and cyclin D1.	[63]
		Dolichol, a PIP isolated from the chloroform : methanol (2:1) leaf extract, exhibited cytotoxicity against WiDr colon cancer cells by reducing G0/G1 growth cycle, up-regulation of p53 expression, and down-regulation of EGFR, PI3K, Akt and mTOR expression.	[64]
11	*Excoecaria agallocha*	The ethanol stem extract exhibited potent cytotoxicity against capan-1 and miapaca-2 pancreatic cancer cells with IC_{50} values of 4.0 and 7.0 μg/mL, respectively.	[65]
		Two flavonoid glycosides isolated from the methanol leaf extract displayed HH inhibition with IC_{50} values of 0.5 and 2.0 μM. Cytotoxicity was IC_{50} values of 0.7 and 1.8 μM against PANC1 pancreatic, and 0.8 and 2.4 μM against DU145 prostate cancer cells.	[66]
12	*Heritiera fomes*	Methanol leaf and stem extracts possessed anticancer properties with 40% inhibition against B16 mouse melanoma and against Swiss albino mice with EAT.	[67]
13	*Lumnitzera racemosa*	The aqueous leaf extract inhibited HepG2 liver cancer cells with an IC_{50} value of 26.0 μg/mL. Viability of cancer cells was 40% at 100 μg/mL of extract.	[47]
		1,5,6-Trihydroxy-3-methoxyxanthone and polygalatenoside E isolated from the methanol leaf extract were cytotoxic to HL-60 leukemia cells with IC_{50} values of 0.15 and 0.60 μM, respectively.	[68]
		The methanol leaf extract exerted moderate cytotoxicity against MCF-7 breast and HeLa cervical cancer cells with IC_{50} values of 46.1 and 59.5 mg/mL, respectively.	[69]
14	*Nypa fruticans*	PIP from the chloroform : methanol (2:1) leaf extract exhibited anticancer activity towards WiDr colon cancer cells with IC_{50} value of 180 μg/mL *via* inhibition of COX-2.	[70]
		PIP from the chloroform : methanol (2:1) leaf extract inhibited WiDr colon cancer cells by modulating the expression of p53, EGFR, PI3K, AKT1 and mTOR.	[71]

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15	*Rhizophora apiculata*	2,6-Dimethoxy-1,4-benzoquinone isolated from the methanol leaf extract exhibited inhibitory effects against SK-LU-1 lung, HepG2 liver and MCF-7 breast cancer cells with IC_{50} values of 13.1, 14.8 and 8.3 μM, respectively.	[72]
		The methanol leaf extract inhibited metastasis in B16F-10 melanoma bearing mice by inhibiting pulmonary tumor nodule formation and increasing the survival rate of mice.	[73]
16	*Rhizophora mucronata*	PIP from the chloroform : methanol (2:1) leaf extract, exhibited weak exhibited cytotoxicity against WiDr colon cancer cells with IC_{50} value of 278 μg/mL. Mechanisms are by inducing apoptosis, cell cycle arrest, and decreasing the expression of Bcl-2 and cyclin D1.	[63]
		Dolichol, a PIP from the chloroform : methanol (2:1) leaf extract, reduced the G0/G1 growth cycle of WiDr colon cancer cells by 82%. Mechanisms were *via* up-regulation of p53 expression, and down-regulation of EGFR, PI3K, Akt and mTOR expression.	[64]
		The methanol leaf extract and stem extract exhibited weak anticancer effects. Their IC_{50} values were 127 and 107 μg/mL for CaCo-2 colon cancer cells, and 158 and 138 μg/mL for MCF-7 breast cancer cells. Against A549 lung cancer cells, the anticancer effect of the stem extract was 2.4 times stronger than the leaf extract.	[74]
17	*Rhizophora stylosa*	Of the compounds isolated from the leaves, taraxerol inhibited HeLa cervical and BGC-823 gastric cancer cells, both with an IC_{50} value of 73.4 μmol/L. Cis-careaborin inhibited BGC-823 cancer cells with an IC_{50} value of 45.9 μmol/L.	[75]
18	*Syphiphora hydrophyllacea*	Hopenone-I, a triterpenoid isolated from the hexane leaf extract, was cytotoxic against MCF-7 breast, HepG2 liver and AN3CA endometrial cancer cells with IC_{50} values of 7.8, 11.6 and 5.0 μM, respectively .	[76]
		UA and EA from hexane and chloroform extracts of leaves showed strong cytotoxic effects. IC_{50} values of UA were 8.5 and 7.8 μg/mL against MCF-7 breast cancer cells, and IC_{50} values of EA were 8.9 and 10.1 μg/mL against NCI-H292 lung cancer cells. IC_{50} values of paclitaxel used as a positive control were 4.3 and 10 μg/mL.	[77]
19	*Xylocarpus granatum*	Four limonoid compounds from the fruit strongly, inhibited the proliferation of Eca109 esophageal cancer cells, with xylogranatin C having the strongest activity (IC_{50} value of 9.5 μmol/L). Mechanism involved apoptosis *via* the DR and ER pathways.	[78]
		Gedunin isolated from the aqueous ethanol fruit extract strongly inhibited the anti-proliferative activity of PA-1 ovarian cancer cells	[79]

