Apocynaceae Species with Anticancer Activities

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Abstract: Apocynaceae is a family of flowering plants that includes trees, shrubs, herbs, succulents and vines. The members of this family have wide variety of medicinal uses both traditionally and in conventional. The medicinal properties of the plants are due to the presence of alkaloids which is either indoline or steroidal. The anticancer bioactivities of Apocynaceae species are well known in barks and roots due to the accumulation of secondary phytocompounds, in turn lead the production of anticancer drugs in future.

Keywords: Apocynaceae, anticancer plants, phytochemical compounds, antiproliferation, cytotoxic

The family Apocynaceae consists of about 366 genera and 5100 species of tropical trees, shrubs and vines. With the inclusion of species of Asclepiadaceae, the family has now been enlarged from two to five subfamilies. 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. Several members of the family had various economic uses and are source of important natural products.

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. The most common cancers are breast, lung, colon, rectum and prostate cancers. Around one-third of deaths from cancer are due to tobacco use, high body mass index, alcohol consumption, low fruit and vegetable intake, and lack of physical activity. Many cancers can be cured if detected early and treated effectively. Vast numbers of naturally derived compounds from medicinal plants are targets for potential anticancer treatments. Apocynaceae plants are presented as a new hope for cancer patients as the plants have toxic secondary metabolites.

1. Anticancer plants in Apocynaceae

1.1. *Catharanthus* G. Don

C. roseus (Nithyakalyani or Shavamnari) is an evergreen subshrub or herbaceous plant growing 1 m tall. The leaves are oval to oblong, 2.5-9 cm long and 1-3.5 cm wide, glossy green, hairless with a pale midrib and a short petiole of 1-1.8 cm long. Leaves are arranged in opposite pairs. The flowers range from white with a yellow or red center to dark pink with a darker red center, having a basal tube 2.5-3 cm long and a corolla 2-5 cm diameter with five petal like lobes. The fruit is a

pair of follicles 2-4 cm long and 3 mm wide.

The species has long been cultivated for herbal medicine. In Ayurveda, the extracts of roots and shoots are used against several diseases including diabetes, malaria and Hodgkin's lymphoma. Other traditional uses include against dengue fever, diarrhea, cancer, skin diseases, menorrhagia/leucorrhea, indigestion, dyspepsia, dysentery, toothache, lower blood pressure, headache and antiatherosclerotic. In 1950s, *Vinca* alkaloids, including vinblastine and vincristine, were isolated from *C. roseus* and screened for antidiabetic drugs. Alkaloids also possess hypertensive, sedative and tranquillizing properties and cause relaxation of plain muscles and depression of the central nervous system.

Anticancer activities: The species is one of the most important and high value medicinal plants known for its anticancer alkaloids. It is the iota of the isolated secondary metabolites used in chemotherapy to treat diverse cancers. Moreover, they have hypoglycemic as well as cytotoxic effects. *Vinca* alkaloids are the second most used class of cancer drugs and stay among the original cancer therapies. Several high performance liquid chromatography (HPLC) methods have been developed to quantify the active alkaloids in the plant. There are four major *Vinca* alkaloids in clinical use including vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). VBL has been used as an integral part of medicinal treatment regimens for testicular carcinoma and both Hodgkin and non-Hodgkin lymphomas. It is also used in breast cancer and germ cell tumours. VRL is same to VBL. It has significant antitumour activity in patients with breast cancer and can be affected on bone tumour cells, osteosarcoma. In addition, VRL decreases the stability of lipid bilayer membranes. In the United States, VRL has been approved for the initial treatment of patients with advanced lung cancer. VCR has been approved to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumour, Hodgkin's disease and other lymphomas. Another characteristic of VCR that has been reported is treating several non-malignant hematologic disorders such as refractory autoimmune thrombocytopenia, hemolytic uremic syndrome and thrombotic thrombocytopenia purpura. VDS has similar effects to VBL. Antineoplastic activity of VDS has been reported in acute lymphocytic leukemia, blast crisis of chronic myeloid leukemia, malignant melanoma, pediatric solid tumours and metastatic renal, breast, esophageal and colorectal carcinomas.

In chemotherapy medications, vincristine and vinblastin used to treat several types of cancers and are biosynthesised from the coupling of the alkaloids catharanthine and vindoline. The newer semi synthetic chemotherapeutic agent vinorelbine, used in the treatment of non small cell lung cancer, can be prepared either from vindoline and catharanthine or from the *Vinca* alkaloid leurosine, in both cases via anhydrovinblastine. The insulin stimulating vincoline is also isolated from the plant. Vinflunine is a synthetic *Vinca* alkaloid which has been in use recently for the treatment of second line transitional cell carcinoma of the urothelium and other malignancies. Mauritianin, a flavonoid, enhances the 12-O-tetradecanoylphorbol-13-acetate (TPA),

which suppresses delayed type hypersensitivity reaction in mice, indicating that mauritianin may augment the resistance of the immune system to cancer. The 2, 3-dihydroxybenzoic acids from periwinkle show a strong radical scavenging activity which is associated with a lower risk of cancer.

