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Prospects of Traditionally important Apocynaceae plants of India in Cancer Remediation

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ABSTRACT

Objectives: Apocynaceae Family plants in India had wide array of traditional uses and practised since years ago. This review aims to report selected plants of this possessing anticancer activity. Selected literature compiled from the search of electronic journals, books and encyclopedias etc. using search engines viz. Google, PubMed, Sciencedirect, GoogleScholar and SciFinder for all periods. The Dogbane family is includes atleast 150 genera and 1700 species. Around 25 genera and 50 species of the family reviewed here possess anticancer activity. The reason for this potential is due to: a) phytoconstituents b) poisonous constituents c) antimalarial activity and d) abundance of literature in traditional medicinal use. Folk medicinal uses and reported anticancer potential suggests that the Apocynaceae plants can be formulated or developed into lead compounds or novel drugs or multidrug complex for treatment of cancer. Detailed screening of each species has to be performed in 64 pannel cell lines, mechanistic study performed clearly and effectiveness of extracts, fractions or pure isolated compounds is to be compared.

Keywords: Apocynaceae; Traditional Medicines; cancer; anticancer plants.

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INTRODUCTION

Cancer has become a curse to all age groups in which 5% cases are strongly hereditary. Cancer possesses heavy loads of economic burden on the families. GLOBOCAN registry estimated 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide. ICMR warned India over 17.3 lakh new cases of cancer and 8.8 lakh deaths especially, cancers of breast, lung and cervix till 2020. A substantial portion of cancer cases and deaths could be prevented by broadly applying effective prevention measures, such as breast feeding, avoiding junk and tinned food, tobacco/alcohol control, vaccination, and the use of early detection tests [1, 2].

Vast numbers of naturally-derived compounds from medicinal plants are targets for potential anticancer treatments. This review is an effort to highlight major apocynaceae plants which decrease growth of cancer or is being used as adjuvant with cancer treatments for patients who already have or have had cancer. Plants which are under trial or is researched for its anticancer potential is reported here. Apocynaceae plants are presented as a new hope for cancer patients as the plants have toxic secondary metabolites. The information disseminated through this review will help the researchers for generating family specific data for different type of cancers.

Methods

Relevant literatures related to the terms "Apocynaceae", "Cancer herbal drugs", "Ethnopharmacology", and "Traditional" were obtained from different sources viz., PubMed, Sciencedirect and SciFinder databases.Medicinal literature was also searched from NISCAIR Online Periodical repository (NOPR), pubfacts and Google Scholar. The data specific to the Cancer Remediation and the Mechanism/Pathway of the particular plant/isolated phytoconstituents was collected and compiled. Research published till February 2018 is included in the study.

Research into herbal medicines for specific cancers

Cancer cells are immortal and exhibit exponential growth. Cancer cell mostly targets metabolic enzymes, gene regulator protein and cytoskeleton protein. An ideal anticancer drug should be able to induce apoptosis and angiogenesis;

blocking metabolic reactions of glucose transport, glycolysis, mitochondrial oxidative phosphorylation, and fatty acid synthesis and regulation of epigenetic processes. The drug should also be selective in action to malignant cell and should have minimum toxicity [3, 4].

Approving herbals as anticancer should have favorable pharmacokinetic properties (ADMET- absorption, distribution, metabolism, excretion and toxicity). Dose, dosage form and Safety are other serious issues. Since ancient times, nature has been a source of medicines to cure many deadly diseases. Clinically proven herbal anticancer drugs are: Taxanes(Docitaxel, paclitaxel (Taxol®),taxotere), vinca alkaloids(vinblastine, vincristine (Oncovin®), vinorelbine (Navelbine®)), Etoposide, teniposide (Vumon®), and various water-soluble analogs of camptothecin (Hycamtin®), brassinosteroids, Flavopiridol, polyphenol epigallocatechin-3-gallate, Pomiferin, histone deacetylase inhibitor, 9-bromo-noscapine;Bromelain, podophyllotoxins(topotecan, irinotecan) as well as epipodophyllotoxins, homoharringtonine, Elliptinium/ ellipticine. Olomucine/ roscovitine, combretastatins (Combretastatin A-4), Betulinic acid, Pervilleine-A, Silvesterol, Resveratrol and Piceatannol a hydroxylated version of Resveratrol and Pterostilbene a methoxylated version of Resveratrol, Coronaridine, Silvesterol, Thapsigargin, jatrophane, Curcuma longa, Ipomoea batatas, Centaurea schischkinii, and many others. Apomorphine hydrochloride, tiotropium bromide, nitisinone, galantamine hydrobromide, arteether are the drugs derived from plants used as approved drugs [5,6,7].