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		with IC_{50} value of 8.1 μM *via* G2/M-phase arrest and oxidative stress-mediated intrinsic apoptosis.	
		The ethyl acetate extract of leaves inhibited HeLa cervical and MCF-7 breast cancer cells by 92.9% and 96.6%, respectively. Inhibition by Dox used as a positive control was 95.7% and 94.0%.	[80]
20	*Xylocarpus moluccensis*	The methanol extract of pneumatophores showed cytotoxicity against AGS gastric and MDA-MB-435S melanoma cancer cells with IC_{50} values of 0.6 and 1.1 mg/mL, respectively.	[49]
		Two novel 30-ketophragmalins (limonoids) isolated from the ethanol seed extract exhibited anticancer activity against MDA-MB-453 breast cancer cells with IC_{50} values of 2.1 and 9.0 μM. The anticancer activity of 30-ketophragmalins against breast cancer cells has been reported for the first time.	[81]
		The diethyl ether leaf extract displayed strong cytotoxicity with an IC_{50} value of 0.22 μg/mL. The methanol leaf extract was much weaker at < 30 μg/mL. Mechanisms involved induction of apoptosis and activation of caspases.	[82]

Abbreviations: Akt: protein kinase B, cAMP: cyclic adenosine 3,5-monophosphate, COX: cyclooxygenase, Dox: doxorubicin, DR: death receptor, EA: eichlerianic acid, EAT: Ehrlich ascites tumor, EGFR: epidermal growth factor receptor, ER: endoplasmic reticulum, HH: hedgehog, mTOR: mammalian target of rapamycin, PI3K: phosphoinositide 3-kinase, PIP: polyisoprenoid and UA: ursolic acid.

In this article, a total of 26 mangrove associate species with anticancer properties belonging to 24 genera and 17 families have been recorded (Table 3). The genera with two species are *Cerbera* (*C. manghas* and *C. odollam*). The most reported mangrove associate species are *T. tiliaceum* or *H. tiliaceus* with four studies, followed by *A. occidentale*, *A. altilis*, *C. manghas*, *P. indica* and *P. pinnata* with three studies each.

Table 3. Anticancer effects and mechanisms of extracts and bioactive compounds of mangrove associate species.