1.2. *Nerium* L.

Oleander (Red Arali) grows to 2–6 metres tall, with erect stems that splay outward as they mature. The first year stems have a glaucous bloom, while mature stems have a grayish bark. The leaves are in pairs or whorls of three, thick and leathery, dark green, narrow lanceolate, 5–21 cm long and 1–3.5 cm broad, and with an entire margin filled with minute reticulate venation. The leaves are light green and very glossy when young, at maturity it becomes dull dark green. The flowers grow in clusters at the end of each branch; they are white, pink to red, 2.5–5 cm diameter, with a deeply 5-lobed fringed corolla round the central corolla tube. They are often, but not always, sweet scented. The fruit is a long narrow pair of follicles, 5-23 cm long, which splits open at maturity to release numerous downy seeds. Even though all parts of the plants are poisonous, it has been traditionally used in the treatment of cardiac illness, asthma, diabetes mellitus, corns, scabies, cancer, epilepsy and in wound healing as an antibacterial or antimicrobial. Leaf decoction is used to reduce swellings. Macerated leaves are used for itch and fall of hair. The flowers are good for inflammations, chronic pains in the muscles and joints, lumbago and headache.

Anticancer activities: Various Research findings prove that *N. oleander* can induce cell death in human cancer and inhibit fibroblast growth factor-2 (FGF-2) in prostate cancer cell lines PC-3 and DU-145. Oleandrin may stimulate apoptosis through activation-suppression of nuclear factor-kB (NF-kB), activator protein-1 (AP-1) and c-Jun NH2-terminal kinase in Hela cell line. Oleandrin treated cells irradiated with 6 Gy of γ-ray, can increase the activation of caspase 3 in humanprostate carcinoma cell line (PC-3); thus inhibit the process of tumourigenesis and inflammatory processes. It is also able to inhibit the growth of myeloma cells in a dose1, 74 x 10-5 M, proportional to the dose of vincristine sulfate 3,4 x 10-5 M.

1.3. *Plumeria* L.

P. alba (Pala) is a shrubby or small plant with a vase shaped canopy. It is grown in rich, dry to medium moisture, coastal thickets and limestone forests. The leaves are strap like and clustered at the end of branches. Flowers are white and fragrant in corymbose fascicles. The fruit is edible. Their medicinal properties are often due to their latex which is frequently drastic and corrosive. Latex is applied to ulcers, herpes and scabies. Seeds possess hemostatic properties. Moreover, its bark is bruised and applied as plaster over hard tumours; whereas the others can be used as purgative, cardiotonic, diuretic and hypotensive. The medicinal value of *Plumeria* species in the treatment of a large number of human ailments is mentioned in Ayurveda, Charaka Samhita, and Sushrita Samhita. In addition, the flowers are edible and eaten as fritters, while the heart of the wood is part of a traditional medical preparation taken as a laxative. The root bark is depurative and purgative, causing thirst. It is

used in the treatment of herpes and syphilis. The root bark is used externally as a lotion on syphilitic ulcers. The latex from the stem is caustic and used for treating ulcers, dartre and scabies. The seeds are using in the treatment of dysentery.

Anticancer activities: The synthesis of silver nanoparticles (AgNPs) from the leaf extract act as an anticancer and antimicrobial agent (Muthuraj et al., 2022). Moreover, it has effective anticancer activity against the glioma U118 MG cancer cell line with an IC_{50} value of 9.77 µg/mL AgNPs by initiating apoptosis as identified by a staining study with flow cytometric annexin V–fluorescein isothiocyanate (FITC) and propidium iodide (PI).

1.4. *Tabernaemontana* L.

T. divaricata is generally known as 'Nanthyarvattam' and grows to a height of 1.5–1.8 metres with dichotomous branches. The large shiny leaves are deep green and about 15 cm in length and 5 cm in width. The waxy blossoms are found in small clusters on the stem tips. The flowers have the characteristic 'pinwheel' shape. Both single and double flowered forms are cultivating type, the flowers of both forms being white. The plant blooms in spring but flowers appear sporadically all year. The flowers have a pleasing fragrance. More than 66 alkaloids are found in the shrub. Its habitat includes montane brush woods and sparse forests. Crape jasmine is widely used as a medicinal herb in the tropics and the plant may well be classified as a panacea for gastro-intestinal and skin affections. The roots are astringent and the decoction is used in the treatment of diarrhoea and abdominal complaints. The roots, leaves and flowers are all used in the treatment of snake and scorpion poisoning. An infusion is applied as a remedy for jungle fever. The roots are used in modern medicine to treat hypertension, headache and scabies.

