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Review Article

Botany, uses, phytochemistry and pharmacology of selected Apocynaceae species: A review

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ABSTRACT: The family Apocynaceae consists of tropical trees, shrubs and vines. Characteristic features of the family are that almost all species produce milky sap. Leaves are simple, opposite or whorled; flowers are large, colourful and slightly fragrant with five contorted lobes; and fruits are in pairs. With the inclusion of species of Asclepiadaceae, the family has now enlarged from two to five sub-families. The expanded family now comprises more than 150 genera and 2000 species. In traditional medicine, Apocynaceae species are used to treat gastrointestinal ailments, fever, malaria, pain and diabetes, including skin and ecto-parasitic diseases. Some are important timber species while many are planted as ornamentals. Non-medicinal uses include food, poisons, fodder, wood, ornamentals, dye and perfume. Species of Apocynaceae have been reported to possess anticancer and antimalarial properties. Species having cytotoxic activity include those of *Allamanda*, *Alstonia*, *Calotropis*, *Catharanthus*, *Cerbera*, *Nerium*, *Plumeria*, *Tabernaemontana* and *Vallaris*. Species of *Alstonia*, *Calotropis*, *Dyera*, *Kopsia* and *Vallaris* are also known to have antimalarial properties. Prompted by their anticancer and antimalarial properties; the botany, uses, phytochemistry and pharmacology of ten selected Apocynaceae species (*Allamanda cathartica*, *Alstonia angustiloba*, *Calotropis gigantea*, *Catharanthus roseus*, *Cerbera odollam*, *Dyera costulata*, *Kopsia fruticosa*, *Nerium oleander*, *Plumeria obtusa* and *Vallaris glabra*) belonging to ten genera are reviewed.

KEYWORDS: Anticancer, antimalarial, alkaloids, cardenolides, triterpenoids

INTRODUCTION

The family Apocynaceae consists of tropical trees, shrubs and vines. Characteristic features of the family are that almost all species produce milky sap.[1,2] Leaves are simple, opposite or whorled; flowers are large, colourful and slightly fragrant with five contorted lobes; and fruits are in pairs.

With the inclusion of species of Asclepiadaceae under the unified classification for Apocynaceae, the family has now been enlarged from two to five sub-families.[3] The sub-families are Apocynoideae, Asclepiadoideae, Periplocoideae, Rauvolfioideae and Secamonoideae. The expanded family now comprises more than 150 genera and 2000 species.[4]

In traditional medicine, Apocynaceae species in the Asia-Pacific region are used to treat fever, malaria, pain, diabetes and gastrointestinal ailments, including skin and ecto-parasitic diseases.[1,5] Some are important timber species while many are planted as ornamentals. Non-medicinal purposes include food, poisons, fodder, wood, ornamentals, dye and perfume.

Apocynaceae species have been reported to possess anticancer properties.[1] Species with cytotoxic activity include those of *Allamanda*,[6] *Alstonia*,[7–9] *Calotropis*,[8,9] *Catharanthus*,[9] *Cerbera*,[10,11] *Nerium*,[9,12,13] *Plumeria*,[9,14] *Tabernaemontana*[15] and *Vallaris*.[8,9] Species of *Alstonia*, *Calotropis*, *Dyera*, *Kopsia* and *Vallaris* are also known to have antimalarial properties.[8,16,17]

Prompted by their anticancer and antimalarial properties, ten Apocynaceae species belonging to ten genera were reviewed (Figure 1). Nine genera are of the sub-family

