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 use 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 antitumor 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 panel 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.

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 potent 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 herbas 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 (Docetaxel, paclitaxel (Taxol®), taxotere), vinca alkaloids (vinblastine, vincristine (Oncovin®), vinorelbine (Navelbine®)), Etoposide, teniposide (Vumon®), and various water-soluble analogs of camptothecin (Hyacintin®), 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, Pervilliene-A. Silvertrastorol and Pyretrinone a hydroxylated version of Resveratrol and Pterostilbene a methoxylated version of Resveratrol, Coronaridine, Silvesterol, Thapsigargin, Jatrophone, Curcuma longa, Ipomoea batatas, Centaurea schischkinii, and many others. Apomorphine hydrochloride, tiotropium bromide, nitosine, galantamine hydrobromide, arteether are the drugs derived from plants used as approved drugs 5, 6, 7.

APOCYNNACEAE PLANTS AS ANTICANCERS

Apocynaceae as anticancer family 8, 9

Apocynaceae family is the 5th largest family of medicinal plants. Toxic secondary metabolite is the plants act against cellular level toxicity and Neoplasms. 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 growth 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 stimulate Ca2+ 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, choleric activity, hypoglycemic activity, antiinflammatory activity, antispasmodic activity, antitumor activity, antiviral activity and purgative activity 17.

Antitumour activity is reported in barbs and root extracts of some Apocynaceae plants such as Allamanda, Alstonia, Calotropis, Catharanthus, Cerbera, Nerium, Plumeria and Tabernanthea. Latex from Himatanthus dracunculoides (Janganbul), 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 alstoniacee- abontia, catharanthus, vinca, amsonia. Tribus-tabernantheanaceae-tabernaemontana, tabernantheae, voacanga. Tribus rauwolfeiacee- kopsia, ochrosia, rauwolva, vallesia. Also present is Sarpa group of indole alkaloids 19-22.

Nature-derived antimalariales have been proved to act as anticancer. 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 Saphaparna, Alstonia scholaris (ASERS), was studied in vitro in cultured human neoplastic cell lines (HeLa, HepG2, HL60, KB and MCF-7) and in Ehrlich ascites carcinoma bearing mice. The IC50 was found to be 5.53, 25, 11.16, 10 and 29.76 μg/mL for HeLa, HepG2, 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 LD50 dose, which increased the MST and AST up to 54 and 49.5. Chemopreventive potential of Alstonia scholaris bark extract in DMB-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 (rhzainicine, 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, digoxigenin (1), oleandrinigenin (2), digoxigenin alpha-L-cymaroside (3), digoxigenin beta-gentiobiosyl-alpha-L-cymaroside (4), and delta 16-digoxigenin 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** 56-60

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 800 μg/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.

**Chromemorpha** 46-49

MTT assay showed that the chloroform extract of callus has potent antitumor potential. The plant has a promising antitumor activity against human colon epithelium, lung carcinoma, and epidermoid carcinoma cell lines. It was found to possess Topo as well as DNA polymerase inhibitory activity.

**Ervatamia** 50-56

T. divaricata screen 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 Tabernaeantiocarpa 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, MDAMB-231, and AS49 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-methoxy camptothecin (3), coronaridine (1), pericalline (25), heyneatine (18) and 10-methoxyglandine- N-oxide (4) displayed cytotoxic activity.

The alkaloid fractions of ethanolic extract of E. coronaria showed cytotoxicity with LC50 values of 65.83 μg/ml in the BSL bioarray. 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 μg/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-HeLa, OVCAR-5, SFla, 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% ethanol 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-fluorouracil, 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 thiadiazol-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 arbores** 66-69

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

Ten new indole alkaloids of the aspidofractin type, the leaf and stem-bark extract of the Malayan Kopsia singapurensis, kopsimalines A-E (1-5), kopsininine (6), kopsinolone (7), and kopsilicosines H-j (8-10), Kopsinalines 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]. Valpacinine isolated from Malayan Kopsia arbores showed pronounced cytotoxic effects against KB and Jurlat 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 NTR-terminal kinase inlfe 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 dose 1.74 x 10-5 M, proportional to the dose of vincristine sulfate 3.4 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; 51 / 63 cell lines investigated showed IC50 < 1.14 μg/ml e.g. Gesiplatin, 5-Fluorouracil 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 Cytophamide and Mitomycin, Adriamycin and alimta.

