Journal of Ayurveda and Integrative Medicine 13 (2022) 100545

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Review Article

Anti-cancer activities of Schedule E1 drugs used in ayurvedic formulations

E.N.T. Vikram [a], R. Ilavarasan [b], R. Kamaraj [a, *]

[a] SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Kancheepuram (Dt.), Tamilnadu 603203, India
[b] Captain Srinivasa Murthy Central Ayurveda Research Institute, Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Arumbakkam, Chennai, Tamilnadu 600106, India

ARTICLE INFO

Article history:
Received 5 October 2021
Received in revised form
13 December 2021
Accepted 11 January 2022
Available online xxx

Keywords:
Anti-cancer
Ayurveda
Schedule E1
Toxic medicinal plants
Drugs and cosmetics act

ABSTRACT

Schedule E1 is an important part of Drugs and Cosmetics Act (Government of India) that comprises the list of poisonous drugs from plant, animal and mineral origins to be consumed under medical supervision. *Ayurveda*, the world's oldest medicinal system has a list of drugs represented in schedule E1 that are used since thousands of years. This review reports the anti-cancer activities of fifteen toxic ayurvedic drugs from plant origin represented in Drugs and Cosmetics Act, 1940. The information was collected from the various authentic sources, compiled and summarised. The plant extracts, formulations, phytoconstituents and other preparations of these drugs have shown effective activities against mammary carcinoma, neuroblastoma, non-small cell lung carcinoma, lymphocytic leukaemia, colorectal adenocarcinoma, Ehrlich ascites carcinoma, prostate adenocarcinoma, glioblastoma asterocytoma and other malignancies. They have various mechanisms of action including Bax upregulation, Bcl_2 downregulation, induction of cell cycle arrest at S phase, G2/M phase, inhibition of vascular endothelial growth factors, inhibition of Akt/mTOR signalling etc. Certain traditional ayurvedic preparations containing these plants are reported beneficial and the possibilities of these drugs as the alternative and adjuvant therapeutic agents in the current cancer care have been discussed. The studies suggest that these drugs could be utilised in future for the critical care of malignancies.

1. Introduction

Cancer is a most complicated disease that results in many comorbidities and adverse effects even after treating patients with advanced techniques such as chemotherapy, radiation therapy and surgery. It can be simply called as a genetic disease that occurs mainly due to DNA damage followed by cell division [1]. Exposure to harmful substances such as tobacco smoke, ultra-violet radiation, carcinogenic chemicals and certain infections can cause mutations and damage to DNA that may end up in development of malignancy. The ability of eliminating cancer cells declines with aging which is the major reason for increased risk in elderley.

In general more than 100 types of cancers exist and they are named mainly based on the organ of origin. Some of the main categories of cancer are carcinoma (formed by epithelial cells), leukemia (formed in blood forming tissue of bone marrow), sarcoma (forms in bone and soft tissue), lymphoma (begins at lymphocytes), multiple myeloma (begins at plasma cells), melanoma (forms at melanocytes) and others such as brain and spinal cord tumors, germ cell tumors and neuroendocrine tumors.

Statistically, in India cancer accounts 9% of all deaths and the number of cases reported for the year 2020 was 1,392,179 [2]. The number of new cases and cancer deaths in India was expected to reach more than 1.7 million and 1.2 million in 2035 from 1 million and 680,000 in 2012 respectively [3]. About 19.3 million new cancer cases and 10 million cancer deaths were reported worldwide in 2020 by the project GLOBOCAN of International Agency for Research on Cancer. Globally 28.4 million cancer cases are expected In the year 2040 [4].

In USA alone, around 1,898,160 new cases and 608,570 deaths are expected due to cancer in 2021. The highest number of new cases in men are expected to be prostate cancer (26%) and in

* Corresponding author.
E-mail: monishakamaraj@gmail.com
Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2022.100545

women as breast cancer (30%) followed by Lung and bronchial cancer in both genders [5].

In order to control the cancer based morbidity and mortality, a wide search for alternative and adjuvant therapeutic agents is carried out by many researchers all around the globe which mainly focus on the natural sources such as medicinal plants and traditional systems of medicines. *Ayurveda* is a traditional system of medicine introduced in India more than 5000 years ago [6] and is becoming a major trend for treating wide ranges of health complications in the patients of all age groups. In the ayurvedic classicals such as '*Sushrutha samhita*' and '*Charaka samhita*', the tumours and cancers are represented as '*Granthi*' or '*Arbuda*'. But, despite of the renowned therapeutic uses many laws are concerned in the usage of Ayurvedic medicines in different countries.

Schedule E1 is an important part of Drugs and Cosmetics Act 1940 and Drugs and Cosmetics Rules 1945 of Government of India described under Rule 161(2) [5–8] that enlists various poisonous drugs on the basis of origin of drugs under different systems of medicines. These drugs should be consumed only under proper medical supervision and with prescription inorder to avoid the risks of toxicity. As per the schedule E1 of D&C Act 1940 (added under G.O.I. Notification No. 1-23/67-D dated 2-2-1970) the system of *Ayurveda* encovers 15 drugs under vegetable origin, 1 drug under animal origin and 9 drugs under mineral origin. The listed drugs of vegetable origin are *Ahipena, Arka, Bhallataka, Bhanga, Danti, Dhattura, Gunja, Jaipala, Karaveera, Langali, Parasika Yavani, Snuhi, Vatsanabha, Vishamushti* and *Shringivisha*. *Sarpa Visha* (Snake poison) is the only drug of animal origin. The mineral origin includes *Hartala* (Arseno sulphide), *Gauripashana* (Arsenic), *Parada* (Mercury), *Manahashila* (Arseno sulphide), *Tuttha* (Copper sulphate), *Rasa Karpura* (Hydrargyri subchloridum), *Sindura* (Red oxide of lead), *Hingula* (Cinnabar) and *Girisindura* (Red oxide of mercury).

In the D&C rules, 1945 the list of Schedule E1 drugs was modified that resulted in the removal of certain drugs. Under Ayurvedic drugs of vegetable origin, *Snuhi* was removed and 14 drugs were listed. The seeds of *Ahipena* and *Bhanga* were exempted and in *Gunja* and *Jaipala* only the seeds were included. In both D&C Act 1940 and Rules 1945, *Acontium chasmanthum* Stapf ex Holm. However, *Aconitum ferox* is discussed as *Vatsanabha* as it was reported so in many texts [9,10]. This review discusses the drugs as per the D&C act 1940 as it encovers the list of drugs in the further amendments also.

2. Sources and methodology

The most relevant and adequate information was collected from the ayurvedic texts, databases, books, official websites and research articles. Databases such as Science Direct, Google Scholar, Scopus, PubMed, Web of science and Google were also explored in order to collect the data. Keywords such as 'anti-cancer activity', 'anti-proliferative activity', 'ayurvedic-drugs', 'mechanism of action' and the scientific names of chosen plants were used. A total of 193 articles were finalized after extraction and analysis in combination with the above keywords.

The inclusion criteria was based on (i) reported anticancer activities of selected plants (ii) reported activities of various extracts and active principles isolated from the chosen plants. The collected information from the various sources were compiled, investigated and reviewed. Different active substances obtained from medicinal plants such as raw drugs, plant extracts and phytoconstituents have been discussed, based on activities against different cancer cell lines, animal models and various mechanisms which may encourage the utilization of *Ayurveda* by various researchers and health care professionals towards the management and cure of cancer.

The suitable data were extracted in table form and the mechanisms were explained under respective subheadings and the relevant representations were made through suitable figures (see Fig. 1).

3. Ayurvedic Schedule E1 drugs of vegetable origin and the anti-cancer activities

The research conducted so far have tested various anti-cancer activities of the fifteen Schedule E1 drugs of vegetable origin. Certain compounds exerted the activities against glioma, neuroblastoma, ovarian, colon, cervical, oral, gastric, prostate, breast, kidney, brain, human lymphoblast, lung adenocarcinoma, human cervical, leukemia and certain other cancer cell lines as represented in Table 1. Apart from those, the general mechanisms and the reported activities of selected plants against different cancer models that are mediated by various pathways are explained below.

3.1. Ahipena (Papaver somniferum Linn.)

Papaver somniferum is a very well-known plant species that belongs to the plant family Papaveraceae. *Ahipena* is generally called as opium poppy or bread seed poppy. This plant is a common source of many alkaloids such as Codeine, Morphine (narcotic analgesics) and several other benzylisoquinoline alkaloids (BIAs) such as Papaverine (vasodilator), noscapine (potential anticancer drug and cough suppressant) and sanguinarine (anti-microbial) [11].

Morphine shows anticancer activities by inhibiting (-)-3-acetyl-6β-(acetylthio)-N-(cyclopropyl-methyl)-normorphine (KT-90) and NF-κB. An isoquinoline alkaloid, Codeinone produces fragmentation of DNA and leads to apoptosis; Noscapine an another alkaloid present in *Ahipena* interacts with α-tubulin and exhibits anticancer and anti-angiogenetic effects [12,13].

Papaver somniferum L. extracts were reported to act by destroying the cellular membrane in tumor cell lines at specific concentrations [14]. Papaverine was reported to act as a HMGB1/RAGE inhibitor [15]. Noscapine arrests metaphase and causes apoptosis by binding to tubulin in cancer cells. In a study where transcriptomic analysis was done revealed the expression of 10 different genes exclusively which encode five classes of enzymes in HN1 poppy. Various studies such as mapping population analysis (F2 type) and bacterial artificial chromosome sequencing have indicated the linkage of these genes to HN1. Gene silencing study (virus induced) reported pathway intermediates accumulation which permits the linkage of gene function to noscapine synthesis [16].

3.2. Arka (Calotropis gigantea (linn.)R. Br. ex. Ait.)

Arka is one of the holy plants of India which belongs to the family of Apocynaceae. The genus *Calotropis* is widely available as two species in India which are *Calotropis procera* and *C. gigantea* [17]. Even though both the plants are generally called as *arka*, in the list of Schedule E1 drugs of Drugs and cosmetic act 1940 *arka* is represented as *C. gigantea* [7] and in Drugs and cosmetic act 1945, it is represented as *C. procera* [8]. In this article, the reported activities of *C. gigantea* are reviewed as it is widely available in the southern part of India from where the article was written. *C. gigantea* is a large shrub which grows upto 4 m tall with white or lavender coloured flowers which are considered to be favourite for Lord Ganesha despite their toxicity and medicinal values.