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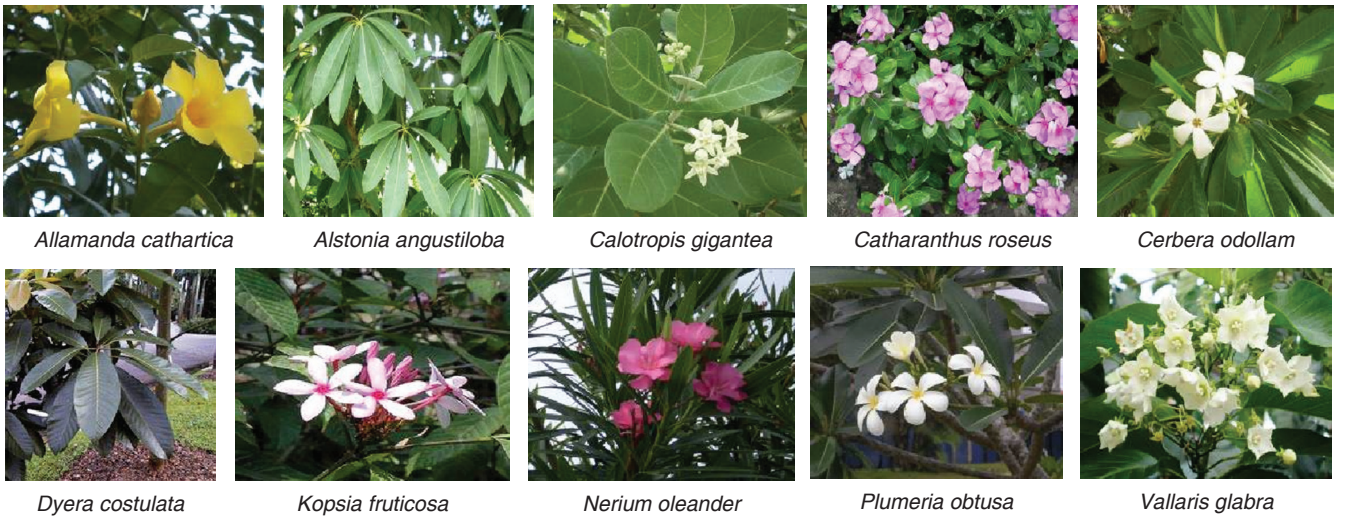

Figure 1. The ten Apocynaceae species reviewed.

Apocynoideae (*Allamanda cathartica*, *Alstonia angustiloba*, *Catharanthus roseus*, *Cerbera odollam*, *Dyera costulata*, *Kopsia fruticosa*, *Nerium oleander*, *Plumeria obtusa* and *Vallaris glabra*) with the exception of *Calotropis gigantea*, which belongs to the sub-family Asclepiadoideae.

ALLAMANDA CATHARTICA

Synonym: *Allamanda hendersonii*
Common name: Common allamanda

Botany and uses

Allamanda cathartica L. are robust shrubs growing up to 6 m tall.[2,4] Leaves are elliptical to obovate, opposite or in whorls. Flowers are yellow and trumpet-shaped with corolla tube. Flowers are similar in size as leaves. Fruits are capsules with spines, and seeds are compressed and winged. Shrubs with their beautiful yellow flowers are popular ornamentals.

Leaves of *A. cathartica* are used as a purgative or emetic in Southeast Asia.[18] Leaves are also used as an antidote, and for relieving coughs and headaches. Plants are used in traditional medicine for treating malaria and jaundice, and the flowers as a laxative.[19]

Phytochemistry and pharmacology

Previous work on *A. cathartica* included the isolation of iridoid lactones (allamandin, allamandicin and allamdin),[20] iridoid glycosides (plumieride coumarate and plumieride coumarate glucoside),[21] and iridoid lactones (isoplumericin and plumericin).[22]

Of the three iridoid lactones isolated from leaf extracts of *A. cathartica*, allamandin had antileukemic properties,[20] while plumericin and isoplumericin were weakly cytotoxic.[22]

Ethanol (EtOH) leaf extracts showed significant tumour inhibition *in vivo* against the P-388 leukemia in the mouse and *in vitro* against human nasopharnyx carcinoma (KB) cells.[20]

Aqueous leaf extract of *A. cathartica* promoted wound healing activity in rats.[19] Compared to controls, treated rats had higher rate of wound contraction, decreased period of epithelialisation, higher skin breaking strength, significant increase in the weight of the granulation tissue and greater hydroxyproline content. Histological studies of the granulation tissue in treated rats showed less inflammatory cells and increased collagen formation.

Another study revealed that aqueous leaf extract of *A. cathartica* induced dose-related purgation in mice by increasing the number of wet faeces and the propulsive movement of intestinal contents.[23] Considering the potency of the extract in stimulating the gut, these properties may explain the rationale for the use of the plant as a purgative in traditional medicine.

ALSTONIA ANGUSTILOBA

Synonym: *Alstonia calophylla*
Vernacular name: Pulai

Botany and uses

Alstonia angustiloba Miq. is a medium-sized to large tree that grows up to 45 m tall.[24] It has a tall, straight and fluted bole up to 100 cm in diameter. When slashed, the bole produces copious white latex. The bark is brown or grey to whitish, rough, fissured and peeling off in rectangular flakes. Leaves are elliptical to obovate and in whorls. The species occurs on a wide variety of soils in rain forests from lowland up to 200 m altitude.