APOCYNACEAE PLANTS AS ANTICANCERS

Apocynaceae as anticancer family [8,9]

Apocyanceae family is the 5th largest family of medicinal plants. Toxic secondary metabolitesin the plants act against cellular level toxicity and Neoplasm. For eg. Reproductive system (R. vomitoria), respiratory disorder (tylophora indica), diabetes (catharanthus roseus), anti-inflammatory and analgesic (funtumia elastic, landolphia owariensis and picralima nitida). [10-15].

Cardenolides, as a group of natural products that can bind to Na+/K+-ATPase with an inhibiting activity, are traditionally used to treat congestive heart failure. Recent studies have demonstrated that the strong tumor cytotoxicities of cardenolides are mainly due to inducing the tumor cells apoptosis through different expression and cellular location of Na+/K+-ATPase α-subunits. The leaves, flesh, seeds and juices of numerous plants from the genera of Nerium, Thevetia, Cerbera, Apocynum and Strophanthus in Apocynaceae family, are the major sources of natural cardenolides. So far, 109 cardenolides have been isolated and identified from this family, and about a quarter of them are reported to exhibit the capability to regulate cancer cell survival and death through multiple signaling pathways. In this review, we compile the phytochemical characteristics and anticancer activity of the cardenolides from this family. Compounds belonging to the cardiac glycosides may stimulateCa2+and increase apoptosis in prostate cancer [16].

Naturally occurring iridoids and secoiridoids in the family are reported as immunomodulators and adaptogens. Iridoids and secoiridoids show cardiovascular activity, antihepatotoxicity, choleretic activity, hypoglycemic activity, antiinflammatory activity, antispasmolytic activity, antitumor activity, antiviral activity and purgative action [17].

Antitumour activity is reported in barks and root extracts of some Apocynaceae plants such as Allamanda, Alstonia, Calotropis, Catharanthus, Cerbera, Nerium, Plumeria and Tabernaemontana. Latex from Himatanthus drasticus janaguba, Alstonia angustiloba, Calotropis gigantea, Dyera costulata, Kopsia fruticosa and Vallaris glabra are active against tumour and ulcers. Latex is rich in saponins, tannins, cardenolides and terpenoids and triterpenes such as Lupeol, betulin, betulinic acid and calenduladiol [18, 23].

The search for improved cytotoxic agents (more potent, more selective, and less toxic) continues to be an important line in the discovery of modern anticancer drugs from natural source.

Indole alkaloids is abundant in plumerioideae subfamily; tribus alstonieae- alstonia, catharanthus, vinca, amsonsia. Tribus-tabernaemontanaeae-tabernaemontana, tabernanthae, voacanga. Tribus rauwolfiaeae- kopsia, ochrosia, rauwolfia, vallesia. Also present is Sarpagine group of indole alkaloids [19-22]

Nature-derived antimalarials have been proved to act as anticancers. [23-25].

Allamanda [26-28]

The root extract of A. schottii was the most active of them. At 80 µg/mL, the root extracts showed a cytostatic effect on K562, whereas at 400 µg/mL, there was a strong cytotoxic effect. Similar cytostatic and cytotoxic effects were seen in the endothelial cells, but at lower doses. Parts of A. schottii were 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 and MCF-7 lines.

Phytochemical investigation of different fractions and isolates has previous evidence of anticancer and antitumoral properties.

Alstonia [29-34]

The anticancer effect of various doses of an alkaloid fraction of Sapthaparna, Alstonia scholaris (ASERS), was studied in vitro in cultured human neoplastic cell lines (HeLa, $HepG_2$, HL60, KB and MCF-7) and in Ehrlich ascites carcinoma bearing mice. The IC_{50} was found to be 5.53, 25, 11.16, 10 and 29.76 µg/mL for HeLa, $HePG_2$, HL60, KB and MCF-7 cells, respectively. The ASERS treatment resulted in a dose dependent elevation in the median survival time (MST) and the average survival time (AST) up to 240 mg/kg ASERS and declined thereafter. The surviving animals were healthy and disease free. The effect of ASERS was better than cyclophosphamide, which was used as a positive control, where all the animals succumbed to death by 40 days and the MST and AST were 19.5 and 18.3 days, respectively. The effective dose of 210 mg of ASERS was 3/10 of the LD_{50} dose, which increased the MST and AST up to 54 and 49.5. Chemopreventive potential of Alstonia scholaris bark extract in DMBA-induced skin tumorigenesis in Swiss albino mice was assertive. A. venenata leaves showed considerable cytotoxicity towards neoplastic cells (DLA cells and EAC cells).

