ISSN 1880-7682
Volume 21, No. 1 **June 2023**

Mangrove and other coastal plant species with anti-cancer properties: An overview

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1. Background

Mangroves are tidal forests of tropical and sub-tropical muddy shores. Mangrove plant species can be categorized into true mangroves and mangrove associates. True mangroves are exclusive species that are adapted to the tidal mangrove habitat, and do not extend into other coastal environments such as sandy beaches and rocky shores. Plants that occur in the coastal environments and also within mangroves are considered as mangrove associates or non-exclusive species [1,2].

In terms of latitudinal distribution of mangroves, those in Japan represent the northernmost limit of the world mangroves. They occur in the Okinawa and Kagoshima Prefectures in the southern part of the country. The total area of mangroves in Japan is 744 ha. Species commonly found on the islands of Ishigaki, Iriomote, Okinawa, and Miyako of the Okinawa Prefecture are *Bruguiera gymnorhiza*, *Excoecaria agallocha*, *Heritiera littoralis*, *Kandelia obovata*, *Lumnitzera racemosa*, *Pemphis acidula*, and *Rhizophora stylosa* [3]. Scientific papers such as Wakushima *et al*. [4] have cited Kiire Town as the northernmost limit of natural mangrove distribution of Japan. However, Inoue *et al*. [3] have corrected that Kamino River of Hioki City is in fact the northernmost limit. Here, the mangroves are stunted stands of purely *K. obovata*. The major use of mangroves in Japan is tourism. The annual number of most Japanese tourists visiting Ishigaki and Iriomote is much higher than the local population of these islands. Popular tourist activities include mangrove river cruises and canoeing, hiking and trekking in the mangroves and inland forests, bird-watching, snookering, scuba diving, and recreational fishing [3]. A case study in a book chapter measured the content of mineral nutrients in mangrove rivers and in the leaves of *B. gymnorhiza* and *R. stylosa* in Okinawa Prefecture to determine their relationship [3]. In recent years, the growth of mangrove species in relation to water, soil and other environmental properties have been studied in Japan, both in the glasshouse [5-7] and in the field [8-10].

Mangroves in Auckland of New Zealand represent the southernmost limit of the global mangroves. Trees of *Avicennia marina* var. *australasica* with stunted growth are the only plant species found in New Zealand [11]. Trials conducted on feeding dairy cattle with *A. marina* foliage showed that the foliage serves both as feed and salt nutrient supplement for the dairy cattle [12]. In New Zealand, duck hunting is a common recreational activity along the mangrove waterways. Recently, hunters have developed an ingenious way of constructing make-shift hides by camouflaging their boats using cut bushes of *A. marina* [13].

In this article, mangrove and other coastal plant species with anti-cancer properties have been identified. Information on their synonyms, common names, families and life-forms is included. Their anti-cancer properties included information on effects and mechanisms.

ISSN 1880-7682
Volume 21, No. 1 June 2023

2. Anti-cancer properties

Mangrove and other coastal plant species with anti-cancer properties are shown in Table 1, Figure 1, and Figure 2.