In Malaysia, leaves of *A. angustiloba* are applied externally to treat fever and headache.[24] The latex is used to heal boils and abscesses. Pounded bark is an ingredient of febrifuges and vermifuges. In Thailand, the latex is used to soothe toothache. Stems, leaves and latex have been used for gynaecological problems and skin sores in Indonesia.[25]

Phytochemistry and pharmacology

Five new alkaloids (alstilobanines A–E) and three known alkaloids (undulifoline, alstonamic acid and 7-*seco*-angustilobine) were isolated from methanol (MeOH) leaf extract of *A. angustiloba*.[26] Using the vasodilation assay, the alstilobanines showed moderate vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta. Alstilobanine A without an ether linkage in its angustilodine skeleton had more potent vasorelaxant activity of 44% compared to 6.8% of alstilobanine E with an ether linkage.

Leaf extracts of *A. angustiloba* have been reported to possess anticancer and antimalarial properties.[8,9] Dichloromethane (DCM) leaf extract displayed positive antiproliferative activity against MDA-MB-231, HeLa and HT-29 human cancer cells with GI_{50} (extract concentration which causes 50% reduction of cancer cell growth) of 20 ± 1.7, 20 ± 1.1 and 16 ± 1.4 μg/ml, respectively. Hexane (Hex), DCM:MeOH (1:1) and MeOH leaf extracts displayed effective antiplasmodial activity against chloroquine-resistant K1 strain of *Plasmodium falciparum* but not against chloroquine-sensitive 3D7 strain.[8]

CALOTROPIS GIGANTEA

Synonym: *Asclepias gigantea*
Common names: Crown flower; giant milkweed

Botany and uses

Calotropis gigantea (L.) Aiton is a large shrub or small tree of 3–4 m tall.[27] Leaves are obovate, woolly with light coloured veins and sub-sessile. Flowers are pale lilac and cream coloured towards the tips. The elaborate crown structure of the flowers is due to the highly modified stigma and stamens. The species is fast growing and flowers throughout the year. Occurring naturally from India and Sri Lanka to Thailand and southern China, *C. gigantea* is planted as a medicinal plant in Malesia. The species can be distinguished from *Calotropis procera* which has white petals with dark purple tips.

In Indonesia, roots of *C. gigantea* are used as an antidote for snake-bite and scabies.[28] In India, plants have been traditionally used for the treating diseases such as leprosy, ulcers, tumours and piles.[29] The roots and leaves are used for the treatment of abdominal tumours, syphilis, leprosy, skin diseases, piles, wounds, rheumatism, insect-bites, ulceration and elephantiasis. Plants are used as analgesia for treating earache, toothache, headache, sprain, stiff joints and pain.[30] Leaves of *C. gigantea* are used to treat skin and liver diseases, leprosy, dysentery, worms, ulcers, tumours and earaches.[31] Its latex has been reported to possess wound healing properties.[32]

Phytochemistry and pharmacology

The chemical constituents of *C. gigantea* have been extensively investigated, leading to the isolation of many cardenolides,[33–38] flavonoids,[39] terpenes[40,41] and pregnanes.[28,42,43]

From the latex of *C. gigantea*, a flavonol glycoside has recently been isolated.[29] Pregnanes (calotroposides A–G) are new oxypregnane-oligoglycosides reported from the MeOH root extract.[28,42] Bioassay-guided fractionation of the EtOH root extract of *C. gigantea* yielded coroglaucigenin (a cardenolide aglycone) and frugoside (its glycoside).[37] From the EtOH root extract, a new pregnanone (calotropone) and a known cardiac glycoside (glycoside gofruside) were isolated.[43]

Three cardenolide glycosides (calotropin, frugoside and 4'-*O*-*β*-D-glucopyranosyl frugoside) isolated from the root extract of *C. gigantea* were found to have cytotoxic activity against human cancer lines but not against mouse cancer lines.[34] Against KB cells, calotropin showed strong cytotoxicity while frugoside and 4'-*O*-*β*-D-glucoside showed moderate cytotoxicity. The EtOH extract from roots showed cytotoxic activity towards K562 human chronic myelogenous leukemia and SGC-7901 human gastric cancer cell lines.[37,43] Coroglaucigenin and frugoside isolated from the extract exhibited significant cytotoxic activity against K-562 and SGC-7901 cell lines. It was postulated that the presence of a deoxysugar at C-3 was responsible for the cytotoxic activity. Calotoxin and frugoside isolated from leaves had potent inhibition against KB, MCF-7 and NCI-H187 cancer cells.[38]

The EtOH extract of *C. gigantea* flowers has been reported to have an analgesic effect on chemically and thermally treated mice using the acetic acid induced writhing test and hot plate method, respectively.[30] There was a significant decrease in the number of writhings and paw licking time. The analgesic effect, observed 30 min after dose administration, reached its maximum after 90 min. Topical application of root bark extract formulated in ointment increased the percentage of wound contraction in rats with wound healing completed by the third week.[44] The accelerated wound healing in rats supports its traditional use.