The ethyl acetate fraction of root extract and a phytoconstituent named calotroposid-A was reported to increase caspase-8 expression and enhancement of cell cycle arrest at G2/M phase [21,22]. *Calotropis gigantea* have shown synergistic effect with 5

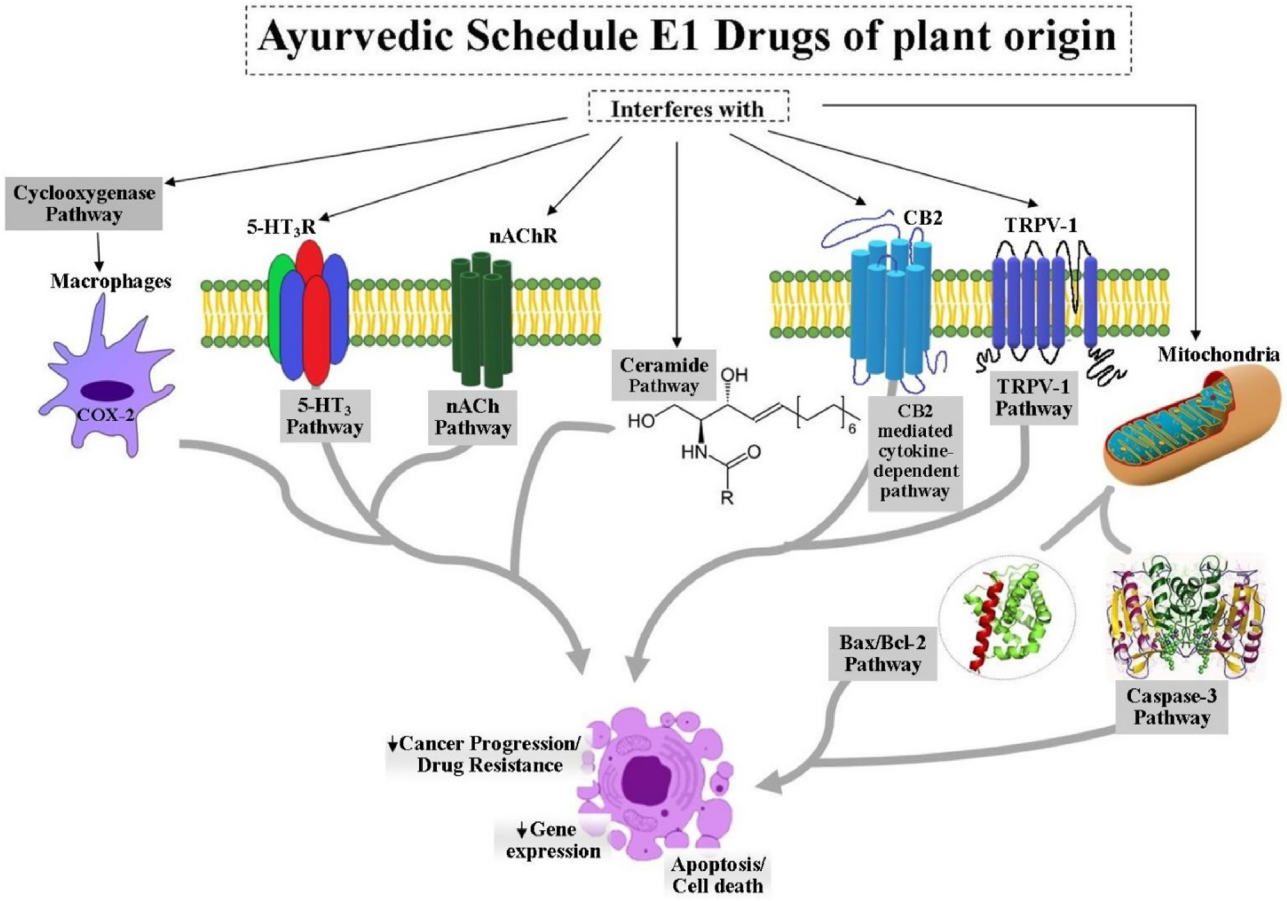

Fig. 1. Certain important pathways of reported anti-cancer activities of Ayurvedic Schedule E1 drugs and their active principles.

Fluorouracil against colon cancer (WiDR) cells [23]. The ethanolic extract of the leaves was reported to inhibit the growth of fibrosarcoma induced by 7,12-Dimethylbenz(α) antrasene (DMBA) in experimental mice and increased the caspase-3 expression significantly [24]. The cardiac glycosides present in *Arka* exhibited cytotoxic effect on MCF-7 cell line by down-regulating p53 and Bcl-2 gene expressions [25].

3.3. Bhallataka (Semecarpus anacardium Linn. F.)

S. anacardium which belongs to anacardaceae family is a deciduous tree distributed in hotter parts of India and the sub-himalayan tract. It is commonly called as marking nut tree and varnish tree. The ripen accessory fruit of *bhallataka* is sweet and edible but the black fruit is considered poisonous. It causes severe allergy when the black fruit and its resin contact the skin. The seed is considered as edible on proper preparation. The milk extract of purified nuts of *S. anacardium* which was prepared as per Formulary of Siddha Medicine (1972) was reported to possess the anti-hepatocellular carcinoma activity induced by aflatoxin B1 in experimental rats [27].

Bhallataka increased PARP cleavage, caspases, cytochrome c, Bax and decreased Bcl(2) [28]. One of the Indian traditional multi drug preparations known as *Kalpaamruthaa* which contains the milk extract of *Bhallataka* was reported to possess protective effect against the abnormal anti-oxidant levels and peroxidative damage in mitochondrial fraction of mammary carcinoma induced rats [29]. Another study suggests that the *S. anacardium* nut milk extract showed clearance of leukemic cells from the bone marrow and the internal organs of leukemic mice and shown restoration of metabolism [30].

The chloroform extract of marking nut have shown significant increase in the life span of animal models of leukemia's advanced P388, L1210, B16 Melanoma and Glioma and sublines of P388 resistant to Adriamycin/Vincristine [33]. The water alcoholic and oil extracts of the marking nut have shown anti-mutagenic activity when studied with Ames test [37]. The oil extracted from *S. anacardium* nut have shown apoptotic activity that was reported to be mediated by activation of caspases [40].

3.4. Bhanga (Cannabis sativa Linn.)

C. sativa which belongs to Cannabaceae is used in India from the early age of *Ayurveda*. This plant is popularly called as Ganja and used as a main source of phytocannabinoids which interact with the human neurotransmitter system called endocannabinoid system. It is used to relieve nausea, stimulate appetite and alleviate pain in cancer patients. The stimulation of cannabinoid receptors using cannabinoids is reported to be anti-tumorigenic. It was reported to inhibit tumor invasion/metastasis, tumor cell proliferation, block angiogenesis and induce apoptosis [42–44]. The anti tumor activities of cannabinoids are more complex as they can appear through many Cb receptor independent pathways such as TRPV1, 5-HT3 or nicotinic acetyl choline receptor (nAChR) pathways [43]. The cannabinoid (CB1 and CB2) receptors are expressed significantly in non-small cell lung cancer, hepatocellular

Table 1
Schedule E1 drugs and their anti-cancer activities against various cell lines.

Drug	Constituent	Activity reported against	Ref.
Ahipena	Noscapine	Glioma cell cancer (LN229, A172, U251), neuroblastoma (SH-EP1, NB1643, SK-SY5Y, LA1-55 N, SK-N-MC, SK-N-AS, IMR32, NB1691, SK-N-SH), Ovarian (Sig C, SK-OV-3), Colon (T84, Caco-2), Cervical (Ca Ski, HeL), prostate (DU145), breast (MCF-7, MDA-MB-231), human lymphoblast (CEM), lung adenocarcinoma (A549), human cervix (HeLa), breast epithelial (MCF-7) cell lines.	[12,13]
	Extracts of *P. Somniferum*	Human Colorectal Adenocarcinoma (HT29), Human Cervix Carcinoma (HeLa), African Green Monkey Kidney (Vero) and Rat Brain Tumor Cells (C6) cell lines	[14]
Arka	Papaverine	Human Gliobastoma (T98G, U87MG) cell lines	[15]
	18,20-epoxycalotropin, calactin, calotropin, 15β-hydroxycalotropin, calactinic acid methyl ester and zarigenin	Human small cell lung cancer (NCI-H187), Breast cancer (BC) and human oral epidermal carcinoma (KB) cell lines	[19]
	Gofruside and calotropone	Human gastric cancer (SGC-7901) and chronic myelogenous leukemia (K562) cell lines	[19]
	Dichloromethane extract	Hep G2, A549 and HCT 116 cell lines	[19]
	Chloroform soluble fractions Of root bark's methanol extract	Ehrlich ascites carcinoma (EAC) in mice	[18]
	Di-(2-ethylhexyl) phthalate	Ehrlich ascites carcinoma (EAC) in mice	[20]
	Ethyl acetate fraction of root extract, calotroposid-A	colon cancer (WiDR) cells	[21,22]
	Cardiac glycosides	breast epithelial (MCF-7) cells	[25]
	Methanolic leaf extract	Cervical (HeLa), Breast (MCF-7) and Lung (A549) cell lines	[26]
Bhallataka	Nut extracts	human breast cancer (T47D) cell line, human epidermoid larynxcarcinoma (Hep 2) cell lines	[28,31]
	Chloroform and n-hexane fractions	ER (-ve) MDA 231, ER (+ve) MCF-7 cell lines	[32]
	Acetylated oil of the nuts	lymphocytic leukemia (P388) cell lines	[34,35]
	Acetylated oil with mitomycin C, 6-mercaptopurine and methotrexate	potentiation effects against P388 lymphocytic leukemia and sarcoma 180	[36]
	Alcoholic extract of the nut	Colo-320 tumor cells	[38,39]
	Pentadecyl catachols I and II	Nasopharyngeal carcinoma and eagles 9 kb cell culture system	[38,39]
	Oil extracted from nuts	acute myeloid leukemia (HL 60) and chronic myeloid leukemia (K-562) cell lines	[40]
Bhanga	*Semecarpus lehyam*	ER (-ve) breast cancer cell lines	[41]
	(−)-trans-Δ9-tetra hydro cannabinol (THC)	Breast cancer (MCF-7), Human Glioblastoma Asterocytoma (U373-MG), Human Lung Mucoepidermoid (NCI-H292), Androgen sensitive Human Prostate Adenocarcinoma (LNCaP), Human Prostate Cancer (DU-145), Human Pancreatic Adenocarcinoma (Capan-2), pancreatic cancer (BxPC-3, MIA Paca-2 and Panc-1) cell lines	[57,63,65,66]
	Cannabidiol (CBD)	Epithelial Human Breast cancer (MDA-MB-231), Human Glioblastoma (M87-MG, T98G), Human Prostate Cancer (LNCaP and PC-3) cell lines	[67,68]
	Cbd + thc	Human Glioblastoma cell lines (SF-126, U251)	[67,68,57]
	Cannabichrome, cannabigerol	Human Prostate Cancer (LNCaP and PC-3)	[57]
Danti	Methanol extract	Cervical cancer (HeLa) cells	[88]
	12-Deoxy-5β hydroxyphorbol 13-myristate, baliospermin, montanin, 12-deoxy-16-hydroxyphorbol-13-palmitate and 12-deoxyphorbol-13-palmitate.	Lymphocytic leukaemia (P-388) cell line	[89]
	Methanolic extract	T-cell leukemia (Jurkat) and breast cancer (MCF-7) cell lines	[90]
	Silver nanoparticle made from the leaf extract	Vero and Hep2 cell lines	[91]
	Ethanolic extract	KKU-M156 and HepG2 cell lines	[92]
	Other extracts	Prostate cancer (PC3) and human colon cancer (HT-29) cell lines	[93,94]
Dhattura	7,27- dihydroxy- 1- oxowitha- 2,5,24-trienolide	Human colorectal carcinoma (HCT 116) cell line	[97]
	Withanolides (I, K, L, N) (Compounds 1,3,4 & 6) isolated from methanolic flower extract	Leukemia (K562), gastric (BGC-823) and lung (A549) cell lines	[98]
	Ethanolic leaf, stem extracts	Vero and MCF-7 cell lines	[99]
	12α-Hydroxy daturametelin	DLD-1 and A549 cancer cell lines	[100]
	Essential oils from six parts of *D. Metel*	Hep G2, HeLa and SGC-7901	[101]
	Fungal culture organic extract of endophytic fusarium solani strain isolated from *D. metel* L.	PC-3, OVCAR-3, MCF-7, HeLa and HepG2 cell lines	[102]
Gunja	Ethyl acetate fraction	breast cancer (MDA-MB-231) cell lines	[106]
	Extracts of red and white forms	Small cell lung carcinoma (A-549) cell lines	[110]
	Abrus agglutinin	Hep G2 cells	[115]
	Ethyl acetate and ethanol extracts	Sup T1, Hep G2, Y79 and Colo-205	[116]
	Bioassay-guided fractions APM-3 and APH-11	human acute monocytic leukemia, peritoneal macrophages and HEK 293 cell lines	[117]
	Ethyl acetate fraction	cervical cancer (HeLa) and Breast cancer (AU565)	[118]