**Ochrlosia 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 acuminata 83-86**
The methanol extract of Plumeria acuminata leaves exhibit 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**
β-carbol ine alkaloids from R.vomitoria are screened using WST-1 method against human LNCaP prostate cancer cell. Rauvolfia 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 Rauwolvia 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 Rauwolvia, respectively. Rauwolvia vomitoria 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 bovinides 1-6, as well as the four known cardenolide glycosides digitoxigenin 3-O-[β-d-glucopyranosyl-(1→4)-α-l-acofriopyranoside], corotoxigenin 3-O-β-d-bovinoside, 17α-cortoxigenin 3-O-β-d-sarmenteside, and uzarignenin 3-O-α-l-rhamnoside from Strophanthus, showed significant antiproliferative activity against the A2780 human ovarian cancer cell line, with bovinide 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-B1). The T. peruviana methanolic extract exhibited cytotoxic activity on four human cancer cell lines: prostate, breast, colorectal and lung, with values of IC50 = 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-003 (human gastric cancer cells), SW1990 (human pancreatic cancer cells), and normal hepatocyte cell LO2. They selectively inhibit the proliferation of cancer cell lines with IC50 from 0.05 to 0.15 μM.

**Trachelospermum 95-97**
The leaves and stems of T. jasminoides contain indole alkaloids like coronaridine, voacangine, apparicine, conolorine, and 19-epi-voacangarine.

**Valarris 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-acetyllacochimperoside P (1) and oleanadrigenin-3-O-α-L-2′-O-acetylvalloarpoyranoside (2) exhibited IC50 values in the range of 0.03–0.07 μM.

**Vinca 102-105**
Vinca alkaloids, Vinblastine, Vinorelbine, Vinristine 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 urethelium and other malignancies.

Mauritainin, a flavonoid, enhanced the 12-O-tetradecanoylphorbol-13-acetate (TPA), which suppressed delayed-type hypersensitivity reaction in mice, indicating that mauritainin 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
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 F-4, oleanolic acid and ursolic 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 ratio, enhanced Annexin-V positivity, caspase 8 activation and DNA fragmentation. The active molecule isolated from fraction F-4, oleanolic acid and ursolic acid.

**DISCUSSION AND CONCLUSION**

With the exploration advancement, 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 [103].