The EtOH root bark extract of *C. gigantea* showed strong hepato-protective activity in Wistar albino rats with induced hepatic injury.[45] An oral dose of 200 and 400 mg/kg normalised the levels of aspartate and alanine amino transferase, alkaline phosphatase, total bilirubin and lactate dehydrogenase in the rats. The effect was comparable to silymarin, a known hepatoprotective drug. The EtOH leaf extract of *C. gigantea* has been reported to have antiviral activity against herpes simplex type-1 and vesicular stomatitis viruses, with MIC of 0.01 mg/ml.[46]

The anti-diarrhoeal activity of aqueous EtOH extract of *C. gigantea* against rats with diarrhoea induced by castor oil has been studied.[47] Results showed that the extract had remarkable anti-diarrhoeal effects on the treated rats, which included significant reduction in the number of stools, and in the weight and volume of intestinal content, as well as modest reduction in intestinal transit.

The latex from *C. gigantea* was reported to have vasodilatory effect on the green frog *Rana hexadactyla*.[48] The crude extract diluted with distilled water to 1:10 and 1:100 concentrations produced 55% and 66% cardiac output, respectively. Results showed that the latex had vasodilatory effect at fixed dose concentration. On a higher dose treatment, the latex damaged the contractility of the cardiac muscle.

The anticancer and antimalarial properties of *C. gigantea* have been reported.[8,9] DCM and DCM:MeOH leaf extracts displayed positive antiproliferative activity against six human cancer cell lines of MCF-7, MDA-MB-231, HeLa, HT-29, SKOV-3 and HepG2, while the DCM:MeOH leaf extract inhibited both K1 and 3D7 strains of *P. falciparum*.

CATHARANTHUS ROSEUS

Synonym: *Vinca rosea*
Common name: Madagascar periwinkle

Botany and uses

Catharanthus roseus (L.) G. Don is a perennial herb that grows up to 1 m tall and produces white sap.[49,50] Leaves are obovate or elliptic with rounded apex. The fragrant trumpet-shaped flowers are purple, red, pink or white with a purple, red, pink, pale yellow or white eye. Fruits consist of two cylindrical follicles producing many minute black seeds. It blooms throughout the year and can be propagated by seeds or cuttings. Horticulturists have developed more than 100 varieties. Native to Madagascar, *C. roseus* is cultivated or naturalised in all tropical countries. The plant is a popular garden ornamental, grown as a perennial in tropical regions and as an annual in temperate regions. It is valued for its bushy habit, showy colourful flowers and dark green foliage. Plants are also cultivated for medicine.

The plant has historically been used to treat a wide variety of diseases.[49,50] A decoction of all plant parts is used to treat malaria, diarrhoea, diabetes, cancer and skin diseases. The species is also well known as an oral hypoglycaemic agent. Extracts prepared from leaves have been used as an antiseptic agent for healing wounds and as a mouthwash to treat toothache. The plant has long been used as a hypoglycaemic agent for the treatment of diabetes.[51]

Commercial drugs have been developed from alkaloids (vinblastine and vincristine) extracted from *C. roseus*.[50] Vinblastine sulphate (sold as Velban) is used to treat Hodgkin's disease. Vincristine sulphate (sold as Oncovin) is effective for treating acute leukaemia in children and lymphocytic leukaemia.

Phytochemistry and pharmacology

Plants of *C. roseus* contain about 130 indole alkaloids of which 25 are dimeric in nature.[50,52] Some major chemical constituents are vinblastine, vindoline, catharanthine, ajmalicine and serpentine.[52] The species is also rich in bisindole alkaloids (about 40 compounds), most of them containing a vindoline or catharanthine moiety. Both the commercially important alkaloids of vinblastine and vincristine have a large dimeric asymmetric structure composed of a dihydroindole nucleus (vindoline ring) and an indole nucleus, linked by a carbon-carbon bond.[53]

Catharanthus alkaloids have been reported in a large number of publications.[54,55] Besides alkaloids, other compounds such as flavonoids and anthocyanins are also reported. Three caffeoylquinic acids and 15 flavonol glycosides have been identified from seeds, stems, leaves and flowers of *C. roseus*.[56] From the flowers, anthocyanins isolated were 3-*O*-glucosides and 3-*O*-(6-*O*-*p*-coumaroyl) glucosides of hirsutidin, malvidin and petunidin.[57]