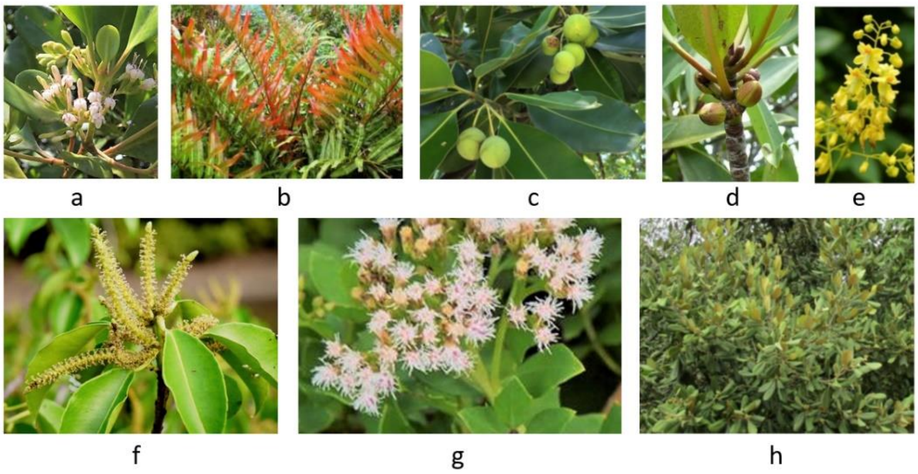

Figure 1. *Scyphiphora hydrophyllacea* (a), *Acrostichum aureum* (b), *Calophyllum inophyllum* (c), *Rhizophora apiculata* (d), *Caesalpinia crista* (e), *Excoecaria agallocha* (f), *Pluchea indica* (g), and *Avicennia rumphiana* (h).

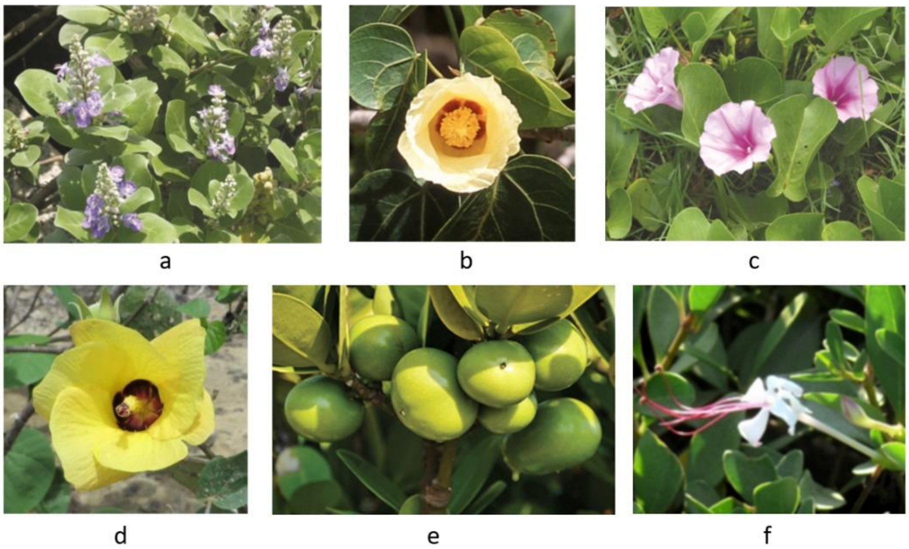

Figure 2. *Vitex trifolia* (a), *Thespesia populnea* (b), *Ipomoea pes-caprae* (c) *Talipariti tiliaceum* (d), *Garcinia subelliptica* (e), and *Volkameria inermis* (f).

Table 1. List of mangrove and other coastal species with anti-cancer properties.

No.	Species (Synonym)	Common name	Family	Life-form	Ref.
1	*Acanthus ilicifolius*	Mangrove holly	Acanthaceae	Shrub	14
2	*Acrostichum aureum* (*Chrysodium aureum*)	Leather fern	Pteridaceae	Fern	15
3	*Aegiceras corniculatum* (*Aegiceras fragrans*)	River mangrove	Primulaceae	Shrub	14