The rhazinilam-type alkaloids (rhazinicine, nor-rhazinicine, rhazinal, and rhazinilam) showed strong cytotoxicity toward human KB, HCT-116, MDA-MB-231, and MRC-5 cells.

Beaumontia [35]

Five known cardenolides, digitoxigenin (1), oleandrigenin (2), digitoxigenin alpha-L-cymaroside (3), digitoxigenin beta-gentiobiosyl-alpha-L-cymaroside (4), and delta 16-digitoxigenin beta-D-glucosyl-alpha-L-cymaroside (5), were isolated from the stems of Beaumontia brevituba Oliver by cytotoxicity-directed fractionation monitored by a cultured

human lung cancer cell line. The cytotoxic activity of these compounds was evaluated with a panel of twelve human and murine cancer cell lines. The lignan glycoside, syringaresinol beta-D-glucoside, was obtained for the first time in the form of its levo-enantiomer.

Carissa [36-40]

C. opaca crude extract showed 78.5% inhibition against MCF-7 breast cancer cell line using MTT assay at 500 µg/mL. Fractions were tested at 200 µg/mL concentration and were more active than crude extracts. Chloroform fraction of C. opaca showed maximum inhibition 99% followed by ethyl acetate and methanol fraction of C. opaca exhibiting 96% and 94% inhibition, respectively. Also exhibited cytotoxicity at 800µg/mL on HeLa cancer cells. IC50 values ranged from 56.72 to 89.24 µg/mL in MTT assay on HeLa, MCF-7, and HepG-2 cell lines besides MG-63.

Cerbera [41-45]

The cytotoxicity of the leaf of Cerbera odollam was investigated against two breast cancer cell lines (T47D and MCF7), two ovarian cancer cell lines (SKOV3 and CaOV3) and a normal (Vero) cell line. It showed potent anticancer activity with IC50 values of 17, 21, 28, 32 and 24 nM, respectively. Tanghinin, isolated from C.odollam exhibited cytotoxic activities against oral human epidermoid carcinoma (KB), human breast cancer cell (BC) and human small cells lung cancer (NCI-H187).

Chonemorpha [46-49]

MTT assay showed 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. It was found to possess Topo as well as DNA polymerase inhibitory activity.

Ervatamia [50-56]

T. divaricata screened on cancer cell line (HeLa) and MTT assay was used to analyze the cell growth inhibition. The extract on Hep 2 cell line up to 7.8 µg/ml and that IC50 value on Hep 2 cell line was 112 µg whereas 94 µg for Vero cell line.

Six new bisindole alkaloids of the iboga-vobasine type, vobatensines A-F (1-6), in addition to four known bisindoles (8-11), were isolated from a stem bark extract of a Malayan Tabernaemontana corymbosa. Nine of these alkaloids (1-5, 8-11) showed pronounced in vitro growth inhibitory activity against human KB, PC-3, LNCaP, HCT 116, HT-29, MCF7, MDA-MB-231, and A549 cancer cells.

The wood and stem bark of Ervatamia heyneana (Apocynaceae) yielded 14 indole alkaloids and 3 triterpenoids. Six of these isolates, camptothecin (2), 9-methoxycamptothecin (3), coronaridine (1), pericalline (25), heyneatine (18) and 10-methoxyeglandine- N-oxide (4) displayed cytotoxic activity.

The alkaloid fractions of ethanolic extract of E. coronaria showed cytotoxicity with LC50 values of 65.83 mg/ml in the BSL bioassay. The purified alkaloid fraction of E. coronaria exhibited highest cytotoxicity in HT-29, A-549 and MCF-7 cell lines with IC50 values of 32.5, 47.5 and 72.5 mg/ml, respectively.

Holarrhena [57-60]

In vitro cytotoxic potential of extracts (95% and 50% ethanolic extract and hot water extract at concentration of 100 microg/ml) from leaves of Holarrhena antidysenterica was evaluated against fourteen human cancer cell lines--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 (breast, colon, cervix, CNS, lung, liver, oral, ovary and prostate) using SRB assay cytotoxic activity was found in the chloroform soluble fraction of 95% ethanolic extract at 100 microg/ml; it inhibited the growth in the range of 71-99% of seven human cancer cell lines from five different tissues viz., OVCAR-5 (ovary), HT-29 (colon), SK-N-MC (neuroblastoma), HEP-2 (liver), COLO-205 (colon), NIH-OVCAR-3 (ovary) and A-549 (lung). The cytotoxic activity of chloroform soluble fraction was found to be higher than 5-flurouracil, adriamycin, mitomycin-c and paclitaxel (anticancer drugs used as positive controls).