Table 1 (*continued*)

Drug	Constituent	Activity reported against	Ref.
	Stigmasterol hemihydrate and B-monolinolein	breast cancer (MDA-MB-231) cell lines	[119]
	Hydroalcoholic and Petroleum ether seed extracts	Breast cancer (Zr-75-1, MCF-7) cell lines	[121]
	Aqueous extract of leaves	Murin mastocytoma (P815) cell lines	[122]
	Crude methanolic extract	human liver carcinoma (Hep G2), human colon carcinoma (HT-29) cell lines	[123]
Jaipala (Jayapala)	12-O tetra decanoyl phorbol-13-acetate (TPA)	Lung cancer, prostate or melanoma, colon and breast cancer, LNCaP cells	[138–142]
	Isoguanosine	solid tumor and ascetic tumor, S-180 ascitic tumor, Ehrlich solid tumor	[130,134]
	Seed extract	Human lung cancer (A549), Non Small Cell Lung Cancer (NSCLC)	[133]
	Methanolic extract	A549 cells	[150]
	Phorboldiesters	hepatic tumor (SNU387) cells	[151]
	Crotonols A and B	leukemia (K562), gastric cancer (SGC-7901) and breast cancer (MCF-7) cell lines	[152]
Karaveera	Essential oil from the flowers	EAC cell lines	[156]
	Oleandrin and Oleandrigenin	DU145 and PC3 cells	[157]
	Oleandrin	human myeloma (BRO), pancreatic tumor (PANC-1) cells	[159,162]
	NOE-4 (new leaf extract)	Human Burkitt's Lymphoma (Raji) cells	[160]
	Leaf, stem and root extract	Leukemia (HL60, K562) cell lines	[161]
	Breastin, a phyto cocktail	63 human tumor cell lines	[163]
Langali	Phytochemical extracts of tubers	Human liver cancer (Hep G2) cell lines	[164]
	Colchicine poor extracts	Pancreatic cancer	[165]
	22 aspergillus fungi and its isolates from *Gloriosa superba*	CVI-1, THP-1, OVCAR-5, MCF-7, HEP-2 and A-549 cell lines	[167]
	Coded extract of *Gloriosa superba* (GS-6)	Lung cancer (A-549), Ovarian Cancer (IGR-OV-1), Leukemia (THP-1), Prostate cancer (PC-3), Breast cancer (MCF-7) and Liver cancer (HEP-2) cell lines	[168]
	Undecane 2,8-dimethyl, Octadecanoic 2-oxo methyl ester, 2H-1-Benzopyran 3,5,6,8-tetrahydro, β-Amyrin trimethylsilyl ether, 1-Butanone 1-(2,4,5 trihydroxy phenyl) and 3-hydroxy-4-methoxy mandelic acid	hepatic carcinoma (Hep-G2) and Squamous skin carcinoma (A431) cell lines	[170]
Parasika- Yavani	Grossamide, Cannabisins D and Cannabisins G	Prostate (LNCaP) cancer cells	[172]
	Alkaloidal extract (apoptotic activity)	Hep-2, human rhabdomyosarcoma (RD), Murine mammary adenocarcinoma (AMN-3), A549 and PC-3 cell lines	[174]
	Ethanolic leaf and seed extracts	Du-145, A549, CCC, K562, MCF-7 and K562	[175]
Snuhi	Methanolic leaf extract	Brine shrimps	[178]
	Diterpenoids (compound 6)	Hep G2/Adr and Hep G2 cells	[182]
	Compound 15	Hep G2 cell lines	[182]
Vatsa-nabha	Alkaloids	Hep-G2, MCF-7 and HCT-116 cell lines	[183]
	Hypaconitine	A549 cells	[184]
	Aconitine	leukemia and melanoma (SK-MEL-28, SK-MEL-5), MDA-MB-468, HT-29, COLO-205 cell lines	[186]
Vishamushti	Brucine	K562, HeLa, HepG2, multiple myeloma, LoVo, HepG2, SMMC-721, Hs578-T and MDA-MB-231	[188–190,196,200,203]
	Gemcitabine and brucine	MCF-7 cells	[191]
	(Loganin 1) Strychnos nuxvomica fruits	MCF-7, PA-1, WRL-68, COLO-320 and CaCo2 cell lines	[192]
	Brucine and strychnine	RPMI 8226 cell lines	[193]
	Methanolic extract of leaf	Hep 2, MCF-7 and HCT	[194]
	Seed extracts	MCF-7 cell line	[195,198]
	Root extract	MM and RPMI 8226 cell line	[197]
Shringivisha	Methanolic extract	Brine shrimps	[205]

carcinoma, chronic lymphatic leukemia, pancreatic cancer, prostate cancer and breast cancer. HER-2 which is a breast cancer cell line induces more CB2 expression which leads to activation of pro-oncogene cascade through tyrosine kinase c-Src and ELK (ERK/MAPK cascade) [45,46].

The MCF-7 cell line has expressed the presence of Transcient Receptor Potential Vanilloid Receptor-1 (TRPV1) and the TRPV1 agonists/antagonists were found to inhibit MCF-7 cell growth significantly [41]. In certain breast cancer cells where the CB1 receptor levels were expressed more showed activation of Akt signaling pathway [47–50] and during severe conditions increased CB1 and FAAH levels were observed [51,52]. In human prostate cancer cells along with the expression of CB1 and CB2 receptors, the expression of other receptors such as TRPV 1 and Transcient Receptor Potential Ankyrin 1 (TRPA 1) were also found except in LNCaP cells. TRPV2 expression was observed only in PC-3 and DU-145 cells. TRPM8 expression was observed in AR-dependent prostate cells such as LNCaP [53–55].

In PC-3 and DU-145 cell lines expression of GPR55 was reported which mediate the effect of Lyso Phosphotidyl Inositol (LPI) [56]. Chemically induced Hepatocellular carcinoma using Diethyl nitrosamine expressed upregulation of CB1 receptors [52] whereas in normal hepatocellular carcinoma overexpression of both CB1 and CB2 receptors were reported [58]. The non-small cell lung carcinoma showed the activation of Akt signaling pathway and Matrix metallo peptidase-9 (MMP-9) expression whereas the chronic lymphocytic leukemia was found to act by CB1 receptor expression along with the expression of high risk markers [59,60]. In

Pancreatic cells the cannabinoids were found to induce apoptosis through CB2 receptors via ceramide dependent pathway [61–63]. The CB2 receptors were reported to be over expressed in Melanoma cell lines and human melanoma tissue [64].

CBD act by the mechanisms of inducing the stress of endoplasmic reticulum, inhibition of Akt and mTOR signaling, down regulation of ERK signaling pathway, inhibition of HIF-1α, decreasing AR mRNA expression, by decreasing the mRNA expression of CB1 and CB2 receptors, by reducing prostate specific antigens, by activation of transient receptor potential; metastatin-8 and by inducing apoptosis [67,68,57]. CBD down regulate vascular endothelial growth factor (VEGF) in prostate cells and pro inflammatory interleukins in LPS-stimulated dermal fibrosis, which suggests its anti inflammatory properties [69].

THC was reported to act by few mechanisms such as through Tumor Necrosis factor alpha converting enzyme (TACE/ADAM 17), by induction of candidate of metastasis 1-Activating Transcriptor factor 4-Tribbles homologue 3 (P8-ATF4-TRIB3) pro apoptotic pathway [66,63]. In combination with CBD, THC was reported to act through induction of ROS, modulation of cell cycle, caspase activities, modulation of ERK and induction of apoptosis [70]. THC administered to mice was reported to cause immune suppression through various mechanismse4 [71].

Even though the natural molecules of *C. sativa* had shown significant anti-proliferative mechanisms, the *in-vivo* experiments were found to be insignificant in few reported studies. Mouse mammary carcinoma 4T1 treated with THC was reported to express low levels of CB1 and CB2 which enhance the tumor growth and metastasis. The compound THC was reported to cause increased IL-4 and IL-10 production in mice. The THC-induced suppression of the immune response was reported to reverse following the injection of anti-IL-4 and anti-IL-10 monoclonal antibodies [72]. Another study reported that THC have promoted cancer by inhibiting antitumor immunity in two murine lung cancer models which were weakly immunogenic [73].

Most synthetic cannabinoids such as dronabinol, nabilone and synthetic CBD were reported to be 100 times more potent when compared with THC [74,75]. Few formulations of dronabinol, nabilone and synthetic CBD are approved to stimulate appetite in AIDS patients and in cancer patients to treat cytostatic-induced nausea/vomiting [76]. Noscapine, a nonsedative isoquinolone alkaloid obtained from the opium latex was reported to effectively inhibit the *in-vitro* and *in-vivo* progression of different cancers such as Breast Cancer, Lymphoma, Ovarian Carcinoma, Melanoma, Colon Cancer, Human Non-small cell Lung Cancer and Glioblastoma in different experimental models [77–86].

Eventhough many *in-vivo* studies were performed and the anticancer activities were reported, insufficient data is available for the clinical trial efficacy of *C. sativa* as an anti-cancer agent [87].

3.5. Danti (*Baliospermum montanum Mull. Arg.*)

B. montanum of Euphorbiaceae family is an endangered monoecious leafy undershrub medicinal plant. It is distributed throughout India, Malaya and Burma. In a study, presence of 14 different compounds including topotecan was confirmed by the GC MS analysis [88]. In another study 5 phorbolic esters were isolated from the roots of *B. montanum* which are 12-deoxy-5β-hydroxyphorbol 13-myristate, baliospermin, montanin, 12-deoxy-16-hydroxyphorbol-13-palmitate and 12-deoxyphorbol-13-palmitate. The isolates showed significant *in vivo* anti-leukemic activity [89].

The methanolic extract of *Baliospermum monatum* revealed dose dependent cytotoxic effect against T-cell leukemia and breast cancer cell lines. But the breast cancer cell line was reported to exhibit a very less cytotoxicity when compared to T-cell leukemia with an IC50 value of 298 μg/ml. The percentage cell cycle arrest was reported as 12.79% at G2/M phase [90]. No cytotoxicity was found against HaCaT, normal cell lines [92] and on normal mouse embryonic fibroblasts (NIH3T3) [94].