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    | Anagarma dichotoma | Malalilata  | Emetic and anthelmintic bronchitis, leprosy, and skin diseases diseases of eyes, snake-bite analgesic, anti diarrheal, anti diabetic, anodyne, and sedative properties. Also used for paraplegia, sciatica and neuralgia. | Flavonoids such as rutin, robinin and other glycospides of kaempferol and quercetin, lupeol, beta setosterol, ursolic acid |
| 2    | Allamanda cathartica | Alokananda  | Scabicide purgative anthelmintic, hyperthermia, laxative and emetic. It is used to cure malaria and jaundice. Antidote for poisoning. Ascites, worm infection. | Iridoid lactones (allamandin, allamandin and alladin), 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 dudhimal | Jaundice/ hepatitis and wounds Used to treat dyspepsia dementia antipyretic, antifertility and antirheumatic. | Apocynin, apocynamarin, cymarin, and rosin. |
| 5    | 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, dropy, jaundice, liver problems, tumors, hemorrhoids, ophthamia and eye diseases. | Apocynin, apocynamarin, cymarin, and rosin. |
| No. | Plant Name | Common Name | Pharmacological Properties |
|-----|------------|-------------|----------------------------|
| 5   | Beaumontia / Jerdoniana / grandiflora | Easter lily vine | Abortifacient, loss in libido, fractures, injury, and backache and leg pain caused by rheumatism. Alkaloids, flavonoids, phenols, glycosides, steroids are present. |
| 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 (carissoine and carindone), tannins, urosoic acid isomer (carissic acid), Volatile constituents, polyphenols coumarin, pentacyclic triterpenoids, α-amin and β-stiosterol, 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. Camptothecin, chonemorphpine, tuntumafraine, japiidine, baurenolacetate, β-stiosterol and taraxasterol. |
| 8   | Ervatamia / tabernaemontana divaricata | Tagara / 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, pericaline, heynatine and 10-methoxyeyglanidine- N-oxide Vaocamine, Apparicine, Vobasinc, Ihogaine, Conophylline, Tabernaemontamine, Vaocangine, Vaocristine, |
| 9   | Holarrhena antidysentrica | Kuta / dudhi | Diarrhea, stomachache, and leukorrea increase milk antidysectric chronic chest complaints, spleen diseases, jaundice, bilious, and calcii toothache anthelmintic menstrual cycle diabetes management rheumatic pain, used for acne treatment. Conessimine, conessine holafrine, holarrhenine, holarrhentine, holarrhimmine, kurchicine, Conamine, conarrhimmine, conessidine, conime concurchine, conurchine holarrhine, holarrhessimine holarrhidine, kurchine, isocessimone, kurchimine, lettuceine, Antidysentericine |
| 10  | Ichnocarpus frutescense | Sariva / Siama ta / dhudhilata | Fevers, gout, rheumatism, arthritis, epilepsy, venereal diseases, herpes, and skin diseases dysentery, measles, spennomay, and tuberculosis antidysectric, 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, genanthocyanidin and phenolic acids), vanillic, syringic and synaptic acid, protocatechuc acid, Ursolic acid acetate, kaemferol, kaemferol-3-galactoside (trifolin), apigenin, luteolin, protocatechuc acid, quercetin and quercetin-3-O-D-glucopyranoside. |
| 11  | Kopsia fruticosa | Shrub vinca | Central nervous system (CNS) effects syphilis and has cholineric malaria. Antimicrobial, antifungal, and cardiac effects Kopsine, fruticosine and fruticosamine, Kopsamine aspidofractinine, kopsin, kopsilongine, kopsaporine, Kopsine, fruticosine and fruticosamine, kurchine, holarrhessimine holarrhidine, kurchine, isocessimone, kurchimine, lettuceine, Antidysentericine |
| 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 allerigy, headache, aphrodisiac malaria and respiratory problems ear pain bad breath and toothache leukorrhea and menorragia. galacturonic acid, two aristolochic acid derivatives and 3-ristoalactan 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 | Kopsine, fruticosine and fruticosamine, Kopsamine aspidofractinine, kopsin, kopsilongine, kopsaporine, kopsingarine, kopsingine, venalstonine derivatives (venacarpines A and B), dioxokopsan derivative (kopsorinine), novel indole alkaloids, triterpenoids |
| 14  | Parameria laevigata | rheumatism, nephritis, menses menemagogue cuts lacerations dysentery, tuberculosis, shrink the uterus after delivery, stomachic, | rheumatism, nephritis, menses menemagogue cuts lacerations dysentery, tuberculosis, shrink the uterus after delivery, stomachic, |
| 15  | Parsonsia alboflavescens | leg swellings, disinfectant, tuberculosis, vulnerary febrifuge, rheumatism, and kidneys | leg swellings, disinfectant, tuberculosis, vulnerary febrifuge, rheumatism, and kidneys |
| 16  | Plumeria rubra | Kathchampa | Malaria, Leproxy, antherpetic, venereal infections, Rheumatism, and abdominal tumors purgative, cardiacotonic, diuretic, hypotensive bronchitis, cholera, cold, and cough antipyretic, antifungal. amyrins, β sitosterol, scopoletin, iridoids, Plumerin, isoplumericin, plumeride, coumarate, geraniol, citronellol, farnesol and phenylethyl lupeol nanoate, allamcin, and allamandin, fulvoplerumin and Rubrinol; Neralidols, naphathalene, linalool, quercetin and kaempferol, benzyl }
17. Rauwolfia 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 dear intestinal worms. Snakebite, insect sting, and animal bite. Stomach distress  
- malaria respiratory problems.