No.	Species	Effect and mechanism	Ref.
1	*Aglaia cucullata*	Two rocaglamide derivatives isolated from the successive hexane and DCM fruit extract exhibited potent cytotoxicity against KB oral and BC breast cancer cells with IC_{50} values of 0.002 and 0.005 μg/mL, and 0.06 and 0.002 μg/mL, respectively.	[83]
		1-*O*-Formylrocagloic acid from the methanol leaf extract displayed potent cytotoxic activity in TRAIL-resistant AGS gastric cancer cells by activating caspase-3/7, enhancing apoptosis, and expressing DR4 and DR5 mRNA.	[84]
2	*Anacardium occidentale*	The ethanol leaf and bark extracts exhibited cytotoxic activity against HL-60 leukemia (79% and 85%) and HCT116 colon (89% and 91%) cancer cells, respectively. The inhibition of extracts was comparable with curcumin (both 92%) used as a positive control.	[85]

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		Zoapatanolide A, a sesquiterpene lactone isolated from the ethanol leaf extract, exhibited anticancer effects on HeLa cervical cancer cells with an IC_{50} value of 36.2 μM.	[86]
		PGG isolated from the ethanol leaf extract exerted cytotoxic activity against HeLa cervical and MRC5-SV2 lung cancer cells with IC_{50} values of 71.4 and 52.2 μg/mL, respectively. Cytotoxicity of PGG was due to the generation of ROS and to oxidative stress in the cancer cells.	[87]
3	*Artocarpus altilis*	The diethyl ether wood extract inhibited the growth of T47D breast cancer cells with an IC_{50} value of 6.2 μg/mL by inducing sub-G1 apoptosis.	[88]
		The leaf and stem methanol extract, and the isolated GD inhibited the growth of DU145 prostate cancer cells with IC_{50} values of 20 μg/mL and 20 μM by inducing apoptosis *via* caspase-3 and PARP degradation. GD also inhibited *in vivo* tumor growth in DU145 cell xenograft mouse model.	[89]
		Isolated from the acetone stem bark extract, artonin E and artobiloxanthone inhibited SAS oral and T.Tn. esophageal cancer cells with IC_{50} values of 6.0 and 8.0 μM, and 11 and 22 μM, respectively. Mechanisms involved cell cycle arrest, apoptosis, and inhibition of invasion and migration of cancer cells.	[90]
4	*Barringtonia asiatica*	A mixture of betulinic acid and 22-*O*-tigloylcamelliagenin A from the DCM bark extract inhibited HCT116 colon and A549 lung cancer cells with IC_{50} values of 8.0 and 6.0 μg/mL, respectively.	[91]
		The methanol seed extract induced cell cycle arrest in yeast cells and inhibited A2780 ovarian carcinoma cells with an IC_{50} value of 35 μg/mL.	[92]
5	*Barringtonia racemosa*	The methanol fruit extract exhibited cytotoxicity and inhibited the growth of MCF-7 breast cancer cells with an IC_{50} value of 57.6 μg/mL.	[93]
6	*Caesalpinia crista*	Two cassane diterpenoids isolated from the $CHCl_3$: methanol (1:1) extract of aerial parts displayed moderate cytotoxic activity towards HL-60 leukemia cells and HeLa cervical cancer cells, with IC_{50} values of 17.4 and 33.4 μM, and 19.8 and 33.9 μM, respectively.	[94]
7	*Calophyllum inophyllum*	Among ten 4-phenylcoumarins isolated from the DMSO aerial part extract and screened for inhibition of EBV-EA activation in TPA-activated Raji cells, eight exhibited inhibitory activity. Calocoumarin A was the most potent and it also markedly inhibited mouse skin carcinogenesis.	[95]
		From the chloroform : methanol (2:1) root bark and fruit extract, calophyllolide, caloxanthone A and inophylloidic acid inhibited KB nasopharynx cancer cells with IC_{50} values of 3.5, 7.4 and 9.7 μg/mL, respectively. Inoxanthone and macluraxanthone were devoid of cytotoxic activity.	[96]