Ichnocarpus [61-65]

In vitro anticancer activity of the residue from methanolic extract of roots of I. frutescens (MIF) and isolated triterpenes were evaluated by 3-(4, 5-dimethyl thiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay using MCF-7, BEL-7402, SPC-A-1 and SGC-7901 cancer cell lines. MIF showed significant anticancer activity on four cancer cell lines with IC50 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 cell lines.

Kopsia arborea [66-69]

Extracts of *Kopsia fruticosa* had the highest TAC against MCF-7 cells.

Ten new indole alkaloids of the aspidofractinine type, the leaf and stem-bark extract of the Malayan Kopsia singapurensis, 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) were found to reverse multidrug-resistance in vincristine-resistant KB cells, with 1 showing the highest potency [78]. Valpacrinine isolated from Malayan Kopsia arborea showed pronounced cytotoxic effects against KB and Jurkat cells (IC50 13.0 and 0.91 µM, respectively).

Nerium [70-79]

Research extract of Nerium oleander (Anvirzel) can induce cell death in human cancer can 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), c-Jun NH2-terminal kinase inHela cell line. Oleandrin given after 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 tumorigenesis and inflammatory processes. Oleandrin is also able to inhibit the growth of myeloma cells in a dose1,74 x 10-5 M, proportional to the dose of vincristine sulfate3,4 x 10-5 M. Three compounds, oleandrin, odoroside A and B evaluated against four human cell lines, normal human fibroblast cells (WI-38), malignant tumor cells induced from WI-38 (VA-13), human liver tumor cells (HepG2), and human lung carcinoma cells (A-549). Activity of Breastin, a defined extract isolated from the plant Nerium Oleander in 63 human cell lines swcreened; 31 / 63 cell lines investigated showed IC50 < 1.14 µg/ml. e.g. Cisplatin, 5-Fluoruracil and Cyclophosphamide. The highest activity was seen in bladder, CNS, colon and NSC lung cancer cell lines as well as in pancreas and prostate models. In systematic combination studies Breastin increased the effect of the tubuline binders Paclitaxel, and Docetaxel in 4/6 cell lines, the alkylating agents Cyclophamide and Mitomycin, adriamycin and alimta.

Ochrosia [80-82]

Ellipticine, a cytotoxic plant alkaloid, is known to inhibit topoisomerase II in human breast MCF-7 cancer cells. Treatment of cells with ellipticine resulted in inhibition of growth, and G2/M phase arrest of the cell cycle. This effect was associated with a marked increase in the protein expression of p53 and, p21/WAF1 and KIP1/p27, but not of WAF1/p21. Ellipticine treatment increased the expression of Fas/APO-1 and its ligands, mFas ligand and sFas ligand, and subsequent activation of caspase-8. The mitochondrial apoptotic pathway amplified the Fas/Fas ligand death receptor pathway by Bid interaction. This effect was found to result in a significant increase in activation of caspase-9.

Plumeria acuminate [83-86]

The methanol extract of Plumeria acuminata leaves exhibited antitumor effect by modulating lipid peroxidation and augmenting antioxidant defense system in EAC bearing Swiss albino mice.

Cytotoxic compounds isolated from the aqueous extract of the bark(iridoid, plumericin and the lignin and liriodendrin), demonstrated general cytotoxic activity against murine lymphocytic leukemia (P-388) and a number of human cancer cell-types (breast, colon, fibrosarcoma, lung, melanoma, KB). Plumeria bracteata is most potent anticancer plant.

Rauvolfia [87-88]

ß-carboline alkaloids from R.vomitoria are screened using WST-1 method against human LNCaP prostate cancer cell. Rauwolfia extract decreased in vitro cell growth in a dose-dependent manner and induced the accumulation of G1 phase cells. PARP cleavage demonstrated that apoptosis was induced only at the highest concentration tested (500 µg/ml) which was confirmed by detection of cells containing sub-genomic DNA. The expression of genes associated with DNA damage signaling pathway was up-regulated by Rauwolfia treatment, including that of GADD153 and MDG. The expression of a few cell cycle genes (p21, cyclin D1 and E2F1) was also modulated. These alterations were confirmed by RT-PCR. Tumor volumes were decreased by 60%, 70% and 58% in the groups fed the 75, 37.5 or 7.5 mg/kg Rauwolfia, respectively. Rauvolfia vomotoria has potent antitumor activity and in combination significantly enhances the effect of Carboplatin against ovarian cancer.

Strophanthus [89-91]

All 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, showed significant antiproliferative activity against the A2780 human ovarian cancer cell line, with boivinide A being the most active at IC50 = 0.17 µM.