Anticancer activities: Hydroalcoholic extract of flowers of *T. divaricata* possesses a moderate amount of anticancer activity and the IC_{50} value is greater than100 µg/mL (Akhila et al., 2012). The cytotoxic activity of the extracts assessed on THP-1 leukemia cell line using MTT assay and the plant demonstrated potential cancer cell inhibitory activity (Rebecca et al., 2013). The gold nanoparticles synthesized from *T. divaricata* demonstrated potent anticancer activity against MCF-7 cell line (Preetam et al., 2016). *Taberinamonatana* leaf extracts exhibit antioxidant and anticancer activity against T-24 human bladder cancer cell lines (Sridevi et al., 2018). The compound, 3'-R/S-hydroxyvoacamine, a potent acetyl cholinesterase inhibitor present in the stem of *T. divaricata* (Chaiyana et al., 2013). The alkaloid acts as non competitive inhibitor of AChE and has IC_{50} value of 7.00 ± 1.99µg/mL. The plant consisted of five novel vobasinyl ibogan type bisindole alkaloids named as tabernaricatines A-E (Bao et al., 2013). About 24 known indole alkaloids isolated from the plant; among them, conophylline has significant anticancer activities with IC_{50} values of 0.17, 0.35, 0.21, 1.02, and 1.493 µg/mL on HL-60, SMMC-7721, A- 549, MCF-7 and SW480 cell lines respectively.

1.5. *Alstonia* R.Br.

A. scholaris (Ezhilampala, Devil's tree) is a glabrous tree that grows up to 40 m tall. Its mature bark is grayish and young branches are copiously marked with lenticels. One unique

feature of this tree is that in some places, such as New Guinea, the trunk is three sided. The upper side of the leaves is glossy, while the underside is greyish. Leaves occur in whorls of three to ten; petioles are 1-3 cm; the leathery leaves are narrowly obovate to very narrowly spathulate, base cuneate, apex usually rounded and up to nine inches long by up to three inches in width. The lateral veins occur in 25 to 50 pairs at 80-90° to midvein. Cymes are dense and pubescent; peduncle is 4-7 cm long. Pedicels are usually as long as or shorter than calyx. The corolla is white and tube like, 6-10 mm long; lobes are broadly ovate or broadly obovate. The ovaries and follicles are distinct and pubescent. The fragrant flowers bloom in the month of October. Seeds are oblong with ciliated margins, and ends with tufts of hairs. The bark is almost odorless and very bitter with abundant bitter and milky sap.

Anticancer activities: Ezhilampala is an important medicinal plant in the various folk and traditional systems of medicine in Asia, Australia and Africa. The decoction, mostly prepared from the bark, is used to treat a variety of diseases of which the most important is malaria. Furthermore, the ethnomedicinal practices also suggest it to be of use in treating cancer. Additionally, the phytochemicals like echitamine, alstonine, pleiocarpamine, O-methylmacralstonine, macralstonine and lupeol are also reported to possess antineoplastic effects. In addition to the cytotoxic effects, the plant is observed to possess radiomodulatory, chemomodulatory and chemopreventive effects and free radical scavenging, antioxidant, antiinflammatory, antimutagenic and immunomodulatory activities, all of which are properties efficacious in the treatment and prevention of cancer.

The anticancer effect of various doses of an alkaloid fraction of *A. scholaris* studied in vitro in cultured human neoplastic cell lines (HeLa, HepG2, HL60, KB and MCF-7). The ASERS treatment results in a dose dependent elevation in the median and average survival time up to 240 mg/kg ASERS. Chemopreventive potential of the bark extract in DMBA induced skin tumourigenesis in Swiss albino mice was assertive.

1.6. *Carissa* L.

C. carandas (Karanta) is a woody shrub to a small tree with long, stout, sharp, horizontal spines at the base of the branchlets. It can grow up to 5m tall. Leaves are broadly ovate to oblong in shape, broadly cuneate to rounded base and apiculate apex, measuring up to 7cm long and 4cm wide. Stem has spines which are simple to slightly forked, measuring about 5cm. Flowers are red, yellow and pink in colour. It produces berry sized fruits that are commonly used as a condiment in Indian pickles and spices. It is a hardy, drought tolerant plant that thrives well in a wide range of soils. The major bioactive constituents, which impart medicinal value to the herb, are alkaloids, flavonoids, saponins and large amounts of cardiac glycosides, triterpenoids, phenolic compounds and tannins. Roots are reported to contain volatile principles including 2-acetyl phenol, lignan, carinol, sesquiterpenes (carissone and carindone), lupeol, β-sitosterol, 16β-hydroxybetulinic acid, α-amyrin, β-sitosterol glycoside and des-Nmethylnoracronycine; whereas leaves contains triterpenoids as well as tannins. The fruits consisted of carisol, epimer

of α-amyrin n, linalool, β-caryophyllene, carissone, carissic acid, carindone, ursolic acid, carinol, ascorbic acid, lupeol and β-sitosterol. Ethnopharmacological significance of the plant has been ascribed due to anticancer, anticonvulsant, antioxidant, analgesic, antiinflammatory, antiulcer, anthelmintic, cardiovascular, anti-nociceptive, antidiabetic, antipyretic, hepatoprotective, neuropharmacological, diuretic and antimicrobial activities.