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8	*Cerbera manghas*	Cardenolide glycosides from the CH_2Cl_2 extract of seeds, 7,8-dehydrocerberin, deacetyltanghinin and tanghinin were cytotoxic towards KB oral, BC breast and NCI-H187 lung cancer cells. Most cytotoxic were 7,8-dehydrocerberin against BC cells (0.001 μg/mL), deacetyltanghinin against BC cells (0.77 μg/mL) and tanghinin against KB cells (0.05 μg/mL).	[97]
		Neriifolin from the methanol seed extract induced cell cycle arrest and apoptosis in HepG2 liver cancer cells with an IC_{50} value of 0.15 μg/mL. Apoptosis was induced *via* the activation of caspases, and the up-regulation of Fas and FasL expression.	[98]
		Ethanol extracts of stems and fruits, and isolated neriifolin effectively inhibited the viability of glioblastoma cells and in mouse xenograft model. Cytotoxicity of extracts was 8.0 and 0.38 μg/mL against U251-MG cells, and 46 and 2.7 μg/mL against U373-MG cells, respectively. Cytotoxicity of the fruit extract was stronger than the stem extract.	[99]
9	*Cerbera odollam*	Cardenolide glycosides from the CH_2Cl_2 seed extract, exerted potent cytotoxicity towards KB oral, BC breast and NCI-H187 lung cancer cells. IC_{50} values were 17α-neriifolin (0.08, 0.05 and 0.03 μg/mL) and 17β-neriifolin (0.02, 0.05 and 0.08 μg/mL), respectively.	[100]
		17βH-neriifolin, a cardenolide glycoside, isolated from the hexane leaf extract, displayed potent anticancer properties against a panel of MCF-7 breast, T47D breast, HT-29 colon, A2780 ovarian, SKOV-3 ovarian and A375 skin cancer cells. IC_{50} values ranged from 0.02–0.03 μM.	[101]
10	*Cynometra ramiflora*	Cytotoxicity of the ethanol stem bark extract was strongest against T47D breast cancer cells (0.9 μg/mL) while that of the leaf extract was strongest against WiDr colon cancer cells (0.4 μg/mL).	[102]
11	*Ficus microcarpa*	Triterpenes from the methanol extract of aerial roots possessed significant cytotoxic activities against HONE-1 nasopharyngeal, KB oral epidermoid and HT29 colon cancer cells with IC_{50} values of 4.0–9.4 μM. Ursonic acid was the most potent.	[103]
12	*Garcinia subelliptica*	The ethanol leaf extract elicited cytotoxicity but not apoptosis in A549 and SNU2292 lung cancer cells. Mechanisms are by inducing autophagy, activating AMPK and suppressing mTOR pathways.	[104]
		The methanol leaf extract was cytotoxic towards THP-1 and Jurkat leukemia cells. Garcinielliptone G, a benzylphloroglucinol, inhibited these cancer cells by inducing apoptosis, and activation of caspase-3 and PARP.	[105]
13	*Ipomoea pes-caprae*	Pescapreins from the ethanol extract of aerial parts modulated multi-drug resistance in MCF-7/ADR adriamycin resistant breast cancer cells. The combined use of these compounds at 5 μg/mL increased the cytotoxicity of doxorubicin (anticancer drug) by 1.5–3.7 times.	[106]