ISSN 1880-7682
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4	*Aglaia cucullata* (*Amoora cucullata*)	Pacific maple	Meliaceae	Tree	16
5	*Anacardium occidentale*	Cashew nut	Anacardiaceae	Tree	17
6	*Artocarpus altilis*	Breadfruit	Moraceae	Tree	18,19
7	*Avicennia marina*	Grey or white mangrove	Avicenniaceae	Tree	20
8	*Avicennia rumphiana* (*Avicennia lanata*)	Velvety mangrove	Avicenniaceae	Tree	21
9	*Barringtonia racemosa*	Common putat	Lecythidaceae	Tree	17
10	*Bruguiera gymnorhiza* (*B. capensis*)	Large-leafed orange mangrove	Rhizophoraceae	Tree	18
11	*Caesalpinia crista* (*C. chinensis*)	Squirrel's claws	Fabaceae	Tree	22
12	*Calophyllum inophyllum* (*Bintangur maritima*)	Beach calophyllum	Clusiaceae	Tree	18, 23
13	*Cerbera manghas*	Sea mango	Apocynaceae	Tree	24
14	*Cerbera odollam*	Sea mango	Apocynaceae	Tree	24
15	*Ceriops tagal*	Indian mangrove	Rhizophoraceae	Tree	25
16	*Excoecaria agallocha* (*E. affinis*)	Milky mangrove	Euphorbiaceae	Tree	26
17	*Ficus microcarpa* (*F. retusiformis*)	Malayan banyan	Moraceae	Tree	27
18	*Garcinia subelliptica*	Happiness tree	Clusiaceae	Tree	28
19	*Heritiera fomes*	Sundri	Sterculiaceae	Tree	14
20	*Ipomoea pes-caprae*	Beach morning glory	Convolvulaceae	Creeper	29
21	*Lumnitzera racemosa*	White-flowered black mangrove	Combretaceae	Tree	14
22	*Nypa fruticans*	Nipah	Arecaceae	Palm	18
23	*Planchonella obovata* (*Pouteria obovata*)	Sea Gutta	Sapotaceae	Tree	14
24	*Pluchea indica* (*Baccharis indica*)	Marsh fleabane	Asteraceae	Shrub	30
25	*Pongamia pinnata* (*Millettia pinnata*)	Pongam, Indian beech	Fabaceae	Tree	14
26	*Rhizophora apiculata*	Tall stilt mangrove	Rhizophoraceae	Tree	31,32
27	*Rhizophora mucronata*	Loop stilt mangrove	Rhizophoraceae	Tree	18

28	*Rhizophora stylosa*	Long-style, stilt mangrove	Rhizophoraceae	Tree	31,33,34
29	*Syphiphora hydrophyllacea*	Chingam, nilad	Rubiaceae	Shrub	14
30	*Talipariti tiliaceum* (*Hibiscus tiliaceus*)	Sea hibiscus	Malvaceae	Tree	35,36
31	*Terminalia catappa* (*T. latifolia*)	Sea almond	Combretaceae	Tree	18
32	*Thespesia populnea*	Portia tree	Malvaceae	Tree	23
33	*Vitex trifolia* (*V. ovata*, *V. rotundifolia*)	Common blue vitex	Lamiaceae	Shrub	29,37
34	*Volkameria inermis* (*Clerodendrum inerme*)	Wild jasmine	Lamiaceae	Shrub	38
35	*Xylocarpus granatum*	Cannon ball mangrove	Meliaceae	Tree	39
36	*Xylocarpus moluccensis*	Cedar mangrove	Meliaceae	Tree	14

2.1. Mangrove plant species

In this article, 17 mangrove plant species belonging to 13 genera possess anti-cancer properties (Table 2). They include three species of *Rhizophora* (*R. apiculata*, *R. mucronata*, and *R. stylosa*), two species of *Avicennia* (*A. marina* and *A. rumphiana*), and two species of *Xylocarpus* (*X. granatum* and *X. moluccensis*).

Table 2. Mangrove plant species with anti-cancer properties.

No.	Species	Effect and mechanism	Ref.
1	*Acanthus ilicifolius*	The root extract inhibited HepG2 liver cancer cells with an IC_{50} value of 40 µg/ml.	40
2	*Acrostichum aureum*	The ethyl acetate leaf extract exhibited cytotoxic activity against HeLa human cervical cancer cells with an IC_{50} value of 6.3 µg/ml.	41
		The methanol root extract showed cytotoxicity against AGS gastric cancer cells with an IC_{50} value of 1.0 mg/ml.	42
3	*Aegiceras corniculatum*	The methanol bark extract showed cytotoxicity against HT29 colon and MDA-MB-435S breast cancer cells with IC_{50} values of 0.3 and 0.7 mg/ml, respectively.	42
		Five alkylated benzoquinones isolated from the stem and twig displayed cytotoxic activity towards HepG2 liver, BGC-823 gastric, and A2780 ovarian cancer cells, including HL-60 leukemia cells.	43
		Methanol leaf extract inhibits HeLa cervical, T47D breast, and WiDr colon cancer cells with IC_{50} values of, 49, 78, and 46 µg/ml.	44
4	*Avicennia marina*	A mixture of avicennones E–F, avicequinone C, and stenocarpoquinone B from the twigs showed strong antiproliferative activities against L-929 mouse fibroblast and K562 human leukemia cells.	45
		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, and in a MDA-MB-231 xenograft model of female nude mice.	46