Anticancer activities: The leaves and unripe and ripe fruits of *C. carandas* extract has anticancer activity using n-hexane, chloroform and methanol as the solvent systems against a three step extraction on the human ovarian carcinoma cells and lung cancer cells. The extracts exhibit good anticancerous activity (Sulaiman et al., 2008). The aqueous leaf extracts show the anticancerous efficiencies and antioxidant potentials by analyzing different antioxidant enzymes such as catalase, superoxide dismutase and glutathione-s-transferase, and non-enzymatic antioxidant, glutathione on MCF-7 cancer lines (Dua & Srivastav, 2013). Hence, the extract has the potential for future development of therapeutic drugs against breast cancer. Further, its fruits can be a good source of natural antioxidants for both pharmaceutical and dietary requirements and appears to be useful in relieving oxidative stress. The DNA damage inhibition potential of methanolic extract of *C. carandas* leaves show significant dose dependent DPPH radical scavenging, H_2O_2 scavenging and reducing power activity (Verma et al., 2015).

1.7. *Allamanda* L.

A. schotti (Manja kolambi) is an erect shrub to 2 m tall with clear sap. Leaves in whorls of 3-5 and subsessile; leaf blade elliptic or narrowly obovate, minutely hispid along veins and lateral veins elevated on abaxial surface. Corolla tube is rather narrowly funnel form, distinctly swollen at base, lobes pale yellow, ovate or orbicular. Fruits are capsules with long spines.

Anticancer activities: *Allamanda* species have been used in systems of traditional medicine for various purposes. *A. schottii* has been used to treat liver tumours, jaundice, splenomegaly and malaria. In analyses, some species have shown some activity against carcinoma cells, pathogenic fungi and HIV. The root extract of the species is the most active. The root extracts show a cytostatic effect on K562 due to the strong cytotoxic effect. Similar cytostatic and cytotoxic effects are seen in the endothelial cells, but at lower doses. Parts of *A. schottii* are assayed against three different cultured cells: K-562, a cell line derived from chronic myeloid leukemia in blastic crisis; BMEC, primary bone marrow endothelial cells; and HUVEC, primary human umbilical cord endothelial cells.

1.8. *Holarrhena* R.Br.

'Kallippala' is a deciduous shrub or small tree which grows well on open wastelands and uplands. Stems are short pale bark with several branches. Leaves are opposite, ovate, obtusely acuminate and long with short stalks. Flowers white and turn creamish yellow at maturity, appear at the end of the branch in corymb like cymes and have oblong petals. Fruits are thin and cylindrical with two follicles which attached together at distal ends and contain 25-30 seeds. Most of the known chemical constituents in *H. antidysenterica* have been found in the stem, bark,

leaves and a few in the seeds as well. The major constituents are steroidal alkaloids, flavonoids, triterpenoids, phenolic acids, tannins, resins, coumarins, saponins and ergostenol. The plant is widely used in traditional medical system for treatment of constipation and diarrhea; hence, proved usefulness in gut motility disorders. The alkaloids present in the ethanolic extract have significant antibacterial and diarrhoeal properties. The plants consist of antidiabetic activities and are used to treat fever, bleeding piles, vomiting, leprosy and herpes.

Anticancer activities: The extracts from leaves of *H. antidysenterica* show cytotoxicity against fourteen human cancer cell lines including A-549, COLO-205, DU-145, HeLa, HEP-2, IMR-32, KB, MCF-7, NCI-H23, OVCAR-5, SiHa, SK-N-MC, SW-620 and ZR-75-1 from nine different tissues like breast, colon, cervix, CNS, lung, liver, oral, ovary and prostate. The cytotoxic activity is found in the chloroform soluble fraction of 95% ethanolic extract at 100 µ/mL and inhibits the growth in the range of 71-99% of seven human cancer cell lines from five different tissues via. OVCAR-5, HT-29, SK-N-MC, HEP-2, COLO-205, NIH-OVCAR-3 and A-549. The cytotoxic activity of chloroform soluble fraction found to be higher than 5-flurouracil, adriamycin, mitomycin-c and paclitaxel.