Strophanthus Wallichii has very good antitubercular, antioxidant and anticancer effect against clear cell renal cell carcinoma induced by DEN and Fe-NTA in male Wistar Albino rats.

Thevetia [92-94]

The cancer cell lines used in this study were human colorectal adenocarcinoma (HTB-38), lung carcinoma (HTB-177), prostate adenocarcinoma (HTB-81), and breast adenocarcinoma (HTB-22), whereas the normal cell lines used were human skin fibroblast (CCL-116) and Vero cell line (CCL-81). The *T. peruviana* methanolic extract exhibited cytotoxic activity on four human cancer cell lines: prostate, breast, colorectal and lung, 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 caused a significant reduction of cell motility and colony formation on all evaluated cancer cell lines. In addition, morphological examination displayed cell size reduction, membrane blebbing and detachment of cells, compared to non-treated cancer cell lines. The *T. peruviana* extract induced apoptotic cell death, which was confirmed by DNA fragmentation and AO/EB double staining. Cardiac glycosides (**1–7**) from seeds of T.peruviana, are cytotoxic toward cancer cell lines P15 (human lung cancer cell), MGC-803 (human gastric cancer cells), SW1990 (human pancreatic cancer cells), and normal hepatocyte cell LO2. They selectively inhibit the proliferation of cancer cell lines with IC_{50} from 0.05 to 0.15 µM.

Trachelospermum [95-97]

The leaves and stems of T. jasminoids contain indole alkaloids like coronaridine, voacangine, apparicine, conoflorine, and 19-epi-voacangarine.

Vallaris [98-101]

Sequential extracts of leaves, flowers and stems, and fractions and isolated compounds from dichloromethane (DCM) leaf extract of V. glabra were assessed for APF activity using the sulphorhodamine B (SRB) assay. Apoptotic effect of MDA-MB-231 cancer cells treated with DCM leaf extract of V. glabra was studied using Hoechst 33342 dye and caspase colorimetry. Both DCM extracts of leaves and flowers possessed broad-spectrum APF activity against HT-29, MCF-7, MDA-MB-231 and SKOV-3 cancer cells. Caspase colorimetry showed that the apoptotic effect involved activation of caspase-8, -9 and -3, but not caspase-6.

Thirteen cardenolide glycosides (1–13) were isolated from the CH2Cl2 and MeOH extracts of Vallaris glabra leaves their cytotoxic activity against human cervix adenocarcinoma, lung carcinoma, and colorectal adenocarcinoma cell lines checked. The two most potent compounds [2′-O-acetylacoschimperoside P (1) and oleandrigenin-3-O-α-l-2′-O-acetylvallaropyranoside (2)] exhibited IC50 values in the range of 0.03–0.07 µM

Vinca [102-105]

Vinca alkaloids, Vinblastine, Vinorelbine, Vincristine and Vindesine are used clinically. 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, enhanced the 12-O-tetradecanoylphorbol-13-acetate (TPA), which suppressed 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 showed a strong radical-scavenging activity, which is associated with a lower risk of cancer.

Wrightia [106-113]

Antiproliferative activity of WTBM was evaluated against MDA-MB-231 and MCF-7 cancer cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, colony formation, and Hoechst staining. In addition, (DPPH) radical scavenging activity and (ABTS) radical cation decolorization assay. Total phenolic content was assessed by Folin–Ciocalteu method. WTBM significantly suppresses colony formation and induces apoptosis in both MDA-MB-231 and MCF-7 cells as evident by morphological assessment, clonogenic. Mixtures of 1 and 2 (1:1 and 1:2), 2,

3, 4, 5, and 6 from the CH2Cl2 extracts of the leaves and twigs of W. pubescens (R.Br.) exhibited varying cytotoxic activities.

The ethanolic extract, subsequent hexane fractions and fraction F-4 of W. tomentosa inhibited the proliferation of human breast cancer cell lines, MCF-7 and MDA-MB231. The fraction F-4 obtained from hexane fraction inhibited proliferation of MCF-7 and MDA-MB-231 cells in concentration and time dependent manner with IC50 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 arrest, reactive oxygen species (ROS) generation, loss of mitochondrial membrane potential and subsequent apoptosis. Apoptosis is indicated in terms of increased Bax/Bcl ratio, enhanced Annexin-V positivity, caspase 8 activation and DNA fragmentation. The active molecule isolated from fraction F4, oleanolic acid and urosolic acid inhibited cell proliferation of MCF-7 and MDA-MB-231 cells at IC50 value of 7.5µM and 7.0µM respectively, whereas there is devoid of significant cell inhibiting activity in non-cancer originated cells, HEK-293. In both MCF-7 and MDA-MB-231, oleanolic acid and urosolic acid induced cell cycle arrest and apoptosis as indicated by significant increase in Annexin-V positive apoptotic cell counts.