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14	*Morinda citrifolia*	Morindone, an anthraquinone from the root bark, extracted with four different solvents, inhibited a panel of HCT116, LS174T and HT29 colon cancer cells with IC_{50} values of 10.7, 20.5 and 19.2 μM, respectively.	[107]
15	*Phoenix paludosa*	Against MCF-7, MDA-MB-231 and SK-BR-3 breast, HEK-293 renal and ACHN kidney cancer cells, the methanol leaf extract displayed the stronger cytotoxic effects than hexane, chloroform and ethyl acetate extracts. Activity was however weaker than paclitaxel, used as a positive control.	[108]
16	*Planchonella obovata*	Three triterpenoid glycosides (6β-hydroxy-conyzasaponin N, mi-saponin A and ursolic acid) from the ethanol leaf extract showed moderate inhibitory activities against HL-60 leukemia cells with IC_{50} values of 16.9, 15.5 and 12.7 μM, respectively.	[109]
17	*Pluchea indica*	The aqueous extract of leaves and roots are cytotoxic to GBM8401 glioblastoma and HeLa cervical cancer cells with 75% and 70% inhibition. Mechanisms included promotion of apoptosis, and suppression of cell proliferation, viability and migration.	[110]
		The ethanol root extract induced apoptosis, anti-proliferation, and migration of NPC-TW 01 and NPC-TW 04 nasopharyngeal carcinoma cells. Cytotoxicity was moderate with IC_{50} values of 108 and 93.2 μg/mL, respectively. Mechanisms are by inducing apoptosis, up-regulating the level of p53 and Bax, and down-regulating the level of Bcl-2.	[111]
		The hexane fraction of the ethanol root extract weakly inhibited proliferation and induced autophagy of U87 and GBM glioblastoma cells. IC_{50} values were 353 and 334 μg/mL, respectively. The fraction suppressed the proliferation of GBM cells by inducing cell cycle arrest and autophagy.	[112]
18	*Pongamia pinnata*	LC, a natural chalcone isolated from the root, exhibited inhibition against H292 lung cancer cells with an IC_{50} value of 10 μM. Cytotoxic activity involved reduction of proliferation by inducing apoptosis, and by modulating caspase-3/-9 pathway. LC also inhibited tumor growth in S180-bearing mice.	[113]
		Pongapin and karanjin, furanoflavanoids from the seed extract, inhibited cell growth against MDA-MB-231 breast, HeLa cervical, NCI H460 and HepG2 liver cancer cells with IC_{50} values of 16.9−39.3 μg/mL and 47.0−63.0 μg/mL, respectively.	[114]
		Pinnatin, a flavonoid isolated from the ethyl acetate fruit extract, displayed potent cytotoxicity against KKU-100 bile duct and HepG2 liver cancer cells with IC_{50} values of 6.0 and 9.0 μg/mL, respectively.	[115]
19	*Sphagneticola triloba*	Wedebicosides A–C and E, new phenolic glycosides isolated from the ethanol flower extract, inhibited MCF-7 breast, HeLa cervical and NCI-H460 lung cancer cells. IC_{50} of wedebicoside C was 27.2, 42.4 and 27.5 μg/mL, respectively.	[116]

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20	*Spinifex littoreus*	Hexane extract of flowers moderately inhibited MCF7 breast and HepG2 liver cancer cells with IC_{50} values of 45.1 and 70.4 μg/mL, respectively.	[117]
21	*Taliparitiliaceum*	HA and HI were isolated from the methanol stem wood extract. HA displayed cytotoxic activity against P388 murine leukemia and HT-29 colon cancer cells with IC_{50} values of 1.7 and 3.8 μg/mL, respectively. HI was only cytotoxic to P388 cells (10.2 μg/mL).	[118]
		Among three tetracyclic triterpenoids isolated from the methanol leaf and branch extracts, the analogue of tiliacol A had potent cytotoxicity against P388 murine leukemia, K562 leukemia and HeLa cervical cancer cells with IC_{50} values of 11.2, 13.5 and 11.5 mmol/L, respectively.	[119]
		HO A–C from the DCM stem extract exhibited cytotoxic activity against MDA-MB-231 breast, HepG2 liver and Huh-7 liver cancer cells with IC_{50} values ranging from 3.1–10.7 μM, 3.5–8.4 μM and 4.9–10.7 μM, respectively.	[120]
		Five cadinane sesquiterpenoids isolated from the DCM stem extract displayed cytotoxic activity against HepG2 and Huh7 liver cancer cells with IC_{50} values ranging from 3.5–6.8 μM.	[121]
22	*Terminalia catappa*	The ethanol leaf extract exerted anti-metastatic effects on A549 and LLC lung cancer cells by inhibiting the expression of MMP-2 and PAI-1. Cytotoxicity against A549 and LLC cells was not significant and 14.5 μg/mL, respectively. The extract also inhibited tumor growth in LLC-bearing mice.	[122]
		The DMSO leaf extract exerted very low anti-metastatic effects on HeLa and SiHa cervical cancer cells by inhibiting the expression of MMP-9 *via* the ERK1/2 pathway.	[123]
23	*Thespesia populnea*	Among sesquiterpenoids isolated from the DCM extract of wood and heartwood, mansonone E exhibited significant anticancer activities against MCF-7 breast (0.05 μg/mL) and HT-29 colon (0.18 μg/mL) cancer cells. (+)-Gossypol was strongly cytotoxic to HeLa cervical and KB oral squamous cancer cells with IC_{50} values of 0.08 and 0.04 μg/mL, respectively.	[124]
24	*Vitex trifolia*	Hexane and DCM extracts of leaf and stem displayed cytotoxicity. Strongest cytotoxic activity was DCM leaf extract against KB prostate cancer cells (1.9 μg/mL), DCM stem extract against HCT-15 colon cancer cells (1.9 μg/mL), hexane leaf extract against HCT-15 colon cancer cells (3.6 μg/mL) and hexane stem extract against HCT-15 colon cancer cells (2.8 μg/mL).	[125]
		Against MCF-7 breast and HT-29 colon cancer cells, the methanol leaf extract showed cytotoxic activities with IC_{50} values of 78.8 and 77.5 μg/mL. Against WRL-68 normal liver cells, cytotoxicity of the extract was 78.3 μg/mL.	[126]