1.9. *Ichnocarpus* R.Br.

I. frutescens (Vettyar valli) is a woody shrub with lianas sprawling to 10 m in maximum length and 6 cm in diameter. The bark produces a creamy white sap. The leaves are up to 11 cm long by 4.5 cm wide. The inflorescence is a head of several flowers. Each flower has a calyx of densely hairy sepals and a five lobed corolla just under a centimeter long. The fruit is a follicle which may be over 14 cm long. The plant has a large number of traditional medicinal uses because of the presence of alkaloids, flavonoids, terpenoids and glycosides which act against rheumatism, asthma, cholera and fever. The extracts of the plant inhibit tumours, protect liver cells from damage in acetaminophen overdose and reduce complications of hyper lipidemia in diabetic rats.

Anticancer activities: The residue from methanolic extract of roots of *I. frutescens* (MIF) and isolated triterpenes show anticancer activity against MCF-7, BEL-7402, SPC-A-1 and SGC-7901 cancer cell lines. MIF exhibits significant anticancer activity on four cancer cell lines with IC_{50} values 163.5±3.58, 156.3±2.95, 142.6±2.60 and 112.4±1.85 respectively. It effectively inhibits in vitro proliferation of U-937 monocytoid leukemia and K-562 erythroleukemia cell lines, U-937 and K-562.

1.10. *Kopsia* Blume

K. fruticosa is a shrub or a tall bush with simple leaves. It is an evergreen shrub growing upto 4m tall. Leaf blade is narrowly elliptic or narrowly oblong, tip sharp or blunt. The plant is hairless except for inflorescence. Flower occurs in bunches of a few. Beautiful light pink flowers, which may also be almost white, have 5 petals that are oblong. *Kopsia* monoterpene alkaloids present in various skeletons, but aspidofractinines, eburnamines and chanofruticosinates are the three major backbones. Mersinines and pauciflorines are new chemical classes of monoterpene alkaloids. With the rich content of monoterpene alkaloids, *Kopsia* constituents are the main objects in pharmacological studies, since the

plant extracts and isolated compounds are proposed for antimicrobial, antiinflammatory, antiallergic, antidiabetic, antimanic, antinociceptive, acetylcholinesterase (AChE) inhibitory, cardiovascular and vasorelaxant activities.

Anticancer activities: Extracts of *K. fruticosa* had the highest TAC against MCF-7 cells. Ten new indole alkaloids of the aspidofractinine type in the leaf and stem-bark extract of the Malayan *K. singapurensis*, include kopsimalines A-E (1-5), kopsinicine (6), kopsofinone (7), and kopsiloscines H-J (8-10). Kopsimalines A (1), B (2), C (3), D (4), and E (5) and kopsiloscine J (10) found to reverse multidrug resistance in vincristine resistant KB cells, with 1 showing the highest potency. Valpacrinine isolated from Malayan *K. arborea* shows pronounced cytotoxic effects against KB and Jurkat cells.

1.11. *Ochrosia* Juss.

O. elliptica (Ochrosia) is an evergreen shrub or small tree usually growing 4-6 m tall but sometimes reaching 12 m. It has leathery dark green elliptic to obovate leaves up to 8-20cm long and 4-8cm wide. The leaves occur in whorls of 3 or 4. The flowers occur in axillary clusters and are small, yellow or white and fragrant. They are followed by pairs of striking red fruit with 5-6 cm long and 2-3 cm diameter. The fruits are poisonous and plants bleed white sap copiously when wounded.

Anticancer activities: The plant is well known as a promising anticancer agent. Carbohydrates, sterols, catechol tannins, flavonoids and alkaloids are present in all the organs of the plant. Ellipticine, a cytotoxic plant alkaloid, is known to inhibit topoisomerase II in human breast MCF-7 cancer cells. Treatment of cells with ellipticine results in inhibition of growth, and G2/M phase arrests of the cell cycle. This effect associates with a marked increase in the protein expression of p53 and, p21/WAF1 and KIP1/p27. Ellipticine treatment increases the expression of Fas/APO-1 and its ligands (mFas ligand and sFas ligand), and subsequent activation of caspase 8. The mitochondrial apoptotic pathway amplifies the Fas/Fas ligand death receptor pathway by Bid interaction in turn result in a significant increase in activation of caspase 9.

1.12. *Rauvolfia* L.