3.6. Dhattura (*Datura metel Linn.*)

D. metel belongs to the plant family *solanaceae*. Various parts of the plant were reported to possess wide range of pharmacological activities [95,96]. Withanolides isolated from *D. metel* were reported to inhibit the proliferation of tumor cells, angiogenesis and they can induce quinone reductase (phase II enzyme) [98].

A withanolide named 12α-hydroxy daturametelin and two other compounds were reported to induce apoptosis in S-phase of cell cycle [100]. The responses such as nuclear chromatin condensation, DNA fragmentation and loss of mitochondrial membrane potential were observed from the fungal culture organic extract of endophytic *fusarium solani* strain isolated from *D. metel* L and hence this study reports the apoptosis inducing property of test extract though the mitochondrial pathway [102].

3.7. Gunja (*Abrus precatorius Linn.*)

Abrus precatorius is a climbing shrub which belongs to the family fabaceae that grows on hedges and bushes all over India. *Abrus precatorius* possesses a number of activities such as anti-cancer, antibacterial, antimicrobial, anti-diabetic, anti-arthritic, anti-fertility, nephroprotective, anti-seratonergic, anti-inflammatory, anti-oxidant activity etc [103,104]. Traditionally an *Ayurvedic* preparation named *Gunjadya tailam* which has *gunja* and *arka* as two of the ten ingredients was used topically to treat ant-hill like tumors [105]. *Abrus precatorius* showed significant apoptosis against cancer which was confirmed by Sub G_0/G_1 (apoptotic) peak by FACS analysis and the cleavage of Caspase-3 and PARP was also reported. The pro-apoptotic genes (*p21, p53, Bax)* up-regulation and anti-apoptotic *Bcl-2* gene down-regulation were also reported as the other mechanisms [106].

From the seeds a protein extract was isolated which was active against fibrosarcoma in mice as well as ascites and solid forms of Yoshida sarcoma in rats. The intraperitoneal administration was found to be more effective compared to subcutaneous route. The Yoshida Ascites Sarcoma when treated with the protein *in-vivo* resulted in vacuolation of cytoplasm followed by disruption that was accompanied by abnormalities of chromosomes and karyolysis and lead to increased survival of the tumor-transplanted animals [107].

The growth of Ehrlich ascites tumor and Dalton's Lymphoma Ascites (DLA) was suppressed by abrine [108,109]. Abrine a highly toxic protein with an LD50 value of 0.029 mg/kg in mice was present up to 0.15% in seeds [111]. Higher toxicity was observed in tumor cells compared to normal cells [112]. The HPTLC assessment reported the presence of alkaloids particularly abrine that was responsible for the anti tumor activity of seeds [113,114].

Abrus agglutinin is a protein that belongs to class II ribosome inactivating protein family and extracted from *Abrus precatorius* seeds. In a time and dose dependent manner *it* was reported to induce apoptosis in Hep G2 cells. The caspase cascade was activated which was observed with a reduction in Bcl-2/Bax ratio and increased activities of caspase 3/7, 8 and 9. The NF-κB expression, Akt phosphorylation and Hsp90 expression were decreased in HepG2 cells and the growth of tumor was reduced in the Hep G2 xenograft bearing nude mice. It has decreased Ki-67 and CD-31 expression and increased expression of TUNEL on comparison with control group [115]. The strongly antiradical *Abrus precatorius*

extracts can chelate Fe2+ ions and have significant anti lipid peroxidation properties [116].

The combination therapy with stigmasterol hemihydrate and β-monolinolein showed decreased tumor volume and recovered body weights of experimental animals. No toxic side effects were reported [119]. In a study forty-five compounds were identified from the leaf essential oils and the cytotoxicity bioassay was carried out using the brine shrimp lethality test which revealed that the oil was found to be active [120].

3.8. Jaipala (Jayapala) (Croton tiglium Linn.)

C. tiglium is a small shrub that grows up to 12 m height. It belongs to the family *Euphorbiac*eae. The only plant in *Croton* species which is native to India is *C. tiglium*. It is widely distributed and cultivated in North-Eastern India. In India the seeds were medicinally familiar before 450 BC. They were reported to be medicinally useful for many problems [124,125].

It is a good source of phorbol derivatives, especially tigliane phorbolesters. Usually these esters which are present in *C. tiglium* are well known co-carcinogens. Through Epstein–Barr virus infection these esters involve in the transformation of normal human epithelial cells. 12-*O*-tetra decanoyl phorbol-13-acetate (TPA) is the main irritant present in the seed which is used to promote tumor in the cancer research using experimental mice [126]. Along with this the seeds contain 8 other phorbol esters [127,128]. Even though the above phorbol esters were reported for their tumor inducing properties, many other phorbol esters can also induce profound beneficial biological effects without causing tumorigenesis. The TPA when administered to patients with myelocytic leukemia was reported to decrease bone marrow myeloblasts. When TPA alone or in combination with AraC and Vit D3 was administered a temporary subsidence of disease symptoms was observed [129].

Isoguanosine was found to be the main constituent of aqueous extract which showed a strong antitumor activity against various cell lines [130,131] and in mice that was implanted S-180 ascitic tumor [134]. Where as in other case the isoguanosine was tested against L1210 leukemia in experimental mice model and reported to have a poor activity [132].

TPA which was previously reported as a cancer promoter can extraordinarily act as a stimulator of differentiation in myeloid leukemia cells at a 10,000-fold lower concentration in *in-vitro* conditions [134–137]. In further studies, the higher concentrations of TPA resulted in apoptosis [138,143–145]. In LNCaP tumor induced immune deficient mice, an inhibitory effect and synergistic tumor regression was observed following TPA and ATRA administration [146]. Even though the synergistic mechanism of action at molecular level was not known, the TPA-dependent increase in TNF-α levels were reported [147]. For the induction of myeloid leukemia cell differentiation and glioblastoma cell apoptosis, the Tumor Necrosis Factor- α was reported to be synergized with ATRA [148,149]. The methanolic extract of *C. tiglium* seeds promotes apoptosis though Bax/Bcl-2 pathway [150]. Through the PARP cleavage, accumulation of Bax and degradation of Bcl-2 *Crotonol A* was reported to promote K562 cell apoptosis [152].

3.9. Karaveera (Nerium indicum Mill.)

Karaveera is a small tree or an evergreen shrub that belongs to the dogbane family *Apocyanaceae*. *Nerium oleander*, common oleander and *Nerium odorum* were considered to be the synonyms of *N. indicum*. The plant is being used medicinally since 1500 BC in ancient Mesopotamia [153]. It is widely used in ethnomedicinal practices for various ailments [154]. Traditionally, in ayurveda for cleansing the post-surgical wounds of cancer, a decoction made with the leaves of *Karaveera* along with the leaves of *Asphota* and *Jati* was used [155].

Two bioactive constituent from oleander leaf named oleandrin and oleandrigenin were reported to inhibit fibroblast growth factor in human prostate cancer cell lines [157]. Oleandrin, isolated from the leaves of *N. indicum* inhibited NF-κβ and Ik βα expression induced by 12-O-Tetradecanoylphorbol-13-acetate following external application on mouse skin [158]. BRO human myeloma cells which were exposed to oleandrin resulted in mitochondrial injury mediated by generation of superoxide radicals. It has also shown loss of antioxidative enzymes and loss of cell viability [159]. The researchers have reported that NOE-4 developed from leaf extract can treat immune resistant cancers as decreased expression of Bcl-2 molecules was observed [160]. It has shown toxicity to the K562 cells which was found to be a result of the affected levels of P-glycoprotein (ATP-binding cassette transporter) by the extracts [161].

Oleandrin was reported to pause the cell proliferation of PANC-1 pancreatic tumor cells and also caused the arrest of cell cycle at G2/M phase. The result showed that oleandrin stimulated death of PANC-1 cells was mediated by apoptotic pathway [162]. Breastin, a phyto cocktail which comprises of glycosides, flavonoids and polysaccharides resulted with a more anti-cancer potential when compared with Cisplatin, 5-Fluoruracil and Cyclophosphamide. On co-examination with Paclitaxel and Docetaxel, Breastin demonstrated elevated tubuline binding capacity [163].

3.10. Langali (Gloriosa superba Linn.)

G. superba of Liliaceae family is one of the poisonous ayurvedic drugs which is fatal on misuse. It is commonly called as glory lily, flame lily, climbing lily or creeping lily and it is a widely cultivated plant which can cure many diseases. Glory Lily, a perennial twining vine climbs up with tendrils at the apex of leaves. It is an alkaloid plant containing phytoconstituents such as colchicine and gloriosine.

As per the ayurvedic texts *Nirgundi tailam* an oily preparation that has *Kalka* of *Langali* as one of the three ingredients was used through the inhalation for the treatment of lymphadenitis [105]. The alcoholic rhizome extract subjected to subsequent fractionation into aqueous, n-butanol, ethyl acetate and chloroform fractions was screened for enzyme inhibition against lipoxygenase, acetyl cholinesterase, butyryl cholinesterase and urease. Among them the chloroform fraction expressed highest inhibition (90%) of lipoxygenase. 46–69% inhibition was reported for acetyl cholinesterase, 10–33% was reported for butyryl cholinesterase. No urease inhibition was reported. This reveals that the extract may possess anticancer activity as the 5-lipoxygenase pathway inhibition has proven to have a chemopreventive effect in the generation of lung cancer. It was also reported that the oxidation of several carcinogens were blocked by the inhibition of this pathway. 5-lipoxygenase inhibitors were reported to have the ability to induce apoptosis and reduce cell proliferation [166].

From various parts of *G. superba,* 22 aspergillus fungi were chosen and finally one isolate was carried out for bioassay guided fractionation which led to the isolation of 3 known compounds and one novel compound and studied for the anti-cancer properties [167]. Through p53 up regulation and NF-κB down regulation, apoptosis was induced in SW620 colon cancer cells by the partially purified peptides isolated from the rhizomes [169].

3.11. Parasika Yavani (Hyoscyamus niger Linn.)

H. niger which is commonly named as henbane or hogs bean in English belongs to the Solanaceae family. *Hyoscyamus* is known well for the tropane alkaloid (anti-cholinergic) production. The *Hyoscyamus* seeds were found to possess various pharmacological properties.

A medicated ayurvedic formulation named *Pancatikta guggulu ghrta* which has *Vatsaka, Ativisa, Visa* and *Yavani* as few of the ingredients was advised for internal use to treat malignant tumors, diseases of *vata* localised in joints, bones and marrow, abdominal tumors, oedema etc. [171]. An antitumor activity study was conducted using *Agrobacterium tumefacians* induced potato-disc tumor assay, in which the aqueous, ethanolic and methanolic extracts of *H. niger* have revealed mild inhibitory action of 7%, 40% and 5% [173]. Alkaloidal extract of *H. niger* was reported to reduce the frequency of chromosomal aberrations and micronuclei assay. In bone marrow cells of mice, it was also reported to increase the mitotic index. The apoptotic activity of alkaloidal extract on cancer cells revealed a change in membrane potential of mitochondria, permeability of cell membrane, size and morphology of nucleus and releasing of cytochrome C [174].