Different extracts of leaf parts of Wrightia tinctoria has been studied against replication of HIV-1(IIIB) in MT-4 cells and HCV in Huh 5.2 cells. The ethanolic extract, subsequent hexane fractions and fraction F-4 of W. tomentosa inhibited the proliferation of human breast cancer cell lines, MCF-7 and MDA-MB-231 [103]. The ethanolic extract, subsequent hexane fractions and fraction F-4 of W. tomentosa inhibited the proliferation of human breast cancer cell lines, MCF-7 and MDA-MB-231. The fraction F-4 induced G1 cell cycle arrest, reactive oxygen species (ROS) generation, loss of mitochondrial membrane potential and subsequent apoptosis. Apoptosis is indicated in terms of increased Bax/Bcl-2 ratio, enhanced Annexin-V positivity, caspase 8 activation and DNA fragmentation. The active molecule isolated from fraction F-4, oleanolic acid and urosolic acid.

DISCUSSION AND CONCLUSION

With the exploration advancedment, human health is at stake with new resistant cases of existent diseases and Cancer is the one! New chemical entities (NCEs) fail to develop as a solid drug. Our Earth has a hidden treasure for all our sufferings in the form of Food, Clothing, Shelter and Medicine. Plants, soil, water, organisms and their remnants have abundant advantages. Medicinal plants are boon to almost all kinds of diseases. Apocynaceae plants are toxic and bitter plants but are sweet to our health. They have proved to a drug for all organ disease.

The integration of Ayurvedic wisdom with drug discovery also brings the need for a paradigm shift in the extraction process from sequential to parallel extraction. Bioassay-guided fractionation of the identified plant may lead to standardized extract or isolated bioactive druggable compound as the new drug [110].

Bioactivity-guided fractionation should be performed with a view to identifying novel compounds which will serve as candidates for preclinical testing. With the advent of combinatorial chemistry and high throughput screening, however, even greater progress may now be expected with natural product leads.

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Table 1: list of Indian apocynaceae plants (growing/cultivated) with Indian name, their traditional uses and phytochemistry.

S.N.	Plant name	Local name	Traditional uses	Phytochemistry
1	Aganosma dichotoma	Malatilata	Emetic and anthelmintic bronchitis, leprosy, and skin diseases diseases of eyes, snake-bite analgesic, antidiarrheal, antidiabetic, anodyne, and sedative properties. Also used for paraplegia, sciatica and neuralgia.	Flavonoids such as rutin, robinin and other glycosides of kaempferol and quercetin, lupeol, beta setosterol, ursolic acid
2	Allamanda cathartica	Alokananda	Scabicide purgative anthelminthic, hyperthermia, laxative and emetic. It is used to cure malaria and jaundice. Antidote for poisoning. Ascites, ringworm infection.	Iridoid lactones (allamandin, allamandicin and allamdin), iridoid glycosides (plumieride coumarate and plumieride coumarate glucoside), and iridoid lactones (isoplumericin and plumericin).
3	Alstonia scholaris	Saptparni	Viper bite wound healing sedative and to treat hypertension.	monoterpenoid indole alkaloids, Alstonoside, a secoiridoid glucoside, Iridoids, coumarins, flavonoids, leucoanthocyanins, reducing sugars, simple phenolics, steroids, saponins and tannins, Alstonic acids A and B, triterpenoids
4	Anodendron paniculatum	bada dudheli mal	Jaundice/ hepatitis cuts and wounds Used to treat dyspepsia dementia antipyretic, antifertility and antirheumatic.	
	Apocynum cannabinum	Indian hemp	baby's cold, earache, headache, nervousness, dizziness, worms and insanity, cardiotonic, diaphoretic, diuretic, emetic and expectorant syphilis venereal warts hydrocephalus, urinary difficulties, dropsy, jaundice, liver problems, tumors, hemorrhoids, opthalmia and eye diseases.	Apocynin, apocynamarin, cymarin, and and rosin.
5	Beaumontia /jerdoniana/	Easter lily vine	Abortifacient, loss in libido, fractures, injury, and backache and leg pain caused by	Alkaloids, flavonoids, phenols, glycosides, steroids are present