		Polyisoprenoids from leaf extract exhibited anti-cancer activity against WiDr cells with an IC_{50} value of 155 μg/ml.	47
		Lupeol, a pentacyclic triterpene, isolated from the leaf and stem suppressed the growth of Hep3B liver cancer cells *via* triggering the apoptotic pathway and down-regulating the anti-apoptotic BCL-2 gene expression.	48
5	*Avicennia rumphiana*	Polyisoprenoids from leaf extract exhibited anti-cancer activity against WiDr cells with an IC_{50} value of 306 μg/ml.	47
6	*Bruguiera gymnorhiza*	The butanol leaf extract exhibited the maximum cytotoxicity against the MCF-7 cells with IC_{50} of 3.4 μg/ml, followed by diethyl ether and methanol extracts with IC_{50} values of 16 and 37 μg/ml, respectively.	49
7	*Ceriops tagal*	Dolabrane-type diterpenes from the bark exhibited potent inhibition against a panel of five tumor cell lines. Tagalsin C exerted the most potent activities with IC_{50} values ranging from 3.7 to 8.8 μM.	50
		Polyisoprenoids from the leaf exhibited cytotoxicity against WiDr colon cancer cells with IC_{50} value of 276 μg/ml by inducing apoptosis, causing cell cycle arrest in the G0/G1 phase, and decreasing the expression of Bcl-2 and cyclin D1.	51
		Dolichol, a polyisoprenoid alcohol from the leaves, reduced G0/G1 growth cycle of WiDr colon cancer cells by 88% by up-regulation of p53 expression and down-regulation of EGFR, PI3K, Akt, and mTOR expression.	52
8	*Excoecaria agallocha*	Two flavonoid glycosides isolated from the leaf displayed HH inhibition with IC_{50} values of 0.5 and 2.0 μM, and cytotoxicity with 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, respectively.	53
9	*Heritiera fomes*	Methanol extract of leaf and stem possessed strong anti-cancer properties with 40% inhibition against B16 mouse melanoma and against Ehrlich Ascites mammary carcinoma in Swiss albino mice.	54
10	*Lumnitzera racemosa*	The leaf extract inhibited HepG2 liver cancer cells with an IC_{50} value of 26 μg/ml.	40
		The methanol leaf extract exerted cytotoxicity against MCF-7 breast and HeLa cervical cancer cells with IC_{50} values of 46 and 59 mg/ml, respectively.	55
11	*Nypa fruticans*	Polyisoprenoids from the leaf exhibited anti-cancer activity towards WiDr colon cancer cells through inhibition of COX-2 expression with IC_{50} value of 180 μg/ml.	56
12	*Rhizophora apiculata*	Methanol aerial part extract exerted significant anti-metastatic activity on B16-F10 metastatic tumor bearing C57BL/6 mice.	57
		Among the compounds isolated from the methanol leaf extract, 2,6-dimethoxy-1,4-benzoquinone exhibited cytotoxic effects towards MCF-7 breast, SK-LU-1 lung, and HepG2 liver cancer cells, with IC_{50} values of 8.3, 13, and 15 μM, respectively.	58
13	*Rhizophora mucronata*	Polyisoprenoids from the leaf exhibited cytotoxicity against WiDr colon cancer cells with IC_{50} value of 278 μg/ml by inducing apoptosis, causing cell cycle arrest in the G0/G1 phase, and decreasing the expression of Bcl-2 and cyclin D1.	51
		Dolichol, a polyisoprenoid alcohol from the leaves, reduced G0/G1 growth cycle of WiDr colon cancer cells by 82% by up-regulation of p53 expression and down-regulation of EGFR, PI3K, Akt, and mTOR expression.	52
		The methanol leaf extract and stem extract exhibited anti-cancer 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.	60
14	*Rhizophora stylosa*	Of the compounds isolated from the leaves, taraxerol inhibited HeLa cervical and BGC-823 gastric cancer cells, both with IC_{50} values of 73 μmol/L.	61