The EtOH flower extract of *C. roseus* has been reported to possess wound healing properties in rats.[58] The extract promoted wound contraction, increased tensile strength, increased hydroxyproline content, and has antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. EtOH leaf, stem, flower and root extracts of *C. roseus* displayed broad-spectrum antibacterial activity against *Escherichia coli*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Salmonella typhi* and *Aeromonas hydrophila*.[59] In a similar study, extracts from different plant parts were reported to inhibit both Gram-positive and Gram-negative bacteria.[60] Catharanthamine isolated from *C. roseus* was cytotoxic to the KB and P-388 human cancer cell lines.[55] DCM:MeOH leaf extract of this

plant displayed positive antiproliferative activity against MCF-7 and HeLa human cancer cells with GI_{50} values of 3.5 ± 0.1 and 4.7 ± 0.6 μg/ml, respectively.[9]

CERBERA ODOLLAM

Synonyms: *Cerbera lactaria*; *Cerbera manghas*
Vernacular name: Pong-pong

Botany and uses

Cerbera odollam Gaertner are evergreen shrubs or small to medium-sized trees up to 30 m tall.[61] The bole when slashed exudes abundant white latex. Leaves are arranged spirally and clustered at the apices of twigs. Flowers are white with a pinkish centre. Fruits are a drupe with a single rounded seed. Trees of *C. odollam* are planted as ornamentals in gardens and along roadsides. The species occurs naturally in coastal areas of tropical Asia and Melanesia.

In Southeast Asia, leaves of *C. odollam* are used in aromatic bath by women after childbirth.[61] Leaves, bark and latex are emetic and purgative, and seeds are toxic and strongly purgative. The bark, latex and leaves are sometimes used as an emetic and a purgative.[4]

Phytochemistry and pharmacology

The chemical constituents and bioactivities of *Cerbera* have been reviewed.[62] Compounds include lignans, cardiac glycosides, terpenoids, flavonoids and progesterones.

The anticancer properties of *C. odollam* are fairly well documented. MeOH leaf extract strongly inhibited MCF-7 and T47D cells with IC_{50} values of 8.5 and 11 μg/ml, respectively.[11] MeOH fruit extract however did not show any antiproliferative activity. A new cardenolide glycoside and three known compounds (17α-neriifolin, 17β-neriifolin and cerberin) isolated from seeds had cytotoxic activity against KB, BC and NCI-H187 human cancer cells.[63] A new cardenolide glycoside and three known cardenolides isolated from seeds of *C. odollam* exhibited cytotoxic activity against KB oral human epidermoid carcinoma cells, BC human breast cancer cells and NCI-H187 human lung cancer cells.[64] Two new cardenolides and a known cardenolide (17β-neriifolin) isolated from roots showed antiproliferative activity against Col2 human colon cancer cells and antiestrogenic activity against Ishikawa endometrial adenocarcinoma cells.[65]

Chloroform ($CHCl_3$) and carbon tetrachloride fractions of the stem bark of *C. odollam* had the strongest antioxidant activity with IC_{50} values of 21.6 and 21.0 μg/ml, respectively, compared to butylated hydroxytoluene (BHT) with a value of 14.5 μg/ml.[66]

DYERA COSTULATA

Synonyms: *Dyera polyphylla*; *Dyera lowii*
Vernacular name: Jelutong

Botany and uses

Dyera costulata Hook trees grow up to 80 m tall.[67] Bark is dark grey, brown or black in colour. Leaves occur in whorls of 4–8 and flowers are white. Paired resembling horns, fruits dehisce when mature, releasing seeds with membranous wings. Occurring naturally in southern Thailand, Malaysia and Sumatra, *D. costulata* are tall forest trees growing up to 1200 m altitude. The latex was formerly an important source of chewing gum. The light and soft timber is excellent for manufacturing a variety of wood products e.g. carvings, toys, pencils, etc. In traditional medicine, leaves and barks have been used for treating fever, inflammation and pain.[68]

Phytochemistry and pharmacology

Six bisindole alkaloids (ochrolifuanine A, ochrolifuanines E and F, and 18-dehydroochrolifuanines A, E and F) have been isolated from leaf extracts of *D. costulata*.[69] From the leaves, β-amyrin and rhamnazin have been isolated from the $CHCl_3$ extract, and quercetin-3-*O*-α-L-rhamnopyranoside from the n-butanol extract.[70]

The free radical scavenging activity of quercetin-3-*O*-α-L-rhamnopyranoside isolated from leaves of *D. costulata* was 8.6 times stronger than butylated hydroxyltoluene.[68] The $CHCl_3$ extract from leaves showed marked analgesic effect but no antipyretic activity in mice.[70] Leaf extracts of *D. costulata* did not display any positive antiproliferative activity but DCM:MeOH and MeOH leaf extracts inhibited both K1 and 3D7 strains of *P. falciparum*.[8,9]