R. vomitoria is a small tree or large shrub growing to 8 m high. The branches grow in whorls, and the leaves grow from swollen nodes in groups of three. The leaf blades are broadly lanceolate or elliptical and tapering to a long point. The small, fragrant flowers follow by globular red fruit. All parts of the plant, except the mature wood, contain latex. *R. vomitoria* has been used across its range in traditional medicine. A decoction or extract of the roots is used for diarrhea, jaundice, rheumatism, snake bites, fever, to calm people with anxiety or epilepsy, and to lower blood pressure. The macerated root or sometimes the pulped fruit is used for a variety of skin conditions. The bark, twigs and leaves are used as a purgative and emetic. The plant contains a number of chemical compounds used by the pharmaceutical industry including reserpine, reserpinine, deserpidine, ajmalicine and ajmaline.

Anticancer activities: The β-carboline alkaloids from *R.vomitoria* are using against human LNCaP prostate cancer cell to block the metastasis. *Rauwolfia* extract decreases in vitro

cell growth in a dose dependent manner and induces the accumulation of G1 phase cells. PARP cleavage demonstrates that apoptosis is induced only at the highest concentration tested which was confirmed by detection of cells containing sub genomic DNA. The expression of genes associated with DNA damage signaling pathway upregulates by *Rauwolfia* treatment including that of GADD153 and MDG. Moreover, the expression of a few cell cycle genes like p21, cyclin D1 and E2F1 modulates by the plant extracts. tumour volumes decrease by 60%, 70% and 58% in the groups fed the 75, 37.5 or 7.5 mg/kg *Rauwolfia*, respectively. *R. vomitoria* has potent antitumour activity against ovarian cancer.

1.13. *Thevetia* L.

T. peruviana (Manjarali) is an evergreen tropical shrub or small tree. The leaves are willow like, linear-lanceolate and glossy green in color. They are covered in waxy coating to reduce water loss. The stem is green turning silver or gray as it ages. The flowers are long funnel shaped, fragrant and yellow in terminal clusters. Its fruit is deep red-black in color encasing a large seed that bears some resemblance to a 'Chinese lucky nut'. Moreover, the plant is rich in phytochemicals like alkaloids, phenolic compounds, tannins, glycosides, cardiac glycosides, flavonoids, diterpenes, steroids and saponins.

Anticancer activities: *T. peruviana* methanolic extract exhibits cytotoxic activity on four human cancer cell lines like colorectal adenocarcinoma (HTB-38), lung carcinoma (HTB-177), prostate adenocarcinoma (HTB-81) and breast adenocarcinoma (HTB-22) with values of IC_{50} 1.91 ± 0.76, 5.78 ± 2.12, 6.30 ± 4.45 and 12.04 ± 3.43 µg/mL respectively. The extract causes a significant reduction of cell motility and colony formation on all cancer cell lines. In addition, the morphological examination displays cell size reduction, membrane blebbing and detachment of cells, compared to non treated cancer cell lines. The *T. peruviana* extract induces apoptotic cell death, which was confirmed by DNA fragmentation and AO/EB double staining. Cardiac glycosides from seeds of *T. peruviana*, are cytotoxic toward cancer cell lines P15, MGC-803, SW1990 and normal hepatocyte cell, LO2. They selectively inhibit the proliferation of cancer cell lines with IC_{50} from 0.05 to 0.15 µM.

1.14. *Wrightia* R.Br.

W. tomentosa (Ayyappala) is a deciduous tree with a rounded crown. It can grow up to 20 m tall and the unbuttressed bole can be up to 35cm in diameter. The plant contains four uncommon sterols, desmosterol, clerosterol, 24-methylene-25-methylcholesterol and 24-dehydropollinastanol in turn help to treat snake bites, scorpion stings and renal complaints.

Anticancer activities: The plant extract exhibits antiproliferative activity against MDA-MB-231 and MCF-7 cancer cells. The CH_2Cl_2 extracts of the leaves and twigs of *W. pubescens* exhibit varying cytotoxic activities. The ethanolic extract, subsequent hexane fractions and fraction F-4 of *W. tomentosa* inhibit the proliferation of human breast cancer cell lines, MCF-7 and MDA-MB231. The fraction F-4 obtained from hexane extract inhibits proliferation of MCF-7 and MDA-MB-231 cells in concentration and time dependent manner with IC_{50} of 50µg/mL and 30µg/mL for 24h, 28µg/mL and 22µg/mL for 48h and 25µg/mL

and 20µg/mL for 72h respectively. The fraction F-4 induced G1 cell cycle arrests reactive oxygen species generation, loss of mitochondrial membrane potential and subsequent apoptosis. Normally, the apoptosis is indicated in terms of increased Bax/Bcl ratio, annexin-V positivity, caspase 8 activation and DNA fragmentation. The active molecule isolated from fraction F4, oleanolic acid and urosolic acid, inhibites cell proliferation of MCF-7 and MDA-MB-231 cells at IC_{50} value of 7.5µM and 7.0µM respectively; whereas there is devoid of significant cell inhibiting activity in non cancer originated cells like HEK-293. Different extracts of *W. tinctoria* leaves have negative impact on replication of HIV-1(IIIB) in MT-4 cells and HCV in Huh 5.2 cells.