3.12. Snuhi (Euphorbia nerifolia Linn.)

E. nerifolia is a plant belongs to the family Euphorbiaceae and belongs to hilly and dry regions of India. *Snuhi* is popularly known as Milk Hedge, Thohar and Sehund. It is a big shrub which is full of spines.

In Ayurveda it is recommended to cut the stem of *Snuhi* into pieces and warmed up on fire as a pack in wet cloth. This pack can be used to treat the tumor by fomenting which may cause destruction of tumors [176]. Euphol, a triterpinoid was isolated as a major constituent from the triterpenoidal sapogenin leaf fraction. It was found that the sapogenin possess moderate antioxidant potential and exerted cytotoxicity on F1 B16 cells. In gamma radiation-induced chromosomal aberration study significant reduction of aberration was reported [177].

Antitumor activity of acetone latex extract was investigated against DLA induced ascites tumor in mice and percentage mortality was studied. Along with the *in-vivo* studies phytochemical studies and *in-vitro* cytotoxicity studies were also conducted. In treatment group an increased recovery and dose dependent significant reduction in mortality rate were observed. Efficacy was observed to be maximum at a dose of 100 mg/kg and the major acetone extract components were reported to be terpenoids [179]. In a study using n-nitroso diethylamine induced liver cancer in mice the hepatoprotective potential of hydro-ethanolic extract was evaluated. In liver the test drug was reported to significantly restore the CAT and SOD levels [180]. The hydro-ethanolic extract was reported to have significant nephroprotective potential [181].

In an isolation study, fifteen diterpenoids (1–15) were isolated. Among them three diterpenoids possessed ent-atisane skeleton which were eupnerias G–I (1–3). These three were subjected for the Anti HIV and Cytotoxicity evaluations and found to be effective [182].

3.13. Vatsanabha (Acontium ferox Wall.Ex. ser)

Aconitum ferox Wall is described as most toxic (Mahavisha) and referred to as 'The King of poisons'. It belongs to the family Ranunculaceae. It is used in various Ayurvedic formulations after the process of purification (*Shodhana*). *Vatsanabha* is used as a universal antidote. It is also used to treat inflammation, tumor and infections. The root is used to treat malignant tumors. The most common phytoconstituents of *Aconitum ferox* are pseudaconitine, aconitine, hypaconitine, mesaconitine, bikhaconitine, chasmaconitine, indaconitine etc. The diterpenoid alkaloids are found to be the major phytochemical constituents.

Aconitum ferox species is found to be 1.5 times more potent than *Aconitum chasmanthum* and seven times than *Aconitum nepellus*. Hypaconitine (HpA), a diterpene alkaloid isolated from *Aconitum ferox* have expressed inactivation of the NF-κB signaling pathway. Through p53 activation, ERK1/2 and p38 MAPK signaling cascade, the alkaloids have shown protective autophagy [183]. Hypaconitine was reported to inhibit the epithelial–mesenchymal transition induced with TGF-1. A study was conducted where a number of drugs with antitumor activities were synthesized from aconitine. Among them a compound named bis[O-(14-benzoylaconine-8-yl)] suberate (BBAS) was found to be most active [185].

BBAS showed the GI_{50} values of 0.12 and 6.5 μM which revealed an above average potential against leukemia and melanoma cell lines. In immunodeficient mice with subcutaneous xenografts T/C values of 43% and 41% against SK-MEL-28 and COLO-205 cell lines were observed respectively with a significant decrease in tumor size at a dose of 10 mg/kg. After treatment at a dose of 20 μM, the BBAS-treated cells were found to be accumulated in G2/M phase [186].

3.14. Vishamushti (Strychnox nuxvomica Linn.)

S. nuxvomica is a deciduous tree that belongs to Loganiaceae family and native to Southeast Asia especially India. It is commonly called as *nux vomica* or poison nut. The *S. nuxvomica* seeds are the chief source of Brucine, a natural plant alkaloid with wide range of pharmacological activities. In chinese medicine *S. nuxvomica* was used to treat liver cancer [187].

In a study which was designed to investigate the combined efficacy of gemcitabine and brucine in MCF-7 cells, it was found that Brucine can inhibit the expression of NF-kB p65 subunit [191]. The cytotoxicity of Loganin-1 isolated from the fruits of *Strychnos nuxvomica* was found to be 13 times more activity than vinblastine (standard) [192]. *S. nuxvomica* was reported to have promising anticancer activity against RPMI 8226 (multiple myeloma) cell lines. The alkaloids brucine and strychnine were the main phytochemical constituents responsible for the anticancer activity [193]. Brucine was reported to act by Bcl-2 down regulation and Bax up regulation [196].

The isolated seed extracts of *S. nuxvomica* were found to inhibit EAC tumor in experimental mice [197]. Brucine decreased the volume of tumor formation, VEGF induced angiogenesis and tumor weight. It was also suggested that in endothelial cells brucine inhibits the migration, invasion and tubular structure formation which was assessed using the mouse matrigel plug model of angiogenesis [199]. Brucine revealed the suppression of HCC cell migration, dose dependent decrease in the lung metastasis and reported to decrease the HIF-1 responsive genes (hypoxia inducible factor) expression levels which are related with the anti-metastasis activity [200].

A dose dependent nodular volume reduction was shown by Brucine in hepatic tumors with a size of >3 mm in experimental rats induced by diethyl nitrosamine and promoted by Phenobarbital [201]. Brucine was found to produce apopotosis of Hep G2 cells by cyclooxygenase and caspase 3 pathways [202]. It was also reported to possess anti adhesion, anti migration and anti invasive properties that was caused by reversing EMT and MMP-2, MMP-9 downregulation [203]. The peptide modified liposomal brucine was found to have enhanced anti-tumor activity as it was specifically recognized by NGR receptors on the tumour cell surfaces which would likely enhance the intracellular uptake of drugs [204].

3.15. Shringivisha (Acontium chasmanthum Stapfex Holm.)

Aconitum chasmanthum, which is called as *Shringivisha* in *Ayurveda* belongs to the plant family Ranunculaceae. It is one of the most unexplored plant of Aconitum species. The anti-bacterial and anti-fungal activities were explored upto an extent, but the cytotoxic properties and anti-cancer properties were not reported as much as the other plants of same genus.

The methanolic extract of *Aconitum chasmanthum* has been reported for cytotoxicity using the brine shrimp lethality test, which reveals that the crude extract have shown LD50 > 1000 μg/ml. The crude methanolic extract have also been reported for the antimicrobial activity against the gram negative bacteria such as *Shigella boydi*, *E. coli*, *Proteus mirabilis* and *Klebsiella pneumonia* at a concentration of 200μg/100 μl [205].

4. Discussion

Ayurveda has a description of countless medicines which are being used for many centuries and it is clearly acceptable that without proper efficacy the system of *Ayurveda* couldn't able to withstand this long. In a general the public opinion is that *Ayurveda* is less efficient in critical care and the Ayurvedic medicines need a long course of intake to manage a disease. But in contrast the ayurvedic drugs are being utilized in various parts of the world for the critical illness such as cancer. Among many potent medications, the Ayurvedic Schedule E1 drugs can also be used as individual drugs if the potency is proven clinically against particular diseases. These toxic herbs which are called as *Visha dravyas* are a set of very effective plant drugs which has shorter onset of action. In modern terms they can be named as fast acting or ultra fast acting agents. On the other hand, if these drugs are consumed as such it may lead to toxic responses in the patients and hence a proper detoxification process called *Shodhana* has to be carried out before use [206]. But unfortunately only 10% plant drugs are in the clinical usage from the stage of preclinical studies due to various reasons and it involves many regulatory requirements to be fulfilled in various countries.

4.1. The regulatory concerns for approval of medicinal preparations using toxic herbs

To utilise these plants for medicinal preparations, safety data is required throughout the globe. Many developed countries are not recognising *Ayurveda* as a system of treating illness and it is generally considered as a system of wellbeing due to lack of scientific documention as per current standards regarding safety and efficacy. This makes the powerful economies of the world like USA, European Union, Canada etc. to restrict the use of Ayurvedic drugs as the alternative medicines for various complications.

In the 'Guidelines on the Prevention of Toxic Exposures' published by WHO, usage of the herbal and Ayurvedic medicine is listed as one of the causes to toxic exposure in India [207]. Whereas the 'General Guidelines for Drug Development of Ayurvedic Formulations' published by Government of India demands the reports of safety and efficacy studies along with the published literature for the issue of license with respect to patent or proprietary medicine that uses any schedule E1 drug of D&C act 1940 of *Ayurveda*, *Siddha* and *Unani* systems as one or more ingredients of the proposed formulation. It is also applicable for usage of any extracts (*Aushadh Ghana*) of above plants [208].

On the other side, in USA the therapeutic claims of the herbal preparations are not legally accepted and they can only be marketed as dietary supplements as per the Dietary Supplement Health and Education Act (DSHEA), 1994. The manufacturers should submit a New Dietary Ingredient (NDI) application to FDA 75 days before marketing a new herbal product to get approval [209]. Due to this reason usage of Schedule E1 drugs as alternative medicine for cancer therapy is not applicable there based on the traditional literature. To do so, the regulations demand New Drug Application (NDA) for Botanical Drug Category and hence necessary toxicity and efficacy data should be submitted for the approval. Similar to USA, Canada also approves the Ayurvedic products only as Natural Health Products and not allowed as herbal medicine [210].

Apart from the above American countries, the European Union (EU) has restricted the utilisation of Ayurvedic drugs due to poor documentation of the required data. The Traditional Herbal Medicine Products Directive (THMPD) controls the registration of ayurvedic drugs as traditional use products as per Article 16a (1) of directive 2001/83/EC where no clinical trials on safety and efficacy is required for grant of license of drugs. But the product safety & efficacy should be reported through the bibliographic references of usage of 30 years outside EU and atleast 15 years inside EU. With the production of proper data the schedule E1 drugs can be utilized as alternative medicine in EU as the *Ayurveda* has been practiced in European countries for more than a century. Other than the *Traditional use registration*, other categories of registrations such as *well-established use marketing authorization* (for medicines with 10 years of use), *stand alone or mixed application* (for newer drugs where companies has to generate data) and *simplified registration* (for traditional herbal medicinal products that cannot provide sufficient scientific literature for well-established use but has evidence for long traditional use) can be applied [210].

In UK, *Traditional Herb Registration* (THR) can be obtained along with EU guidelines. As per Medicines & Health products Regulatory Agency (MHRA) of UK, the toxic herbal ingredients listed under 'Banned and Restricted Herbal Ingredients for Medicinal Use' cannot be used in the manufacturing, import and sale of unlicensed medicines in UK, where as in licensed medicines they can be used with certain restrictions. Five of the above Schedule E1 drugs are currently listed as Banned and Restricted Herbal Ingredients including *Papaver somniferum, H. niger, Aconitum ferox, S. nuxvomica* and *Aconitum chasmanthum*. These drugs are represented under the legal category of POM and SI 2130 P-II & III. Hence for these drugs, no dose is permitted unless made available by a prescription from a registered doctor or dentist and can be sold only in registered pharmacies under the supervision of pharmacist. In both EU and UK, GMP standards should be maintained as the evidence of quality [210,211].

In the Association of South East Asian Nations (ASEAN) which includes Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia, the ayurvedic drugs and formulations can be registered under any of the following four categories which are *traditional herbal medicine, indigenous herbal medicine, modified herbal medicine* and *imported products with a herbal medicine base*. These categores will be decided only by the Ministry of Health on the basis of submitted sample dossier [210].