KOPSIA FRUTICOSA

Synonyms: *Kopsia singapurensis*; *Cerbera fruticosa*
Common name: Pink kopsia

Botany and uses

Kopsia fruticosa (Ker.) A. DC. is an evergreen shrub that grows up to 4 m tall.[71] Leaves are elliptic or oblong, thin, shiny above and pale beneath. Inflorescences are a compact cyme bearing few pink flowers that resemble those of *Ixora*. The corolla tube is slender. Fruits are a lattened drupe bearing a single seed. The species is native to Myanmar and has naturalised in India, Indonesia, Malaysia, the Philippines and Thailand. It is sometimes cultivated as an ornamental or medicinal plant. Leaves are used to treat sores and syphilis, and have cholinergic effects.[72]

Phytochemistry and pharmacology

From leaves of *K. fruticosa*, alkaloids of kopsine, fruticosine and fruticosamine have been isolated.[73] Kopsine was the first *Kopsia* alkaloid isolated. The complete ^{1}H and ^{13}C NMR spectral assignments of these three compounds have been reported.[74] Leaf extract yielded novel indole alkaloids of kopsifolines A–F, venacarpine A and B, and kopsorinine.[75] From the stem bark, kopsorinine and 11 other known alkaloids were isolated. Further isolation work on leaf and stem bark extracts of *K. fruticosa* yielded new alkaloids of kopsimalines A–E, kopsinicine, kopsofinone and kopsiloscines H–J.[76]

Kopsimalines A–E and kopsiloscine J were found to inhibit vincristine-resistant KB human cancer cells, with kopsimaline A showing the highest potency (IC_{50} = 3.9 μg/ml) followed by kopsimaline D (IC_{50} = 9.2 μg/ml) in the presence of 0.1 μg/ml vincristine.[76] DCM:MeOH and MeOH leaf extracts of *K. fruticosa* inhibited K1 strain of *P. falciparum* while DCM leaf extract inhibited 3D7 strain.[8]

NERIUM OLEANDER

Synonyms: *Nerium indicum*; *Nerium odorum*
Common name: Oleander

Botany and uses

Nerium oleander L. is an evergreen shrub or small tree ranging from 2–6 m tall with spreading to erect branches.[2] Leaves are in pairs or whorls of three, thick and leathery, dark green, narrow lanceolate with entire margin. Flowers are borne in clusters at the end of each branch. They vary from white, pink, red or yellow in colour and 2.5–5.0 cm in diameter. The corolla is deeply 5-lobed fringing round the central corolla tube. They are often sweetly scented. The fruit is a long narrow capsule which splits open at maturity to release numerous downy seeds. Plants of *N. oleander* are extensively planted as ornamentals in landscapes, parks, and along roadsides. There are over 400 varieties with additional flower colours of red, purple, and orange.[77] The pink and white varieties are the most common. Plants are highly poisonous and contain toxic compounds such as oleandrin and neriine. Anvirzel, the extract of this plant promoted to treat cancer, AIDS and congestive heart failure. The extract was reported to induce cell death in human but not murine cancer cells.[13]

Phytochemistry and pharmacology

Triterpenoids are major constituents of *N. oleander*.[78–80] Other compounds such as pregnanes[81] and cardenolides[82–84] were also reported. The phytochemical and pharmacological properties of this species have recently been reviewed.[85]

Extracts from roots and leaves of *N. oleander* displayed antibacterial activity against *Bacillus pumilus*, *Bacillus subtilis*, *S. aureus* and *E. coli*.[86] Triterpenes isolated from leaves,[80] and cardenolides isolated from stems and twigs,[85] were cytotoxic to WI-38, VA-13 and HepG2 human cancer cells. EtOH leaf, stem and root extracts have cytotoxic effects on leukaemia cell lines.[87] Cytotoxicity index was 66.2%, 57.8% and 58.1% against K562 cells, and 69.3%, 66.5% and 62.8% against HL60 cells, respectively. DCM and DCM:MeOH leaf extracts of *N. oleander* displayed positive antiproliferative activity against MCF-7, MDA-MB-231, HeLa, HT-29 and SKOV-3 cancer cells.[9] Inhibition of leaf extracts was most effective against MCF-7 cells with GI_{50} values of 3.7 ± 0.1 and 4.3 ± 0.2 μg/ml, respectively.