15	*Syphiphora hydrophyllacea*	Hopenone-I, a triterpenoid isolated from the hexane leaf extract, was cytotoxic against MCF-7 breast (7.8 μM), HepG2 liver (11.6 μM), and AN3CA endometrial (5.0 μM) cancer cells at 48 h.	62
		UA and EA isolated from 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 of EA were 8.9 and 10 μg/ml for NCI-H292 lung cancer cells.	63
16	*Xylocarpus granatum*	Four limonoids from the root strongly inhibited the proliferation of Eca109 esophageal cancer cells, with xylogranatin C having the strongest activity. Mechanism involved promotion of apoptosis *via* the DR and ER pathways.	64
		Ethyl acetate leaf extract inhibited HeLa cervical and MCF-7 breast cancer cells by 93% and 97%, respectively. Inhibition by Dox was 96% and 94%.	65
17	*Xylocarpus moluccensis*	The methanol bark extract showed cytotoxicity against AGS gastric cancer cells with an IC_{50} value of 0.6 mg/ml.	42
		Two novel 30-ketophragmalins (limonoids) isolated from the seeds exhibited anti-cancer activity against breast MDA-MB-453 cancer cells with IC_{50} values of 2.1 and 9.0 μM.	66

Abbreviations: Akt1 = protein kinase B, COX = cyclooxygenase, Dox = Doxorubicin, DR = death receptor, EA = eichlerianic acid, EGFR = epidermal growth factor receptor, ER = endoplasmic reticulum, HH = Hedgehog, mTOR = mechanistic target of rapamycin kinase, PI3K = phosphoinositide 3-kinase, UA = ursolic acid.

Endophytic fungi and their compounds isolated from some mangrove species also possess anti-cancer properties. Examples are endophytic fungi from *Rhizophora mucronata* [67] *Ceriops decandra* [68], and *Sonneratia alba* [69].

2.2. Other coastal plant species

In this article, 19 other coastal plant species belonging to 18 genera have been recorded (Table 3). The genus *Cerbera* has two species (*C. manghas* and *C. odollam*).

Table 3. Other coastal plant species with anti-cancer properties.

No.	Species	Effect and mechanism	Ref.
1	*Aglaia cucullata*	Three rocaglamide derivatives isolated from the fruit exhibited potent cytotoxicity against KB oral, BC breast, and NCI-H187 lung cancer cells.	69
		A rocagloic acid derivative isolated from the leaf showed potent TRAIL-induced apoptosis in AGS cells *via* activation of caspase-3/7, and enhanced expression of DR4 and DR5 mRNA.	70
2	*Anacardium occidentale*	Pentagalloylglucose, isolated from the leaf extract, exerted significant cytotoxic activity against HeLa cervical and MRC5-SV2 lung cancer cells with IC_{50} values of 71 and 52 μg/ml, respectively.	71
3	*Artocarpus altilis*	The wood extract inhibited the growth of T47D breast cancer cells by inducing apoptosis and sub-G1 phase formation.	72
		Partially purified fraction of the leaf and stem and the isolated geranyl dihydrochalcone inhibited the growth of DU145 prostate cancer cells by inducing apoptosis *via* caspase-3 and PARP degradation. The compound also inhibited tumor growth in DU145 cell xenograft model.	73
4	*Barringtonia racemosa*	Methanol fruit extract exhibited cytotoxicity against MCF-7 breast cancer cells with an IC_{50} value of 58 μg/ml.	74