4.2. Traditional usage of Schedule E1 drugs in cancer care

The classical references were found for six plants among the above fifteen such as *Karveera, Yavani, Snuhi, Langali*, *Gunja and Arka* for the treatment of various cancers. The decoction made with the leaves of *Karaveera, P. guggulu ghrta* which has *Yavani,* warmed wet pack made with stem of *Snuhi, N. tailam* which has *Langali and G. tailam* which has both *Gunja* and *Arka* are the various preparations used traditionally to treat different types of cancers. Even though these drugs are used in various forms from early ages it needs the proper clinical evidence to utilise these effective medicines in the current cancer care scenario.

4.3. Some important mechanisms reported

In support to the above classical statements the anti-cancer activities of the Ayurvedic Schedule E1 drugs, their extracts, phytoconstituents and formulations were widely reported against various cancer models which build hope in view of developing newer and novel therapeutic principles in cancer care. These drugs are reported to act by various mechanisms by inhibiting, elevating, down regulating, up regulating and decreasing various signals and pathways. Some of the important pathways by which these drugs influence are TRPV1, 5HT3, nAChR [41], ceramide dependent [59–61], cyclooxygenase [195], caspase 3 [189], Bax/Bcl-2 [99], mitochondrial [43] and CB2 receptor-mediated cytokine-dependent [44] pathways. The inhibition of NF-kB signaling pathway [184], peroxidative damage in mitochondria [27], tumour cell proliferation and angiogenesis, cell migration [41,42], Akt and mTOR signalling [65], elevation of DNA fragmentation [99], interaction with α-tubulin [10,11], elevating the levels of cell cycle arrest at G2/M phase, Caspase expression [19,20], decreasing the levels of Bcl(2), mRNA expression of AR & CB1 and CB2 receptors, vascular endothelial growth factor [65–67] are considered to be some of the major mechanisms exerted by the Ayurvedic Schedule-E1 drugs and their active principles.

4.4. Scope of utilization as alternative medicine in comparison with the currently marketed anti-cancer drugs

In the current cancer care a lot of phytoconstituents have taken important roles as therapeutic agents. The most rem*arka*ble among them are paclitaxel, Vincristine, Vinblastine, Docetaxel, Thiotepa etc. and these molecules are effective against various types of cancers [212]. In a similar fashion, many Schedule E1 drugs and their active constituents are also effective against various cancers. For instance, as paclitaxel is effective for breast cancer, colon cancer, pancreatic cancer, basal cell carcinoma and gastric cancer, noscapine isolated from *Ahipena* is active ovarian cancer, colon cancer, cervical cancer, breast cancer, lung adenocarcinoma, neuroblastoma etc. Tetrohydrocannabinol isolated from the *Bhanga* is active against breast cancer, glioblastoma, asterocytoma, lung mucoepidermoid carcinoma, prostate adenocarcinoma & pancreatic adeno carcinoma. So many other molecules represented in Fig. 2 isolated from the different plants of Schedule E1 drugs have also shown tremendous activities against different cancers.

Topotecan is a phytoconstituent of *Danti* which is currently marketed in the name of Hycamtin [213] is widely used for the treatment of cervical cancer, small cell lung cancer, ovarian cancer & fallopian tube cancer. In certain cases, the derivatives of the existing phytocompounds such as synthetic cannabinoids, dronabinol, nabilone have reported tremendously higher activities than the natural compounds which paves platform for the procurement of newer anti-cancer agents. Loganin-1 which is isolated from *Vishamushti* have shown 13 times higher activity than Vinblastine which can be considered in treating Breast cancer, colon cancer, ovarian cancer and hepatic cancer [185].

The increasing number of cases in the hospitals and the developing resistance against drugs in various diseases demands the adjuvant therapies in the clinical set ups for quicker recovery of patients. In connection to this, the ethyl acetate fraction of *Arka* root

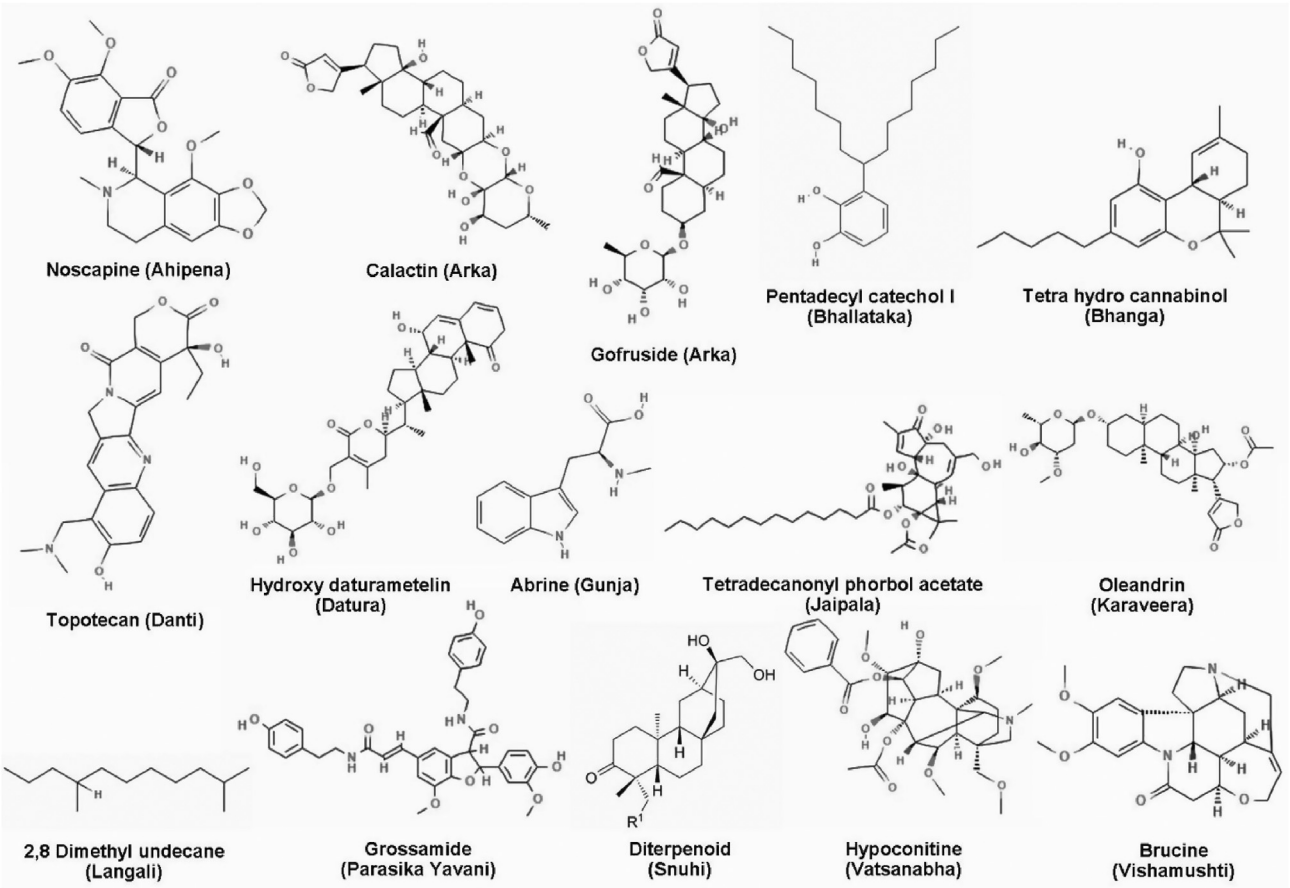

Fig. 2. Few molecules responsible for the anti-cancer activities of Ayurvedic Schedule E1 drugs. (Plant source of molecule is given in the bracket).

extract and calotroposid-A have shown synergistic properties with 5-flurouracil against colon cancer [16]. It is a clue for the utilization of the same against various other cancers such as Breast cancer, Rectal cancer etc where 5-flurouracil is widely used. Similarly TPA from *Jaipala* has shown synergism with ATRA against colon cancer and leukaemia [139,140] with the help of various researches in the exploration of synergistic potentials of phytoconstituents by which a new era of clinical treatment can be initiated.

The mechanism based comparison between the currently marketed anti-cancer drugs and the Schedule E1 drugs can give newer insights about the utilization of the natural remedies in various conditions. As various principles of these drugs are effective through different pathways, the mechanism specific comparisons can be made to understand the activities more clearly.

4.5. The mechanism specific comparisons

4.5.1. Bax/Bcl2 pathway

The Bax/Bcl2 pathway is a common pathway for different anti-cancer agents. B-cell lymphoma-2 (Bcl-2) is a family of proteins that act by binding with and inactivating BH3 domain pro apoptotic proteins. These BH3 domain proteins may act by the activation of pro apoptotic proteins. Downregulation of Bcl-2 is an important mechanism of anti-cancer activity and so many agents such as venetoclax, navitalax, oblimersen sodium, gossypol, ABT 737, ABT 263 have undergone clinical trials which act by downregulation of Bcl2 [214]. The principles such as nut extract of *Bhallataka* against Breast cancer cell lines, Ethyl acetate fraction of *Gunja* against Breast cancer cell lines. Abrus agglutinin isolated from *Gunja*, against hepatic carcinoma, Crotonol A&B (leukemia), methanolic extract of *C. tiglium* seeds (NSCLC), NOE-4 isolated from *N. indicum* against Brukitt's lymphoma, Brucine isolated from *Vishamushti* against colon cancer also act by downregulation of Bcl2 & upregulation of Bax. Hence these principles can be considered as the alternative therapeutic agents that are being developed to act by the Bax/Bcl2 pathway.

4.5.2. Tubulin binding pathway

It is one of the important pathways of anticancer activity and different phytoconstituents exert their activities through this pathway. Among them, Noscapine isolated from *Ahipena* was reported to act by binding to Tubulin and arrest metaphase that leads to apoptosis in different types of cancers. The most effective naturally derived anti-cancer agents Vincristine, Vinblastine are also act by the same mechanisms which are effective in market against different cancers such as Rhabdomyosarcoma [215]. Loganin 1 isolated from *Vishamushti* has 13 times more activity than Vinblastine.

4.5.3. Cell cycle arrest and active principles of Schedule E1 drugs

Cell cycle arrest can be caused by different mechanisms and is an important step by many anti-cancer agents. The anti-metabolites such as thioguanine, mercaptopurine, methotrexate, 5-flurouracil, hydroxycarbamide act by causing cell death at S-Phase by interfereing with DNA/RNA synthesis [214]. The cell cycle arrest is also caused by various active principles of current interest such as the ethyl acetate fraction of root extract of *Arka*, calotroposid A (G2/M phase), against colon cancer methanolic extract of *Danti* (G2/M phase), against T-cell leukaemia & breast cancer 12-α hydroxyl daturametelin (S-phase) against colorectal adenocarcinoma, adenocarcinoma of alveolar basal epithelial cells, ethyl acetate fraction of *Gunja* (sub Go/G1 phase) against Breast cancer, oleandrin isolated from *Karaveera* (G2/M phase) against pancreatic cancer, BBAS from *Vatsanabha* (G2/M phase) against leukemia.