1.15. *Beaumontia* Wall.

B. brevituba is often rampant climber. Leaves are large, smooth and opposite with sticky white sap from petiolar glands. The large white fragrant flowers are borne in terminal corymbs and in the leaf axils. The calyx is 5-lobed and the corolla is dark funnel or bell shaped with 5 lobes. Stamens are attached near the base of the corolla tube and have slender filaments with arrow shaped anthers. They are very showy when in full bloom and are regarded as among the most outstanding vines of the world. The fruits comprise a pair of thick woody follicles. The seeds are compressed and apex gradually narrows with a silky coma.

Anticancer activities: Five known cardenolides, digitoxigenin, oleandrigenin, digitoxigenin alpha-L-cymaroside, digitoxigenin beta-gentiobiosyl-alpha-L-cymaroside, and delta 16-digitoxigenin beta-D-glucosyl-alpha-L-cymaroside isolated from the stems of *B. brevituba* show cytotoxicity against cultured human lung cancer cell line. The compounds have cytotoxic activity on human and murine cancer cell lines. The lignan glycoside, syringaresinol beta-D-glucoside, isolated for the first time in the form of its levo-enantiomer from the species which is also anticancerous.

1.16. *Cerbera* L.

C. odollam (Othalanga) is a tree species commonly known as the 'Suicide tree'. The branchlets are whorled about the trunk and leaves are terminally crowded, with tapering bases, acuminate apices and entire margins. The plant as a whole yields a milky white latex. Fruit, when still green, looks like a small mango, with a green fibrous shell enclosing an ovoid kernel measuring approximately 2 cm × 1.5 cm and consisting of two cross matching white fleshy halves. On exposure to air, the white kernel turns violet, then dark grey and ultimately brown or black.

Anticancer activities: The cytotoxicity of the leaf of *C. odollam* against two breast cancer cell lines (T47D and MCF-7), two ovarian cancer cell lines (SKOV3 and CaOV3) and a normal (Vero) cell line was investigated. It shows potent anticancer activity with IC_{50} values of 17, 21, 28, 32 and 24 mM, respectively. Tanghinin, isolated from *C. odollam*, exhibits cytotoxic activities against oral human epidermoid carcinoma (KB), human breast cancer cell (BC) and human small cells lung cancer line (NCI-H187).

1.17. *Chonemorpha* G. Don.

C. fragrans, the 'Frangipani vine' or 'Climbing frangipani' is a vigorous, generally

evergreen, climbing shrub producing stems 30 m or more long that can climb to the tops of the tallest trees in the forests of Southeast Asia. It has scented white flowers and large shiny leaves.

Anticancer activities: The plant is commonly used as medicine in Ayurveda and contains alkaloids including camptothecin, chonemorphine and funtumafrine. Camptothecin is a monoterpene indole alkaloid and several synthetic drugs which are analogs of captothecin are used in chemotherapy for various cancer types. MTT assay shows that the chloroform extract of callus has potent anticancer potential. The plant has a promising anticancer activity against human colon epithelium, lung carcinoma and epidermoidal carcinoma cell lines.

1.18. *Strophanthus* DC.

The genus name is a compound of the Greek words '*Strophes*' (twisted) and '*Anthos*' (flower) in reference to the corolla lobes. In *S. petersianus*, corolla resembles long twisted ribbons or threads and can reach a length of 30-35 cm. *Strophanthus* has been used medicinally as a cardiac stimulant and in the treatment of peptic ulcer and snake bites. The extract possesses antimicrobial, wound healing, antioxidant, analgesic and anticarcinogenic properties. The plant contains toxic alkaloids and cardiac glycosides including g-strophanthin (ouabain), k-strophanthin and e-strophanthin.

Anticancer activities: Six new compounds, cardenolide glycosides boivinides 1–6 as well as the four known cardenolide glycosides, digitoxigenin 3-O-[β-d-glucopyrananosyl-(1→4)-α-l-acofriopyranoside], corotoxigenin 3-O-β-d-boivinoside, 17α-corotoxigenin 3-O-β-d-sarmentoside and uzarigenin 3-O-α-l-rhamnoside from *Stropanthus* show significant antiproliferative activity against the A2780 human ovarian cancer cell line, with boivinide A being the most active at IC_{50} of 0.17 μM. *S. Wallichii* has very good antitubercular, antioxidant and anticancer effect against renal cell carcinoma induced by DEN and Fe-NTA in male Wistar Albino rats.

1.19. *Vallaris* Burm.f.

V. glabra is a moderate growth woody climber with clusters of fragrant white flowers, which can grow up to about 2-3 m tall. Leaves are light green, glossy, opposite, elliptic or ovate with wavy leaf margin. Leaf apex is acute or has a distinct drip tip. Stems are thin, woody, light grey and having smooth bark.