Deserpidine, reserpidine, reserpine,  
reserpine resinominaine, ajmalicine  
sarpagine, serpine, yohimbine,  
ajmaline, isoreserpine, connescine,  
coryantheme, desmethoxyreserpine  
rauemidine, rauannesine, rauwolscine,  
recanescine, tetraphyllicine,  
tetraphylline, sandwicine, micranthe  
serpentine.  

18. Strophanthus wallichii  
- Heart stimulant and to treat injury and snake bites diuretic.

Cardiac glycosides.  

19. Thevetia nerifolia/peru viana, Peel Kaner  
- Abortificient, purgative, rheumatism, dropsy, intermittent fevers violent emetic, hemorrhoids snake bite skin complaints.

Cardiac glycosides (triosides or monosides type), adigotxinogen, or cannogenin (the 19-oxo form of digitoxigenin) or cannogenol (the 19-oxo form of digitoxigenin). Triosides: Thevetin, 2'-O-acetyl cerberoside, Monosides (nerifolin),  
verbenin (2'-O-acetylnnerifolin),  
peruvoside, theverinin ( ruvoside) and perubosic acid (perustin).  

20. Trachelospermum asiaticum, Star Jasmine  
- Restorativ and tonic. Analgesic, antibacterial,  
antisapmodic, deparative, emmenagogue,  
ferfrigue, cardiotonic and hemostatic.

E-noridolido 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 soreisleprosy, sprue, dyspnea,  
piles/hemorrhoids bone fracture Hanthi paon.  

23. Vinca rosea, Sankhpushpi  
- Malaria, dengue fever, diarrhea, diabetes, cancer, and skin diseases  
- menorrhagia/leukorrhrea indigestion, dyspepsia, dysentery, toothache purgative and toothache. Lower blood pressure menstrual  
complaint/leukorrhrea, headache diabetes  
antiatherosclerotic.  

24. Wrightia tinctoria, Pala indigo/indraj ao/dhudla  
- Cures diseases of pitam and vatam, skin  
- diseases, ezcema, dysentery, psoriasis,  
venereal diseases, stringent, antimentitic,  
 stomachic, antipyretic, tonic, antidysenteric,  
diarrhea, piles, leprosy, worm Infestation,  
thrist, pain, diarrhea. Used for renal  
complications, menstrual disorders and  
americ dysentery.

Lupeol, stigmasterol campetasterol,  
Indigotin, indirubin, tryptanthrin, isatin,  
anthrannilate and rutin Triacontanol,  
Wrightial, cycloartenone, cycloecuclanenol,  
β-amyrin, Alpha-Amyrin,  
β-sitosterol, 14a-methylzymosterol. Four  
uncommon sterols, desmosteroel,  
clerosterol, 24-methylene-25-  
methylchololesterol, 24-  
dehydropollinastanol and Triterpinoids.

REFERENCES

1. Malath MK et al; The growing burden of cancer in India:  
epidemiology and social context. THE LANCET Oncology. 2014, 15(6):e205–e212.

2. World Health Organisation. The World Health Organisation’s Fight  
against Cancer: Strategies that prevent, cure and care. WHO Press;  
Geneva: 2007.

3. Gibbs LR, Anticancer drug targets: growth factors and growth  
factor signaling. J Clin Invest, 2000; 105:9-13.

4. Pratheeshkumar P, Sreekala C, Zhang Z, et al. Cancer prevention  
with promising natural products: mechanisms of action and  
molecular targets. Anticancer Agents Med Chem. 2012; 12:1159-1184.