ISSN 1880-7682
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5	*Caesalpinia crista*	Two cassane diterpenoids isolated from the aerial parts displayed moderate cytotoxic activity towards HL-60 leukaemia cells and HeLa cervical cancer cells, with IC_{50} values of 17 and 33 µM, and 20 and 34 µM, respectively.	75
6	*Calophyllum inophyllum*	Among the compounds isolated from the aerial part and screened for inhibition of EBV in TPA-activated Raji cells, all eight coumarins (apetatolide, calocoumarins A and B, calophyllolide, inophyllums A, D, and E, and isocalophyllic acid) exhibited inhibitory activity against EBV with calocoumarin A being the most potent.	76
		From the root bark and nut, 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.	77
7	*Cerbera manghas*	Cardenolide glycoside from the seeds, notably, 7,8-dehydrocerberin, deacetyltanghinin, and tanghinin, are cytotoxic towards KB oral epidermoid, BC breast, and NCI-H187 lung cancer cells.	78
		Neriifolin from the seed induced cell cycle arrest and apoptosis in HepG2 liver cancer cells. Apoptosis was induced *via* activation of caspases, and up-regulation of Fas and FasL expression.	79
		Extracts of stems and fruits including isolated neriifolin effectively inhibited the viability of glioblastoma cells *in vitro* and in mouse xenograft model.	80
8	*Cerbera odollam*	Cardenolide glycoside from the seed, notably, 17α-neriifolin, 17β-neriifolin, exerted potent cytotoxic activities towards KB oral epidermoid, BC breast, and NCI-H187 lung cancer cells.	81
		17βH-neriifolin, a cardiac glycoside isolated from leaves, displayed anti-cancer properties against breast MCF-7 breast, T47D breast, HT-29 colon, A2780 ovarian, SKOV-3 ovarian, and A375 skin cancer cells yielded IC_{50} values that ranged from 0.02 to 0.03 µM.	82
9	*Ficus microcarpa*	Triterpenes from the aerial roots bearing a carboxylic acid functionality at C28 showed 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.	83
10	*Garcinia subelliptica*	The ethanol leaf extract elicited cytotoxicity, but not apoptosis, in A549 and SNU2292 lung cancer cells, by inducing autophagy, activating AMPK, and suppressing mTOR pathways.	84
		The methanol leaf extract showed cytotoxic activity in THP-1 and Jurkat leukemia cells. Garcinielliptone G inhibited cancer cells by inducing apoptosis, caspase-3 activation, and caspase-independent apoptosis.	85
11	*Ipomoea pes-caprae*	Pescapreins from the aerial parts modulated multi-drug resistance in MCF-7/ADR breast cancer cells. The combined use of these compounds at 5 µg/ml increased the cytotoxicity of doxorubicin by 1.5-3.7 times.	86
12	*Planchonella obovata*	Three triterpenoid glycosides from leaf extract showed moderate inhibitory activities against HL-60 leukemia cells with IC_{50} values of 16.9, 15.5, and 12.7 mM.	87
13	*Pluchea indica*	The aqueous extract of roots and leaves are cytotoxic to GBM8401 glioblastoma and HeLa cervical cancer cells *via* suppression of cell proliferation, viability, and migration.	88
		The ethanol root extract induced apoptosis, anti-proliferation, and migration of NPC-TW 01 and NPC-TW 04 nasopharyngeal carcinoma cells.	89
		The hexane fraction of the ethanol root extract inhibited proliferation and induced autophagy of U87 glioblastoma cells.	90