Anticancer activities: Sequential extracts of leaves, flowers and stems, and fractions and isolated compounds from dichloromethane (DCM) leaf extract of *V. glabra* show anticancer effect against MDA-MB-231 cancer cells. Both DCM extracts of leaves and flowers possess broad spectrum APF activity against HT-29, MCF-7, MDA-MB-231 and SKOV-3 cancer cells and the apoptotic effect is due to the activation of caspase 8, 9 and 3. Thirteen cardenolide glycosides consist in CH_2Cl_2 and MeOH extracts of *V. glabra* leaves that induce cytotoxic activity against human cervix adenocarcinoma, lung carcinoma and colorectal adenocarcinoma cell lines.

1.20. *Calotropis* R.Br.

C. gigantea is a large shrub growing to 4 m tall. It has clusters of waxy flowers that are either white or lavender in colour. Stem is erect, branched, cylindrical, solid and contains

milky latex. Leaves are 100–200 mm long, decussate, obovate or elliptic-oblong, shortly acute, subsessile, cordate or often amplexical at the base. Flowers are in umbellate cymes, large, white, not scented and peduncles arising between the petioles. Calyx lobes 5, divided to the base and corolla broadly rotate, valvate, lobes 5, deltoid ovate, reflexed, coronate appendages broad, obtusely 2 auricled below the rounded apex which is lower than the stamina column. Stamens 5, anthers short with membranous appendages, inflexed over the depressed apex of the pentagonal stigma. Pollinium is one in each cell with pendulous caudicles slender. Carpels and styles are two in number which unite to the single pentagular stigma. Fruit is a pair of follicles with many hairy seeds. Given the potent bioactivity of calotropin, *C. gigantea* has been used as a folk medicine in India for many years and has been reported to have a variety of uses. In Ayurveda, Indian practitioners have used the root and leaf of *C. procera* in asthma, bacterial infection, swelling with redness, boils and shortness of breath. The plant is effective in treating skin, digestive, respiratory, circulatory and neurological disorders and also to treat fevers, elephantiasis, nausea, vomiting and diarrhea.

Anticancer activities: Recent studies have displayed the use of calotropin as a contraceptive and promising cancer medication. In study of the cancer fighting properties of *C. gigantea*, DCM extracts demonstrate to be strongly cytotoxic against non small cell lung carcinoma (A549), colon carcinoma (HCT116) and hepatocellular carcinoma (HepG2). These extracts show promise as cancer medications and warrant further clinical research. The extract from the stem bark of *C. gigantea* exhibits potent anticarcinogenic effects against DEN induced hepatic cancer, including a reduction in apoptosis induced cancer progression (Suphunwadee et al., 2022). Eight different cardenolides from *C. gigantea* have been shown to inhibit transcription by hypoxia-inducible factor-1 transcription. Interestingly, these cardenolides exhibit strong cytotoxic effects against MCF-7 cells, but less on normal cells. The cardenolides present in *C. gigantea* able to induce transcription of pro apoptotic genes, while repressing antiapoptotic gene expression and impart apoptosis in MCF-7 cells (Kiran & Arun, 2019).

The antitumour activity of ethyl acetate extract from the flower of the *C. gigantea* against EAC in Swiss mice is very prominent. The flower extract exhibits a significant decrease in both viable tumour cells and body weight gain induced by the tumour burden and prolonged survival time. The PUMA family proteins involve apoptosis pathways through controlling mitochondrial membrane permeability and cell death. The BH3 proteins only promote apoptosis through neutralizing apoptosis inhibitory proteins (Bcl-2 and Bcl-xL) and also by promoting the opening of mitochondrial pores comprised by the death-promoting members of the Bcl-2 family, Bax and Bak. The root extracts from *C. gigantea* has antiproliferative activity against human hepatocellular carcinoma cells, HepG2 and MCF-7 cells. Gene expression studies of Bcl-2 family of genes (Bax, Bcl-2, and p53) show significantly increased expression in Bax and p53; but significantly reduced Bcl-2 expression. The ratio of Bax/Bcl-2 is a decisive factor and plays an important role in determining apop-tosis under experimental conditions promoting cell death.

2. Outlook

Cancer is becoming a high profile disease in developed and developing worlds. Even though chemically derived drugs have been developed and other cancer treatments pre-exist, there is a demand for alternative treatments with naturally derived anticancer agents with plants being the desired source. The secondary metabolites in the plant kingdom such as polyphenols, flavonoids and brassinosteroids have been studied for their potential use as anticancer agents. Among them, anticancer and antiproliferative properties of Apocynaceae members will play significant role in future anticancer drug designing.

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