5. Greenwell M, Rahman P.K.S.M.; Medicinal Plants: Their Use in  
Anticancer Treatment. Int J Pharm Sci Res. 2015 Oct 1; 6(10):4103-  
4112.

6. Solowey E, Lichtenstein M, Sallon S, Paavilainen H, Elaine Solowey,  
and Haya Lorberboum-Galski. Evaluating Medicinal Plants for  
Anticancer Activity. Hindawi Publishing Corporation. Scientific World  
Journal Volume 2014.

7. Cragg GM, Newman DJ. Plants as a source of anti  
cancer agents. Journal of Enthnopharmacology. 2005; 100:72-79.

8. Solowey E, Lichtenstein M, Sallon S, Paavilainen H, Elaine Solowey,  
and Haya Lorberboum-Galski. Evaluating Medicinal Plants for  
Anticancer Activity. Hindawi Publishing Corporation. Scientific World  
Journal Volume 2014.

9. Marcy J. Balunas, A. Douglas Kinghorn. Drug discovery from  
medicinal plants. Life sciences; 2005; 78(5):431-441.
from Allamanda schottii. Revista Brasileira de Farmacognosia Rev. bras. farmacogn. 2014; 24(5).

29. Keeawpradub N, Eno-Amooquaye E, Burke PJ, Houghton PJ. Cytotoxic activity of indole alkaloids from Alstonia macrophylla. Planta Med. 1999; 65:311–5

30. Jahan S, Chaudhury R, Goyal PK. Anticancer Activity of an Indian Medicinal Plant, Alstonia scholaris, on Skin Carcinogenesis in Mice. Integrative Cancer Therapies. 2009; 8(3):273-279.

31. Ganesh Chandra Jagetia, Manjeshwar Shriniath Baliga. Treatment with Alstonia scholaris Enhances Radio sensitivity In vitro and in vivo. Cancer Biotheraphy & Radiopharmaceutica. 2004: 917-929.

32. Baliga MS. Alstonia scholaris Linn Br in the Treatment and Prevention of Cancer: Past, Present, and Future. Integrative Cancer Therapies. 2010; 9(3):261-269.

33. Keeawpradub N, Houghton PJ, Eno-Amooquaye E, Burke PJ Activity of extracts and alkaloids of Thai Alstonia species against human lung cancer cell lines. Planta Med. 1997; 63:97-101.

34. Jagetia GC, Baliga MS. Evaluation of anticancer activity of the alkaloid fraction of Alstonia scholaris (Sapathaparna) in vitro and in vivo. Phytother Res. 2006; 20:103–9.

35. Kaneda N, Chai H, Pezzuto JM, AKiinghorn AD, N. Farnsworth NR, Tuchinda P, Udchachon J, T. Santisuk, V. Rentrakul. Cytotoxic activity of cardenolides from Beaumontia brevituba stems. Planta Med. 1992.

36. Gupta P, Bhattachar J, S-Kwon Kim, Verma AK, Anbhutti Sharma. In-vitro cancer cell cytotoxicity and alpha amylase inhibition effect of seven tropical fruit residues. Asian Pacific Journal of Tropical Biomedicine. 2014; 4(4):5655–5661.

37. Bodakhe SH.; Devi N; Gupta S K.; Namdeo K.P.; Jain S K. Hepatoprotective Activity of Carissa carandas Linn. Fruit ethanol extract in carbon tetrachloride intoxicated rats. Advances in Pharmacology & Toxicology. 2014; 15(3):5-18.

38. Begum S, Syed SA, Siddiqui BS, Sattar SA, M. Iqbal Chaudhury. Cardinalis: First isohopane triterpene from the leaves of Carissa carandas L. and its cytotoxicity against cancer cell lines. Phytochemistry Letters. 2013; 6(1):91-95.

39. Sahreens K, Khan MR, Khan RA, Shah NA. Estimation of flavonoids, antimicrobial, antitumor and anticancer activity of Carissa opaca fruits. BMC Complement Altern Med. 2013; 27:3:372.