PLUMERIA OBTUSA

Common name: Frangipanni

Botany and uses

Plumeria obtusa L. trees grow up to 5 m tall.[4] Stems are succulent and produce a milky sap. Leaves are simple, spirally arranged, and clustered at the stem tips. They are obovate, leathery, glossy dark green on the upper surface and have a rounded apex. Flowers are funnel-shaped, white, ~4 cm in diameter with a yellow throat yellow and slightly recurved. Flowering is continuous throughout the year. The species is Native to the Caribbean Islands, *P. obtusa* is commonly planted as an ornamental. In Asia, a decoction of leaves is used for treating wounds and skin diseases. Its latex and bark are known to have purgative and diuretic properties.

Phytochemistry and pharmacology

Triterpenoids are the major constituents of leaves of *P. obtusa* with iridoids also reported.[88–90] Triterpenoids included kaneroside, oleandrin, δ-amyrin, neriucoumaric acid, isoneriucoumaric acid, alphitolic acid, oleanonic acid, betulin, betulinic acid, ursolic acid, obtusilinin and scopoletin. Iridoids were plumieride, plumieride *p*-*Z*-coumarate and plumieride *p*-*E*-coumarate. From the flowers, plumieride coumarate glucoside (an iridoid β-glucoside) was isolated.[91]

The MeOH stem bark extract of *P. obtusa* has been reported to be effective in healing gastric ulcers induced by pylorus ligation and indomethacin in rats.[92] Extract at doses of 250 and 500 mg/kg significantly diminished the ulcer index, total ulcer area and percentage of ulcer protection

in treated groups compared to the control group. The Hex leaf extract of *P. obtusa* inhibited MCF-7 and HeLa human cancer cells with GI_{50} values of 5.7 ± 0.8 and 10 ± 1.4 µg/ml, respectively.[9] DCM leaf extract inhibited only HeLa cells with GI_{50} value of 19 ± 4.0 µg/ml.

VALLARIS GLABRA

Common name: Bread flower
Vernacular name: Kesidang

Botany and uses

Vallaris glabra Kuntz or bread flower is a woody climber with broadly elliptic leaves of 7–9 × 4–6 cm in size.[93] Inflorescences are long-stalked with clusters of fragrant cup-like white flowers of 1.0–1.5 cm in diameter. The plant is well known in Thailand and Malaysia because its flowers have a scent of leaves of pandan (*Pandanus amaryllifolius*) or newly cooked fragrant rice. The aromatic compound is 2-acetyl-1-pyrroline, first reported in cooked rice and in pandan leaves. Originated from Java in Indonesia, the species grows in full sun and can be propagated by marcotting. With its attractive clusters of white flowers that emit a strong pandan fragrance, *V. glabra* is becoming a popular ornamental plant in botanic and home gardens of Southeast Asia. Potted plants can be purchased from nurseries. There are no reports of the use of this species in traditional medicine.

Phytochemistry and pharmacology

Little is known on the phytochemistry and pharmacology of *V. glabra*. Recently, bioassay-guided separation of leaves led to the isolation of two cardiac glycosides.[94] Compound 1 was identified as acoschimperoside P, 2'-acetate and compound 2 was a new cardiac glycoside. Compound 1 was active in hedgehog signalling inhibition, and showed strong cytotoxicity against human pancreatic (PANC1) and human prostate (DU145) cancer cells.

The anticancer and antimalarial properties of *V. glabra* have been reported.[8,9] DCM and DCM:MeOH leaf extracts displayed positive antiproliferative activity against six human cancer cell lines of MCF-7, MDA-MB-231, HeLa, HT-29, SKOV-3 and HepG2 while Hex, DCM, DCM:MeOH and MeOH extracts inhibited K1 strain of *P. falciparum* but not 3D7 strain. Similar to leaves, flower extracts of *V. glabra* displayed broad-spectrum antiproliferative activity with effective inhibition of HT-29, MCF-7, MDA-MB-231 and SKOV-3 cancer cells.[95] Inhibition of stem extracts was more specific to MCF-7 and SKOV-3 cells.

From the MeOH leaf extract of *V. glabra*, caffeoylquinic acids (3-CQA, 4-CQA and 5-CQA), and a flavonol (quercetin 3-*O*-glucoside or isoquercitrin) were isolated.[95,96] Content of 5-CQA in *V. glabra* was two times higher than flowers of *Lonicera japonica* (the commercial source), while 3-CQA and 4-CQA content was 16 times higher. From the DCM leaf extract, stearic acid and ursolic acid were isolated.[96] Antiproliferative activity of stearic acid from the DCM leaf extract displayed weak inhibitory activity and ursolic acid is known to have anticancer properties. MDA-MB-231 cancer cells treated with DCM leaf extract of *V. glabra* and stained with Hoechst 33342 dye showed that the extract had an apoptotic effect on the cells (Figure 2). Based on caspase colorimetry, the apoptotic effect involved activation of caspase-8, -9 and -3, but not caspase-6 (Figure 3).