4.5.4. TNF-α and Schedule E1 drugs

TNF-α is a set of proteins that not only in inhibition of cancer but also promotes tumor growth in certain cases [214]. The ethyl acetate and hexane fractions of *Gunja* which are active against cervical cancer and breast cancer act by inhibiting cytokine TNF-α. Whereas TPA isolated from *Jaipala* act by increasing TNF- α levels and found to be active against lung cancer, prostate, melanoma, colon, breast cancer etc.

4.5.5. Caspases & Schedule E1 drugs

Caspase are protease enzymes that play various important roles in inducing apoptosis. 11 genes were found in human genome which can encode to 11 different caspases that is caspase-1 to caspase-10 and caspase-14 [216]. Calotroposid A and ethyl acetate fraction of *Arka* act by elevating the caspase-8 expression against colon cancer. It has also expressed the synergistic activity with 5-Flurouracil which is a potent anti-cancer agent that is effective against various cancers like breast cancer, pancreatic cancer and stomach cancer. The ethanolic extract of *Arka* act against fibrosarcoma by increasing caspase-3 expression. Nut extract of *Bhallataka* was found to be active against breast cancer by increasing the levels of Caspases and cytochrome C. The oil extract of *Bhallataka* activates the caspases and exerts anti-cancer activity against acute myeloid leukemia and chronic myeloid leukemia. The tetrahydro cannabinol inhibits the anti-tumor immunity against glioblastoma, asterocytoma by modulating ERK, caspases activity and by enhancing apoptosis by induction of Reactive oxygen species.

The ethylacetate fraction of *Gunja* induces cleavage of caspases 3 and PAPR against breast cancer cell lines. The abrus agglutinin increases the Caspase 3/7, 8 and 9 activities against hepatic carcinoma. APM3 and APH11 are the newly developed principles from *Gunja* that act by caspase 3/7 and PARP cleavage. Brucine an active phytoconstituent from *Vishamusti* acts by cyclo-oxygenase and caspase-3 pathways and found to be effective against human erythro leukemia, cervical cancer, hepatic carcinoma and multiple myeloma.

4.6. Drawbacks and pitfalls of current ayurvedic system in cancer care

The first drawback is the lack of reliability on system towards cancer therapy among different world countries. Cancer is still considered as an incurable health problem and needs a high recovery result based approach towards patients. Study of various ayurvedic drugs using latest techniques has become an essential need of the day to globally establish the system in the cancer care. Schedule E1 drugs are well known for their cytotoxic nature and even in the current cancer care, a lot of *Ayurvedic* practitioners are prescribing these drugs in various formulations based on the *tridosa* status of patients [217]. Even though it helps in the recovery of many patients, this knowledge is not well documented due to various reasons. Many of the practitioners in the folk practice are not ready to reveal their formulations due to Intellectual property rights issues. The knowledge which was already reported in various classical texts is helpful up to an extent and needs a lot more research that reveals the pharmacological and therapeutic aspects of the drugs. The paucity of evidence regarding the particular health benefits of patients is restricting the co-operation between the system and the current health care professionals to act with mutual trust in cancer care. Hence the reverse pharmacological evaluations and clinical trial level research works are considered to be the current day needs of the system to satisfy the international standards and to implement Ayurvedic medicines in the world market [218].

Apart from the utilization of knowledge in the treatment of diseases, procurement of raw drugs has become an even bigger challenge. Many of the drugs of Schedule E1 category are commonly not available in the market and leads to the availability of spurious drugs. The mindset of the general public doesn't encourage the cultivation and preservation of poisonous plants that commonly leads to unavailability. The authenticated plant samples of *Parasika yavani*, *Snuhi*, *Vatsanabha*, *Shringivisha* and certain varieties of *Gunja* are not available due to lack of cultivation and literature for identification. The present geographical features and climatic changes lead to variations in the phytoconstituent levels that result in variations in the therapeutic efficacy of the herbal medicines. Hence standardization of formulations is required between various batches in order to reduce the batch to batch variations which lead to produce the same therapeutic effect. This is even more challenging in the plant based medicines as it may undergo a lot of phytoconstituent variations. The other parameters such as stability, dosage, pharmacokinetics etc. has to be analyzed and the techniques should be standardized for various formulations for the world wide acceptance of ayurvedic system in the treatment of acute and fatal chronic disorders.

5. Conclusion

The Ayurvedic Schedule E1 dugs of plant origin have undergone a vast exploration of activities in different cancer models. They possess a wide range of anti-cancer activities and can be utilized in clinical practices after ensuring proper evaluation of raw drugs and standardization of dosage forms. Despite of these studies further more evaluation is required in the aspects of cultivation and collection, phytochemical variation, formulation making, quantification of effective dosage and clinical usage. The semisynthetic and synthetic derivatives of the active principles may be derived to explore the potency in the different dimension of modern chemistry. The molecular level studies can be taken up which can provide a deeper view about the interaction of various active principles inside and outside the biological system. Apart from research and exploration, the current trend is moving towards usage of natural remedies as adjuvant therapies due to effectiveness of the herbal principles in the faster recovery of patients. Such a step can also be considered which can pave the path in reducing chemotherapy based adverse effects and occurrence of drug resistance in cancer patients.

Source of funding

None.

Conflict of interests

None.

Author contributions

E.N.T. Vikram: Conceptualization, Writing - Reviewing. **R. Ilavarasan:** Visualization, Editing. **R. Kamaraj:** Supervision, Validation.

Acknowledgement

Authors would like convey sincere thanks to Dr Swamy CT (RO-Microbiology), Dr Kusuma Ganji (RO-Pharmacy), Dr Ashwathi Mohan (RO-Pharmacy), Dr Arunadevi (RO-Pharmacology) and Mr Prem Kumar (ARO-Pharmacognosy) of CSMCARI, Chennai for their continuous support and ideas for the enrichment of content throughout the work.

References

[1] Institute NC. What is cancer?. 2021. https://www.cancer.gov/about-cancer/understanding/what-is-cancer.
[2] Prashant M, Krishnan S, Meesha C, Priyanka D, Kondalli L S, Stephen S, et al. Cancer statistics, 2020: report from National Cancer Registry Programme, India. JCO Global Oncol 6:1063–1075.
[3] Mallath MK, Taylor DG, Badwe RA, Rath GK, Shanta V, Pramesh CS, et al. The growing burden of cancer in India: epidemiology and social context. Lancet Oncol 2014;15:e205–12. https://doi.org/10.1016/S1470-2045(14)70115-9.
[4] Hyuna S, Jacques F, Rebecca LS, Mathieu L, Isabelle S, Ahmedin J, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
[5] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33. https://doi.org/10.3322/caac.21654.
[6] Swami Sadha Shiva Tirtha. The ayurveda encyclopedia. Ayurveda Holistic Center Press; 2005. p. 3.
[7] Drugs and Cosmetics Act and Rules. Schedule E (1), Rule 161(2). Government of India, Ministry Of Health And Family Welfare; 1940. p. 317.
[8] Drugs and Cosmetics Act and Rules. Schedule E (1), Rule 161(2). Government of India, Ministry Of Health And Family Welfare; 1945. p. 300.
[9] Deore SL, Moon KV, Khadabadi SS, Deokate UA, Baviskar BA. Evaluation of toxicity of 'Vatsanabha' (Aconitum ferox, Ranunculaceae) before and after Shodhana. J Young Pharm 2013;5:3–6. https://doi.org/10.1016/j.jyp.2013.01.001.
[10] Rastogi S. A review of Aconite (Vatsanabha) usage in Ayurvedic formulations: traditional views and their inferences. Spat DD – Peer Rev J Complement Med Drug Discov 2011;1:233. https://doi.org/10.5455/spatula.20111220112858.
[11] Hao Da Cheng, Gu Xiao-Jie, Xiao Pei Gen. Medicinal plants: chemistry, biology and omics. Elsevier; 2015. p. 217.
[12] DeBono A, Capuano B, Scammells PJ. Progress toward the development of noscapine and derivatives as anticancer agents. J Med Chem 2015;58:5699–727.
[13] Sajadian S, Vatankhah M, Majdzadeh M, Kouhsari SM, Ghahremani MH, Ostad SN. Cell cycle arrest and apoptogenic properties of opium alkaloids noscapine and Papaverine on breast cancer stem cells. Toxicol Mech Methods 2015;25:388–95.
[14] Guler D, Aydın A, Koyuncu M, Parmaksız İ, Tekin Ş. Anticancer activity of papaver somniferum L. J Turk Chem Soc – Sec A 2016;3(3):349–66.
[15] Inada M, Shindo M, Kobayashi K, Sato A, Yamamoto Y, Akasaki Y, et al. Anticancer effects of a non-narcotic opium alkaloid medicine, Papaverine, in human glioblastoma cells. PLoS One 2019;14(5):e0216358. https://doi.org/10.1371/journal.pone.0216358.
[16] Winzer T, Gazda V, He Z, Kaminski F, Kern M, Larson TR, et al. A papaver somniferum 10-gene cluster for synthesis of the anticancer alkaloid noscapine. Science 2012;336(6089):1704–8. https://doi.org/10.1126/science.1220757.
[17] Carr G. Manoa campus plants. University of Hawaii, Dept. of Botany; 2003. Available on, htpp://www.botany.hawaii.edu/faculty/carr/160webindex.htm.
[18] Habib MR, Karim MR. Evaluation of antitumour activity of Calotropis gigantea L. root bark against Ehrlich ascites carcinoma in Swiss albino mice. Asian Pac J Trop Med 2011:786–90.
[19] Jacinto SD, Chun EAC. Cytotoxic cardenolide and sterols from Calotropis gigantea. Nat Prod Commun 2011;6(6):803–6.
[20] Habib MR, Karim MR. Antitumour evaluation of di-(2-ethylhexyl) phthalate (DEHP) isolated from Calotropis gigantea L. flower. Acta Pharm 2012;62:607–15.
[21] Mutiah R, Widyawaruyanti A, Sukardiman S. Ethyl acetate fraction of Calotropis gigantea roots induce apoptosis through increased G2/M and increased expression of caspase-8 in colon cancer WiDr cell line. J Appl Pharmaceut Sci 2017;7(7):197–201.
[22] Mutiah R, Widyawaruyanti A, Sukardiman S, Calotroposid A: A glycosides terpenoids from Calotropis gigantea induces apoptosis of colon cancer WiDr cells through cell cycle arrest G2/M and caspase 8 expression, Asian Pac J Cancer Prev APJCP, 19 (6), 1457-1464.
[23] Mutiah R, Widyawaruyanti A, Sukardiman S. Calotropis gigantea leaf extract increases the efficacy of 5-fluorouracil and decreases the efficacy of doxorubicin in widr colon cancer cell culture. J Appl Pharmaceut Sci 2018;8(4):51–6.
[24] Mutiah R, Griana TP, Ula QN, Andhyarto Y. The effect of Calotropis gigantea leaves extract on fibrosarcoma growth and caspase 3 expression. Int J Pharmaceut Chem Res 2016;8(3):167–71.
[25] Bhat KS, Sharma A, Venkatramana DK. Antiproliferative effect of Calotropis gigantea (L.) R. BR. on breast cancer cells MCF-7. Int J Pharmaceut Sci Res 2014;5(9):3918–23.
[26] Damodaran B, Nagaraja P, Jain V, Manuja Viraj Wimalasiri MP, Sankolli GM, Kumar GV, et al. Phytochemical screening and evaluation of cytotoxic activity of Calotropis gigantea leaf extract on MCF7, HeLa, and A549 cancer cell lines. J Nat Sci Biol Med 2019;10:131–8.
[27] Premalatha B, Muthulakshmi V, Sachdanandam P. Anticancer potency of the milk extract of Semecarpus anacardium Linn. Nuts against aflatoxin B1 mediated hepatocellular carcinoma bearing wistar rats with reference to tumour marker enzymes. Phytother Res 1999;13:183–7.