40. Nisa S, Bibi Y, Zia M, Waheed A, Chaudhary MF. Anticancer investigations on Carissa opaca and Toona ciliata extracts against human breast carcinoma cell line. Pak J Pharm Sci. 2013; 26(5):1009-12.

41. Eric Wei Chiang Chan, Siu Kuin Wong, Hung Tuck Chan, Shigeyuki Baba, and Mio Kezuka et al. Cerbera are coastal trees with promising anticancer properties but lethal toxicity: A short review. / J. Chin. Pharm Sci 2016; 25 (3): 161 – 169.

42. Sarot Cheenpracha, Chatchanok Karalai, Yanisa Rat-a-pa, Chanita Pongbhumannot, Kan Chanthronpoom. New Cytotoxic Cardenolide Glycoside from the Seeds of Cerbera manghas Chemical and Pharmacetical Bulletin. (Chem Pharm Bull) 2004; 52(8):1023-1025.

43. Siti Syarifah MM, Nurhanan MY, Mohd Haffiz J, A Mohd Ilham, K Geetha, O Asiah, I Norhayati, H Lili Sahira & S Anee S. Potential Anticancer compounds from Cerbera oddalum. Journal of Tropical Forest Science. 2011; 23(1):89-96.

44. Chang I.C, Gills JL, Bhat KP, Luyengi L, Farnsworth NR, Pezzuto JM, Kinghorn AD. Activity-guided isolation of constituents of Cerbera manghas with antiproflliative and antiestrogenic activities. Bioreg Med Chem Levt. 2000; 10(21):2431-2434.

45. Mohd Mutalip syarifah Siti, Nurhanan Yunos, 3rd J, Mohd Haffiz et al. Potential anticancer compound from Cerbera oddalum. Journal of Tropical Forest Science. 2011; 23(1):89-96.

46. Shah VC, Adolf S. D’sa, Noel Jde Souza. Chonomorphine, stigmasterol, and ecydysterone: Steroids isolated through bioassay-directed plant screening programs.Steroids. 1989; 53(3-5):559-565.

47. Kedari P, Malpathak N. Quantification of Camptothecin in Different Plant Parts of Chonemorpha Fragrans. Advances in Zoology and Botany. 2013; 1(2):34-38.
Devi et al. 2017.

Journal of Drug Delivery & Therapeutics. 2019; 9(1):293-302

ISSN: 2250-1177

CODEN (USA): JDDTAO

singapurensis Rkl. Journal of Chemical and Pharmaceutical Research (JCPR), 2014; 6(5):815-822.

67. Lim KH, Hiraku O, Komiyama K, Keyano T, Hayashi M, Kam TS. Biologically active indole alkaloids from Kopsia arborea. J Nat Prod. 2007; 70(8):1302-7.

68. Subramaniam G, Hiraku O, Hayashi M, Koyama T, Komiyama K, Kam TS. Biologically active aspidofractline alkaloids from Kopsia singapurensis. J Nat Prod. 2008; 71(1):53-7.

69. Lim SH, Sim KM, Abdulah U, Hiraku O, Hayashi M, Komiyama K, Kam TS. Leuconoxine, kopssitaine, kopsitiamine, and kopssione derivatives from Kopsia. J Nat Prod. 2007 Aug; 70(8):1380-3.

70. Wahyuningsih MSH, Mularika S, Mark T, Hamann Gandjar, IG, Wahyuno S. Structure identification of potential compound as selective renal anticancer isolated from Nierium Indicum Mill. Leaves. Indonesian Journal of Pharmacy, 2008; 19(2):57-64.

71. Siddiqui BS, Begum S, Siddiqui S, Lichter W. Two cytotoxic pentacyclic triterpenoids from Nerium oleander. Phytochemistry. 1995; 39:71-4.

72. Pathak S, Multani AS, Narayan S, Kumar V, Newman RA. Anvirzel™, an extract of Nerium oleander, induces cell death in human but not murine cancer cells. Anticancer Drugs. 2000; 11:455–63.