	grandiflora		rheumatism.	
6	Carissa carandas	Karaunda	Diarrhea, dysentery, cold, and fever, appetite. delivery pain muscular pain bronchitis and asthma	flavonoids, saponins, large amounts of cardiac glycosides, terpenes(carissone and carindone), tannins, urosolic acid isomer (carissic acid), Volatile constituents, polyphenols coumarin, pentacyclic triterpenoids , α-amyrin and β-sitosterol, carandinol, betulinic acid, Carisol, carinol, ascorbic acid.
7	Chonemorpha fragrans/grandiflora	Moorva	Used gynecological problems skin diseases, leprosies, syphilis, leprosy, dyspepsia, flatulence, colic constipation, helminthiasis, hyperdipsia, cardiac debility, diabetes, jaundice, bronchitis, and intermittent fever.	Campothecin, chonemorphine, funtumafrine, japindine, baurenolacetate, β-sitosterol and taraxasterol
8	Ervatamia/tabernaemontana divaricata	Tagaar / chandni	Jaundice. Chronic herpes. Rheumatism. Lymph node enlargement.mastitis, tonsillitis, and mumps whitlow, cuts, and wounds. Scabies intestinal worms throat pain and phlegm erysipelas and eczema. Tonsillitis, pharyngitis, and laryngitis wounds, snake/scorpion bite and rheumatism.	9-methoxy camptothecin coronaridine, pericalline, heyneatine and 10-methoxyeglandine- N-oxide Voacamine, Apparicine, Vobasine, Ibogaine, Conophylline, Tabernaemontamine, Voacangine, Voacristine,
9	Holarrhena antidysentrica	Kutaja/dudhi	Diarrhea, stomachache, and leukorrhea increase milk antidysentric chronic chest complaints, spleen diseases, jaundice, bilious, and calculi toothache anthelmintic menstrual cycle diabetes management rheumatic pain, used for acne treatment.	Conessimine, conessine holafrine, holarrhenine, holarrhetine, holarrhimine, kurchicine, Conamine, conarrhimine, conessidine, conimine conkurchine, conkurchinine holarrhine, holarrhessimine holarrhidine, kurchine, isoconessimine, kurchamine, lettocine, Antidysentericine
10	Ichnocarpus frutescense	Sariva/Siamlata/dhudhilata	fevers, gout, rheumatism, arthritis, epilepsy, venereal diseases, herpes, and skin diseases dysentery, measles, splenomegaly, and tuberculosis antidysentric, antipyretic, demulcent, diaphoretic, and hypoglycemic rheumatic pain. Improve memory power. Jaundice. galactogogue diuretic and diaphoretic treatment of skin eruptions	Phenylpropanoids, phenolic acids, coumarines, flavanoids, sitosterol and sitosterol palmitate.α-amyrin, and its acetates, lupeol and its acetates, flavones (apigenin and luteolin), glycoflavones (vitexin and isovitexin, proanthocyanidin and phenolic acids), vanillic, syringic and synapic acid, protocatechuic acid, Ursolic acid acetate, kaemferol, kaemferol-3-galactoside (trifolin), apigenin, luteolin, protocatechuic acid, quercetin and quercetin-3-O--D-glucopyranoside.
11	Kopsia fruticosa	Shrub vinca	Central nervous system (CNS) effects syphilis and has cholinergic malaria. Antimicrobial, antifungal, and cardiac effects	Kopsine, fruticosine and fruticosamine, Kopsamine aspidofractinine, kopsinine kopsiflorine, kopsilongine, kopsaporine, kopsingarine, kopsingine, venalstonine derivatives(venacarpines A and B), dioxokopsan derivative (kopsorinine), novel indole alkaloids, triterpenoids
12	Nerium indicum	Kaner	Abortifacient; scabies with itching sensation and eczema septic carbuncles, leprosy piles easy delivery.warts and ringworm. Impetigo for chronic ulcers antidote to snake bite rubbed on body in allergy, headache, aphrodisiac malaria and respiratory problems ear pain bad breath and toothache leukorrhea and menorrhagia.	galacturonic acid, two aristolochic acid derivatives and 3-aristolactam derivatives, two pentacyclic triterpenoids, Cardiac glycosides (kaneroside and neriumoside), digitoxigenin and uzarigenin glycosides oleanderigenin glycosides. Adynerin, flavonoid glycosides (quercetin and kaempferol)
13	Ochrosia elliptica/oppositifolia		Used in gynecological disorders	ellipticine and its derivatives, 9-methoxy ellipticine, retellipticine, ellipticiniums
14	Parameria laevigata		rheumatism, nephritis, menses emmenagogue cuts lacerations dysentery, tuberculosis, shrink the uterus after delivery, stomachic,	
15	Parsonsia alboflavescense		leg swellings, disinfectant, tuberculosis, vulnerary febrifuge, rheumatism, and kidneys	
16	Plumeria rubra	Kath- champa	Malaria, Leprosy, antiherpetic, venereal infections, Rheumatism, and abdominal tumors purgative, cardiotonic, diuretic, hypotensive bronchitis, cholera, cold, and cough antipyretic, antifungal.	amyrins, β sitosterol, scopoletin, iridoids, Plumericin, isoplumericin, plumeride, coumerate, geraniol, citronellol, farnesol and phenylethyl lupeol nanoate, allamcin, and allamandin, fulvoplumerin and Rubrinol; Nerolidols, naphathalene, linalool, quercetin and kaempferol, benzyl salicylate, benzyl benzoate.