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25	*Volkameria inermis*	Against A549 lung cancer cells, the ethanol leaf extract displayed cytotoxicity with an IC_{50} value of 15.6 μg/mL.	[127]
		HWA from the methanol extract of leaves was strongly cytotoxic to HCT116 colon cancer cells with an IC_{50} value of 3.5 μM.	[128]
26	*Ximenia americana*	The aqueous leaf extract strongly inhibited MCF-7 breast and CC531 colon cancer cells, including BV173 leukemia cells with IC_{50} values of 1.7, 3.3 and 1.8 μg/mL, respectively. No cytotoxicity was observed against MCF-10 non-tumorigenic epithelial cells.	[129]

Abbreviations: ADP: adipose, AMPK: AMP-activated protein kinase, Bax: Bcl-2–associated X protein, CH_2Cl_2: methylene chloride, DCM: dichloromethane, DMSO: dimethyl sulphoxide, DR: death receptor, EA: early antigen, EBV: Epstein-Barr virus, ERK: extracellular signal-regulated kinase, FasL: Fas ligand, HI: hibiscusin, HA: hibiscusamide, HO: hibisceusones, HWA: hardwickiic acid, LLC: Lewis lung carcinoma, GD: geranyl dihydrochalcone, LC: lonchocarpin, MAPK: mitogen-activated protein kinase, MMP: matrix metalloprotein, mRNA: messenger ribonucleic acid, mTOR: mammalian target of rapamycin, PAI: plasminogen activator inhibitor, PARP: poly-ADP-ribose polymerase, PGG: pentagalloylglucose, ROS: reactive oxygen species, TNF: tumor necrosis factor, TPA: 12-*O*-tetradecanoylphorbol-13-acetate and TRAIL: TNF-related apoptosis-inducing ligand.

In the conservation of mangrove and associate species with anticancer properties, two approaches can be adopted. In *in-situ* conservation, species are protected in their natural surroundings as ecosystems while in *ex-situ* conservation, species are protected outside their natural habitats [130]. *In-situ* and ex-situ conservation strategies are a comprehensive approach towards conservation of wildlife, biodiversity and sustainable use of natural resources [131].

Ex-situ conservation *via* botanical gardens and arboreta is appropriate for protecting rare, endangered and threatened species such as *A. rumphiana* that also has anticancer properties. Previously known as *A. lanata*, the species has dense tomentose at the underside leaves and is only found at Bagan Lalang at the southernmost part of Selangor [132]. Biodiversity refers to the variety of flora and fauna, their habitats and interrelationships between organisms and the environment. The conservation of biodiversity *via in-situ* conservation is important when the ecosystem is being degraded by human development and economic activities. Other advantages of *in-situ* conservation of mangroves are safeguarding livelihoods, sequestering carbon, and protecting coastal areas against sea level rise, climate change, extreme weathers, storms and coastal erosion [133].