73. Heinz H, Fiebig, Gerhard Kelter, Armin Maier, Thomas Metz and Luay J. Rashan. Abstract 5572: Breast a natural product from Nierium Oleander exhibits high activity in a panel of human tumor cell lines. A. Experimental and Molecular Therapeutics. 2013: 73(8 Supplement).

74. Turan N, Akgün-Dar K, Kurucu SE, Kılıçaslan-Ayın T, Seyhan VG, Atasever B, et al. Cytotoxic effects of leaf, stem and root extracts of Nerium oleander on leukemia cell lines and role of the p-glycoprotein in this effect. J Exp Ther Oncol. 2006; 6:31–8.

75. Siddiqui BS, Khatoon N, Begum S, Farooq AD, Kehkaskan Qamar, Huma Aslam Bhatti, Syed Kashif Ali, Flavonoids and cardenolide glycosides and a pentacyclic triterpene from the leaves of Nerium oleander and evaluation of cytotoxicity. J Ethnopharmacol. 2011; 134:781–788.

76. Qamar KA, Farooq AD, Siddiqui BS, Kabir N, Khatoon N, Ahmed S, Erum S, Begum S. Antiproliferative Effects of Nerium oleander Stem and Mitotic Arrest Induced by Cardenolide Odoroside B on OCI-H460 Cancer Cells. Letters in Drug Design & Discovery. 2018; 15(1):84-94.

77. Su Jin Song, Cheng Yun Jin, Yang Hyn Choi and Won Deok Hwang. Induction of Apoptosis by Ethanol Extract of Nierium indicum Stem Is Associated with Activation of JNK in Human Renal Carcinoma Caki-1 Cells. Cancer prevention research 2011; 1:6269-79.

78. Nagewa M. El Sawi, Neveen S. Geweely, Safaa Qusti, M. Mohamed, A. Kamel. Cytotoxicity and Antimicrobial Activity of Nerium oleander Extracts Journal of Applied Animal Research 2010; 37:25-31.

79. Garbett NC, Graves DE. Extending nature’s leads: the mechanism of ellipticine – the anticancer agent ellipticine. Curr Med Chem Anticancer Agents. 2004; 4(2):149-72.

80. Po-Lin Kuo, Ya-Ling Hsu, Cheng-Hsiung Chang, Chun-Ching Lin. The mechanism of ellipticine-induced apoptosis and cell cycle arrest in human breast MCF-7 cancer cells. Cancer Letters. 2005; 223:293-301.

81. Raham A. El-sheikh, Dalia A. Al-Mahdy, Mohamed S. Hifnawy, Tzvetomira Tsanova, Emile Evain-Banna, Stéphanie Philippot, Denise Bagrel, Essam A. Abdelsattar. Chemical and Biological Investigation of Ochosoria elliptica Labill. Cultivated in Egypt. Rec. Nat. Prod. 2017; 11(6):552-557.

82. Periyasamy G, Gupta M, Mazumder UK, Gebrelibanos, Mebratu, Sintayehu, Biruk. Antioxidant and Antitumor Activity of Plumeria acuminata in Ehrlich Ascites Carcinoma Bearing Swiss Albino Mice. British Journal of Pharmaceutical Research; 2013; 3(4):671-685.
84. Leonardus B. S. Kardono, Soefjan Tsauri, Kosasih Padmawinata, John M. Pezzuto, A. Douglas Kinghorn. Cytotoxic constituents of the bark of Plumeria rubra collected in Indonesia. J. Nat. Prod. 1990; 53(6):1447-1455.

85. Periyasamy G, Gupta M, Mazumder UK, Mebrahtu Gebrebianos and Biruk Sintayehu. Antioxidant and Antitumor Activity of Plumeria acuminata in Ehrlich Ascites Carcinoma Bearing Swiss Albino Mice. British Journal of Pharmaceutical Research. 3(4): 671-685.