14	*Pongamia pinnata*	Lonchocarpin, a natural chalcone from the root, exhibited 97.5% inhibition at 100 μM against H292 lung cancer cells. Reduction of proliferation was by inducing apoptosis, and by modulating bax/caspase-3/-9 pathway. Lonchocarpin also inhibited tumour growth in S180-bearing mice.	91
15	*Talipariti tiliaceum*	Hibiscusamide isolated from the stem wood displayed cytotoxic activity against P388 murine leukemia and HT-29 colon cancer cells with IC_{50} values of 1.7 and 3.8 g/ml, respectively.	92
		The aqueous leaf extract showed cytotoxicity against AGS gastric and HT29 colon cancer cells with IC_{50} values of 0.2 and 0.8 mg/ml, respectively.	42
		Among the three tetracyclic triterpenoids isolated from the leaf and branch extracts, the analog of tiliacol A had potent cytotoxicity against P388 murine leukemia and HeLa cervical cancer cells with IC_{50} values of 11.2 and 11.5 mmol/L, respectively.	93
		Cadinane-type sesquiterpenoid dimeric diastereomers named hibisceusones A-C from infected stems exhibited cytotoxic activity against triple-negative breast cancer cells.	94
		Five cadinane sesquiterpenoids isolated from infected stems displayed cytotoxic activity against HepG2 and Huh7 liver cancer cells with IC_{50} values ranging from 3.5 to 6.8 μM.	95
16	*Terminalia catappa*	Leaf extract exerted anti-metastatic effects on A549 and LLC lung cancer cells by inhibiting the expression of MMP-2 and PAI-1.	96
		Leaf extract exerted anti-metastatic effects on HeLa and SiHa cervical cancer cells by inhibiting the expression of MMP-9 through the ERK1/2 pathway.	97
17	*Thespesia populnea*	Among the compounds isolated from the wood and heartwood, mansonone E and (+)-gossypol showed significant anti-cancer activities against MCF-7 breast, HeLa cervical, HT-29 colon, and KB oral squamous cancer cells.	98
18	*Vitex trifolia*	Hexane and DCM extracts of leaves and stem displayed cytotoxic activity against SQC-1 squamous, OVCAR-5 ovarian, HCT-15 colon, and KB prostate cancer cells.	99
		When tested against MCF-7 breast and HT-29 colon cancer cells, the methanol leaf extract showed positive cytotoxic activities with IC_{50} values of 79 and 77 μg/ml.	100
19	*Volkameria inermis*	Against A549 lung cancer cells, the ethanol leaf extract displayed cytotoxicity with an IC_{50} value of 16 μg/ml.	101
		Hardwickiic acid isolated from the methanol leaf extract showed strong cytotoxicity against HCT116 colon cancer cells with an IC_{50} value of 3.5 μM	102

Abbreviations: ADP = adipose, AGS = human gastric adenocarcinoma, AMPK = AMP-activated protein kinase, DCM = dichloromethane, DR = death receptor, EBV = Epstein-Barr virus, ERK = extracellular signal-regulated kinase, LLC = Lewis lung carcinoma, MAPK = mitogen-activated protein kinase, MMP = matrix metalloprotein, mRNA = messenger ribonucleic acid, mTOR = mammalian target of rapamycin, PAI = plasminogen activator inhibitor, PARP = polyADP-ribose polymerase, TNF = tumor necrosis factor, TPA = 12-*O*-tetradecanoylphorbol-13-acetate, and TRAIL = TNF-related apoptosis-inducing ligand.

3. Acknowledgment

The authors are thankful to Prof. Shigeyuki Baba for some of the photos in Figure 1 and Figure 2 are taken by him.

4. Conclusion

There are bright prospects in conducting further research on the anti-cancer properties of mangrove and other coastal plants. The *in vitro* anti-cancer properties of extracts are fairly well-studied but not *in vivo* using animal models and clinical trials. Recently, the anti-cancer properties of endophytic fungi from mangrove plants have attracted the attention of scientists. There are opportunities for isolating and identifying novel bioactive compounds with anti-cancer properties. Equally exciting is to determine their molecular targets and mechanisms. Molecular docking studies are just as exciting. Their structure activity relationships (SAR) of compounds are a challenge for scientists to unravel. The anti-cancer efficacy of natural plant compounds when used in combination with other anti-cancer drugs is worthy of further analysis.

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