17	Rauvolfia serpentina	Sarpgandha	Stimulate uterine contraction in case of difficult delivery, stomachache, muscular and rheumatism pain, cough and cold, skin disease cure mental disorders high blood pressure ulcer and clear intestinal worms. Snakebite, insect sting, and animal bite. Stomach distress malaria respiratory problems.	Deserpidine, reserpiline, reserpine, reserpinine rescinnamine, ajmalicine sarpagine, serpentine, yohimbine, ajmaline, isoreserpiline, connescine, corynanthine, desmethoxyreserpine raujemidine, raunescine, rauwolscine, recanescine, tetraphyllicine, tetraphylline, sandwicine, micranthine serpentidine.
18	Strophanthus wallichii		heart stimulant and to treat injury and snake bites diuretic	Cardiac glycosides
19	Thevetia nerilifolia/peruviana	Peeli Kaner	Abortifacient, purgative, rheumatism, dropsy, intermittent fevers violent emetic, hemorrhoids snake bite skin complaints.	Cardiac glycosides (triosides or monosides type), adigitoxigenin, or cannogenin (the 19-oxo form of digitoxigenin) or cannogenol (the 19-oxy form of digitoxigenin), Triosides: Thevetin, 2'-O-acetyl cerberoside, Monosides (neriifolin), cerberin (2'-O acetylneriifolin), peruvoside, thevenerin (ruvoside) and perubosidic acid (perusitin).
20	Trachelospermum asiaticum	Star Jasmine	Restorative and tonic. Analgesic, antibacterial, antispasmodic, depurative, emmenagogue, febrifuge, cardiotonic and hemostatic.	E-nerolidol and phellandrene trans-linalool oxide and citronellol
21	Urceola micrantha		Treatment of infantile paralysis, rheumatalgia, injury, and fractures.	
22	Vallaris solanaceae	Choudhari Bel	Ringworm infection, eczema, cut, sores, and wounds bite fixing teeth, applied to wounds and soresleprosy, sprue, dyspnea, piles/hemorrhoids bone fracture Hanthi paon.	cardiac glycosides; acoschimperoside P, mono-O-acetylvallaroside,mono-O-acetylsolanoside, mono-O-acetylaco-schimperoside P, vallaroside, vallarosolanoside, solanoside and 16-deace- tyl-16-anhydroacoschimperoside P, O- Palmitic, oleic and linoleic acids.β-sitosterol, β-amyrin and ursolic acid.
23	Vinca rosea	Sankhpushpi	malaria, dengue fever, diarrhea, diabetes, cancer, and skin diseases menorrhagia/leukorrhea indigestion, dyspepsia, dysentery, toothache purgative and toothache. Lower blood pressure menstrual complaint/leukorrhea, headache diabetes antiatherosclerotic.	vincanidine vincanine, vincamajoreine , vincamajorídine, isovincamine, perivincine, vincamine, vincaminorine, vinine, ajmalicine, catharanthine, leurosine, perivine, vincaleucoblastine, vinceine, (raubasine), lochnerine, lochnericine, vindoline, vinblastine, vinflunine, serpentine,vincristine,Vindesine and vinorelbine (semisynthetic derivatives of vinblastine), caffeoylquinic acid, flavonol glycosides, anthocyanins.
24	Wrightia tinctoria	Pala indigo/indrajao/dhudla	Cures diseases of pittam and vatam, skin diseases, eczema, dysentery, psoriasis, venereal diseases, stringent, anthelmintic, stomachic, antipyretic, tonic, antidysenteric, diarrhea, piles, leprosy, worm Infestation, thirst, pain, diarrhea. Used for renal complications, menstrual disorders and amebic dysentery	Lupeol, stigmasterol campetosterol, Indigotin, indirubin, tryptanthrin, isatin, anthranillate and rutin Triacontanol, Wrightial, cycloartenone, cycloeucalenol, β-amyrin, Alpha-Amyrin, β-sitosterol, 14α-methylzymosterol. Four uncommon sterols, desmosterol, clerosterol, 24-methylene-25-methylcholesterol, 24-dehydropollinastanol and Triterpinoids.

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