86. Guevara AP1, Amor E, Russell G. Antimitogens from Plumeria acuminata Ait.; Mutat Res. 1996; 361(2-3):67-72.

87. Rens D, Capodice JL, Gorroochurn P, A.E. Katzand R. Buttyan. Anti-prostate cancer activity of a fl-carboloid alkaloid enriched extract from Rauwolfia vomitoria. International Journal of Oncology. 2006; 29:1065-1073.

88. Jun Yu, Yan Ma, Jeannie Drisko, Qi Chen. Antitumor Activities of Rauwolfia vomitoria Extract and Potentiating of Carboplatin Effects against Ovarian Cancer. Curr Ther Res Clin Exp. 2013; 75:8-14.

89. Rong-Fu Chen, Fumiko Abe, Tatsuo Yamauchi, Masakatsu Taki. Cardenolid glycosides of Strophanthus divaricate. Phytochemistry. 1987; 26(8):2351-2355.

90. Pezzani R, Rubin B, Redaeli M, Radu C, Barollo S, Maria Verena Cicala, Monica Salvà, Caterina Mian, Carla Mucignat-Caretta, Paolo Simioni, Maurizio Iacobone, Franco Mantero. The antiproliferative effects of ouabain and everolimus on adrenocortical tumor cells. Endocr J. 2014; 61(1):41-53.

91. Karkare S, Adou E, Cao S, Brodie P, James S, Miller, N. M. Andrianjafy, J. Razaftalsama, Rabobo Andriantsifetana, Vincent E. Rasamin, and David G. I. Kingston. Cytotoxic Cardenolid Glycosides of RoupeBina (Strophantus) boiviniifrom the Madagascan Rainforest. J. Nat. Prod.2007; 70(11):1766-1770.

92. Tamiris Caroline Barbon, Cásio Prinholato da Silva, Suely Vilela Sampaio, Mateus Amiral Baldo. Evaluation of Anticancer Activity Promoted by Molecules Contained in the Extracts of Thevetia peruviana Toxicon. 2012; 60(2):179-180.

93. Hoo-Yun Cheng, Dan-Mei Tian, Jin-Shan Tang, Wei-Zai Shen & Xin-Sheng Yao. Cardiac glycosides from the seeds of Thevetia peruviana and their pro-apoptotic activity toward cancer cells. Mar2016. Journal of Asian Natural Products Research. 2016, 18(9): 837-847.

94. Ramos-Silva A, Tavares-Carréon F, Figueroa M, Susana De la Torre-Zavala, Angel Gasteum-Arellanez, Aida Rodríguez-García, Luis J. Galán-Wong and Hamlet Avilés-Arnau. Anticancer potential of Thevetia peruviana fruit methanolic extract. 2017 May 2. BMC Complement Altern Med. 2017; 17:241.

95. Salama M, El-Hawary S, Mousa O, El-Askari N, Esmat RA. In vivo TNF-α and IL-1β inhibitory activity of Phenolics isolated from Trachelospermum jasminoides (Linnld.) Lem. Journal of Medicinal Plants Research. 2010; 9 (2):30-41.

96. Xing-Qi Tan, Liang-Jun Guo, Yi-Hua Qiu, Hai-Sheng Chen & Chang-Heng Tan, Chemical constituents of Trachelospermum jasminoides. 11 Aug 2009. Natural Product Research Formerly Natural Product Letters. 2010; 24(13):1248-1252.

97. Fatima T, Ijaz S, Crank G, Wasti S. Indole Alkaloids from Trachelospermum jasminoides. Planta Med. 1987; 53(1):57-9.

98. Siu Kiuin Wong, Eric Wei Chiang Chan. Botany, uses, phytochemistry and pharmacology of Vallaris: A short review. Pharmacognosy Journal. 2013; 5:242-246.

99. Dong-Woong Sim, Yoon-Jin Kim, Chiang-Chang Shen, Consolacion Y Ragasa. Cytotoxic Compounds from Wrightia pubescens (R.Br.) Phcog Res. 2018; 10(1):9-15.