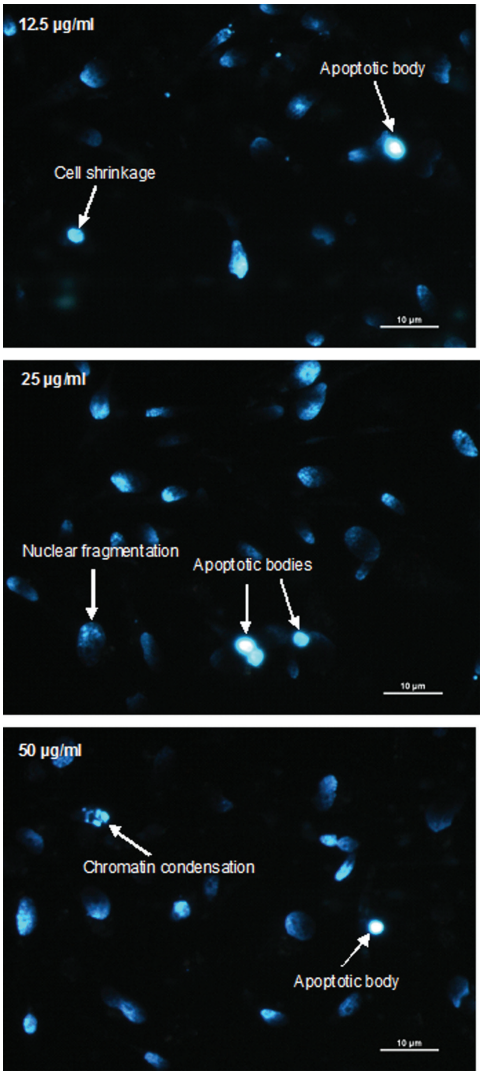

Figure 2. DCM leaf extract of *Vallaris glabra* at 12.5, 25 and 50 µg/ml showed apoptotic effects on treated MDA-MB-231 breast cancer cells.[96]

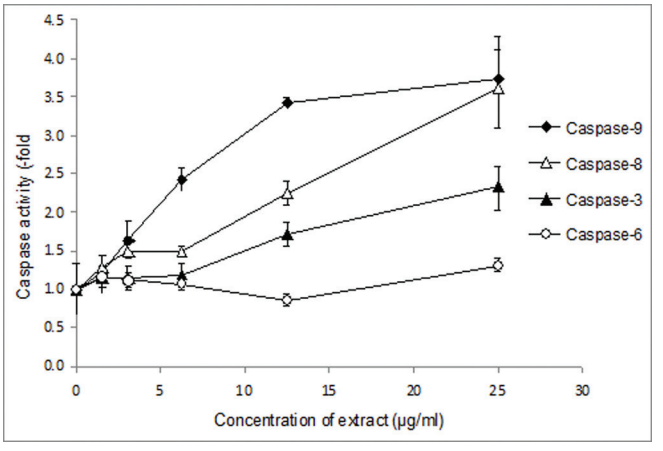

Figure 3. Graph of fold-increase in the activity of caspase-3, -6, -8 and -9 vs. concentration of DCM leaf extract of *Vallaris glabra*.[96]

CONCLUSION

Out of the ten Apocynaceae species reviewed, compounds commonly isolated were alkaloids, cardenolides and triterpenoids. Other compounds included iridoids, pregnanes, flavonoids and phenolic acids. Extracts of nine species (*A. cathartica*, *A. angustiloba*, *C. gigantea*, *C. roseus*, *C. odollam*, *K. fruticosa*, *N. oleander*, *P. obtusa* and *V. glabra*) displayed antiproliferative activity against human cancer cells. Extracts of five species (*A. angustiloba*, *C. gigantea*, *D. costulata*, *K. fruticosa* and *V. glabra*) had antiplasmodial activity against chloroquine-resistant K1 strain of *P. falciparum* with those of *C. gigantea*, *D. costulata* and *K. fruticosa* effective against chloroquine-sensitive 3D7 strain. Assessment on the antiplasmodial activity of *A. cathartica*, *C. roseus*, *C. odollam*, *N. oleander* and *P. obtusa* has yet to be undertaken. Besides their anticancer and antimalarial activities, all ten species possess a wide range of other pharmacological properties.

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