An example of *ex-situ* conservation of mangroves is the King Rama IX International Mangrove Botanical Garden (King Rama IX-IMBG) in Chanthaburi province, Thailand. Covering an area of 83 ha, the garden is managed by the Department of Marine and Coastal Resources [134]. King Rama IX-IMBG is the world's first mangrove botanical garden and it serves as an arboretum for mangrove forest plants worldwide, and functions as a learning and research centre for mangrove conservation and rehabilitation. The Ranong mangroves (19,310 ha in area) are an *in-situ* mangrove area in southern Thailand [135]. Designated a biosphere reserve in 1997 and drained by the Klong Ngao tidal creek, the Ranong mangroves are not pristine, but they retain a high level of biodiversity and productivity.

In situ conservation of mangrove areas in Malaysia include virgin jungle reserves (VJRs) and Ramsar sites. VJRs are located in Perak (Pulau Kecil, 40 ha) [136] and in Sabah (Sepilok Laut, 1,200 ha; Sungai Gologob, 8,100 ha; and Batumapun 160 ha) [137]. Ramsar sites are located in Sungai Pulai (9,100 ha), Johor and in Lower Kinabatangan-Segama (78,800 ha), Sabah. Dryland mangroves (2,200 ha) in Matang, Perak are protected old-growth reserves, rich in species diversity of mangrove and other coastal species [138]. In Sumatra, Indonesia, mangrove conservation takes the form of community-based mangroves managed for silvo-fisheries and for eco-tourism [139,140].

In-situ mangrove forest reserves have also been reported elsewhere. The Can Gio Biosphere Reserve (CGBR) near Ho Chi Minh City, Vietnam [141], and Kanhlyashay natural mangrove forest

 doi:10.20944/preprints202410.0045.v2

in Kungyangon township, Myanmar [142], are also examples of *in-situ* mangrove forest conservation. Mangrove species found in Can Gio are *A. ebracteatus*, *R. apiculata* and *T. populnea*. Those found in Kanhlyashay include *A. corniculatum*, *A. alba* and *B. sexangula*. It is important to note that these mangrove and associate species are reported to possess anticancer properties in this article.

The CGBR is 57,000 ha in area, and consists of core, buffer and transition zones. It plays an important role in protecting the coast from damage caused by storms, floods, waves, erosion and sea level rise, as well as safeguarding local communities, properties and infrastructures [141]. Covering 197 ha, Kungyangon is a natural mangrove regrowth following the destruction by Cyclone Nargis in 2008. The forest serves as a natural barrier against natural disasters such as sea-level rise, storm surges, coastal erosion and floods. It also protects properties and livelihoods in the Letkhutkon village. [142].

3. Conclusions

There are promising prospects in conducting further research on the anticancer properties of mangrove and associate species. The *in vitro* anticancer properties of extracts in terms of cytotoxicity against different cancer cells are fairly well-studied. *In vivo* studies using animal models are very few and there is no clinical evidence based on clinical trials. The isolation of novel bioactive compounds and the analysis their anticancer properties based on their effects and mechanisms involving molecular targets and pathways present an exciting field of research. Equally challenging is to determine their molecular targets and mechanisms, and to conduct molecular docking studies. The structure activity relationships (SAR) of compounds are worthy of further research. The anticancer efficacy of natural plant compounds when used in combination with other anticancer drugs is another challenging topic for research. When bioactive compounds with anticancer properties are isolated from mangrove and associate species, determination of their chemical structures would be a logical step. Initial efforts in developing protocols to synthesize these anticancer compounds are yet to be conducted and is currently beyond research reality.

Author Contributions: Conceptualization, H.T.; compilation of data and references, S.K.; revising, H.T.; writing—original draft preparation, H.T., S.K., W.C.; writing—review and editing, H.T., W.C.; project administration, H.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The article contains all available data.

Acknowledgment: The authors are thankful to the management of the International Society for Mangrove Ecosystems (ISME), Xiamen University Malaysia and UCSI University for allowing the publication of this article.

Conflicts of Interest: The authors do not have any conflicts of interest.

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