[28] Mathivadhani P, Shanthi P, Sachdanandam P. Apoptotic effect of Semecarpus anacardium nut extract on T47D breast cancer cell line. Cell Biol Int 2007;31:1198–206.
[29] Arulkumaran S, Ramprasath VR, Shanthi P, Sachdanandam P. Alteration of DMBA-induced oxidative stress by additive action of a modified indigenous preparation– Kalpaamruthaa. Chem Biol Interact 2007;167:99–106.
[30] Sugapriya D, Shanthi P, Sachdanandam P. Restoration of energy metabolism in leukemic mice treated by a siddha drug: Semecarpus anacardium Linn. nut milk extract. Chem Biol Interact 2008;173:43–58.
[31] Patel SR, Suthan AP, patel RM. Invitro cytotoxicity activity of Semecarpus anacardium extract against Hep2 cell line and Vero cell line. Int J Pharm Tech Res 2009;1(4):1429–33.
[32] Sowmyalakshmi S, Nur-E-Alam M, Akbarsha MA, Thirugnanam S, Rohr J, chendil D. Investigation on Semecarpus anacardium L a siddha medicine for breast cancer. Planta 2005;220(6):910–8.
[33] Chitnis MP, Bhatia KG, Phatak MK, Kesava Rao KV. Anti-tumour activity of the extract of Semecarpus anacardium L. nuts in experimental tumor models. Indian J Exp Biol 1980;18(1):6.
[34] Phatak MK, Ambaye RY, Indap MA, Bhatia KG. Cytotoxicity of the acetylated oil of Semecarpus anacardium Linn. Indian J Phys Pharm 1983;27(2):166.
[35] Indap MA, Ambaye RY, Gokhale SV. Antitumour and pharmacological effects of the oil from Semecarpus anacardium Linn. F. Indian J Physiol Pharmacol 1983;27(2):83.
[36] Indap MA, Ambaye RY, Gokhale SV. Potentiation of activity of anti-cancer drugs by acetylated oil of Semecarpus anacardium Linn. F. in experimental tumours. Indian Drugs 1986;23(8):447.
[37] Kothari AB, Lahiri M, Ghaisas SD, Bhide SV. In vitro studies on anti-mutagenecity of water, alcoholic and oil extracts of Semecarpus anacardium. Indian J Pharmacol 1997;29(5):301.
[38] Smit HF, Woerdenbag HJ, Singh RH, Meulenbeld GJ, Labadie RP, Zwaving JH. Ayurvedic herbal drugs with possible cytostatic activity. J Ethnopharmacol 1995;47(2):75.
[39] Hembree JA, Chang CJ, McLaughlin JL, Peck G, Cassady JM. The anticancer activity of Semecarpus anacardium. I.9 KB active pentadecylaccatechols. Lloydia 1978;41(5):491.
[40] Chakraborty S, Roy M, Taraphdar AK, Bhattacharya RK. Cytotoxic effect of root extract of Tiliacora racemosa and oil of Semecarpus anacardium Linn. nut in human tumour cells. Phytother Res 2004;18(8):595.
[41] Sowmyalakshmi S, Nur-E-Alam M, Akbarsha MA, Thirugnanam S, Rohr J, Chendil D. Investigation on Semecarpus Lehyam-a siddha medicine for breast cancer. Planta Med 2005;220(6):910.
[42] Velasco G, Sanchez C, Guzman M. Endocannabinoids and cancer. Handb Exp Pharmacol 2015;231:449–72. https://doi.org/10.1007/978-3-319-20825-1_16.
[43] Demuth DG, Molleman A. Cannabinoid signalling. Life Sci 2006;78(6):549–63. https://doi.org/10.1016/j.lfs.2005.05.055.
[44] Velasco G, Sanchez C, Guzman M. Anticancer mechanisms of can-nabinoids. Curr Oncol 2016;23(Suppl 2):S23–32. https://doi.org/10.3747/co.23.3080.
[45] Perez-Gomez E, Andradas C, Blasco-Benito S, Caffarel MM, Garcia-Taboada E, Villa-Morales, et al. Role of cannabinoid receptor CB2 in HER2 pro-oncogenic signaling in breast cancer. J Natl Cancer Inst 2015;107(6):djv077. https://doi.org/10.1093/jnci/djv077.
[46] Caffarel MM, Andradas C, Mira E, Perez-Gomez E, Cerutti C, Moreno-Bueno G, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. Mol Cancer 2010;9:196. https://doi.org/10.1186/1476-4598-9-196.
[47] Chung SC, Hammarsten P, Josefsson A, Stattin P, Granfors T, Egevad L, et al. A high cannabinoid CB1 receptor immunoreactivity is associated with disease severity and outcome in prostate cancer. Eur J Cancer 2009;45(1):174–82. https://doi.org/10.1016/j.ejca.2008.10.010.
[48] Cipriano M, Haggstrom J, Hammarsten P, Fowler CJ. Association between cannabinoid CB1 receptor expression and Akt signalling in prostate cancer. PLoS One 2013;8(6):e65798. https://doi.org/10.1371/journal.pone.0065798.
[49] Velasco G, Hernandez S, Davila D, Lorente M. The use of canna-binoids as anticancer agents. Prog Neuro-Psychopharmacol Biol Psychiatry 2016;64:259–66. https://doi.org/10.1016/j.pnpbp.2015.05.010.
[50] Thors L, Bergh A, Persson E, Hammarsten P, Stattin P, Egevad L, et al. Fatty acid amide hydrolase in prostate cancer: Association with disease severity and outcome, CB1 receptor expression and regulation by IL-4. PLoS One 2010;5(8):e12275. https://doi.org/10.1371/journal.pone.0012275.
[51] Sarfaraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H. Cannabinoids for cancer treatment: progress and promise. Cancer Res 2008;68(2):339–42. https://doi.org/10.1158/0008-5472.CAN-07-2785.
[52] Orellana-Serradell O, Poblete CE, Sanchez C, Castellon EA, Gallegos I, Huidobro C, et al. Proapoptotic effect of endocannabinoids in prostate cancer cells. Oncol Rep 2015;33(4):1599–608. https://doi.org/10.3892/or.2015.3746.
[53] Sanchez MG, Sanchez AM, Collado B, Malagarie-Cazenave S, Olea N, Carmena MJ, et al. Expression of the transient receptor potential vanilloid 1 (TRPV1) in LNCaP and PC-3 prostate cancer cells and in human prostate tissue. Eur J Pharmacol 2005;515(1–3):20–7. https://doi.org/10.1016/j.ejphar.2005.04.010.
[54] Pecze L, Josvay K, Blum W, Petrovics G, Vizler C, Olah Z, et al. Activation of endogenous TRPV1 fails to induce overstimulation-based cytotoxicity in breast and prostate cancer cells but not in pain-sensing neurons. Biochim Biophys Acta 2016;1863(8):2054–64. https://doi.org/10.1016/j.bbamcr.2016.05.007.
[55] De Petrocellis L, Ligresti A, Schiano Moriello A, Iappelli M, Verde R, Stott CG, et al. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. Br J Pharmacol 2013;168(1):79–102. https://doi.org/10.1111/j.1476-5381.2012.02027.x.
[56] Pineiro R, Maffucci T, Falasca M. The putative cannabinoid receptor GPR55 defines a novel autocrine loop in cancer cell proliferation. Oncogene 2011;30(2):142–52. https://doi.org/10.1038/onc.2010.417.
[57] Mukhopadhyay B, Schuebel K, Mukhopadhyay P, Cinar R, Godlewski G, Xiong K, et al. Cannabinoid receptor 1 promotes hepatocellular carcinoma initiation and progression through multiple mechanisms. Hepatology 2015;61(5):1615–26. https://doi.org/10.1002/hep.27686.
[58] Xu X, Liu Y, Huang S, Liu G, Xie C, Zhou J, et al. Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma. Cancer Genet Cytogenet 2006;171(1):31–8. https://doi.org/10.1016/j.cancergencyto.2006.06.014.
[59] Preet A, Qamri Z, Nasser MW, Prasad A, Shilo K, Zou X, et al. Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis. Cancer Prev Res 2011;4(1):65–75. https://doi.org/10.1158/1940-6207.CAPR-10-0181.
[60] Freund P, Porpaczy EA, Le T, Gruber M, Pausz C, Staber P, et al. Cannabinoid receptors are overexpressed in CLL but of limited potential for therapeutic exploitation. PLoS One 2016;11(6):e0156693. https://doi.org/10.1371/journal.pone.0156693.
[61] Michalski CW, Oti FE, Erkan M, Sauliunaite D, Bergmann F, Pacher P, et al. Cannabinoids in pancreatic cancer: correlation with survival and pain. Int J Cancer 2008;122(4):742–50. https://doi.org/10.1002/ijc.23114.
[62] Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. Oncotarget 2014;5(15):5852–72. https://doi.org/10.18632/oncotarget.2233.
[63] Carracedo A, Gironella M, Lorente M, Garcia S, Guzman M, Velasco G, et al. Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes. Cancer Res 2006;66(13):6748–55. https://doi.org/10.1158/0008-5472.CAN-06-0169.
[64] Zhao Z, Yang J, Zhao H, Fang X, Li H. Cannabinoid receptor 2 is upregulated in melanoma. J Cancer Res Therapeut 2012;8(4):549–54. https://doi.org/10.4103/0973-1482.106534.
[65] Cridge BJ, Rosengren RJ. Critical appraisal of the potential use of cannabinoids in cancer management. Cancer Manag Res 2013;5:301–13. https://doi.org/10.2147/CMAR.S36105.
[66] Hart S, Fischer OM, Ullrich A. Cannabinoids induce cancer cell proliferation via tumor necrosis factor alpha-converting enzyme (TACE/ADAM17)-mediated transactivation of the epidermal growth factor receptor. Cancer Res 2004;64(6):1943–50. https://doi.org/10.1158/0008-5472.CAN-03-3720.
[67] Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. Mol Cancer Therapeut 2011;10(7):1161–72. https://doi.org/10.1158/1535-7163.MCT-10-1100.
[68] Solinas M, Massi P, Cinquina V, Valenti M, Bolognini D, Gariboldi M, et al. Cannabidiol, a non-psychoactive cannabinoid compound, inhibits proliferation and invasion in U87-MG and T98G glioma cells through a multitarget effect. PLoS One 2013;8(10):e76918. https://doi.org/10.1371/journal.pone.0076918.
[69] Sharma M, Hudson J, Adomat H, Guns E, Cox M. In vitro anticancer activity of plant-derived cannabidiol on prostate cancer cell lines. Pharmacol Pharm 2014;5(8):806–20. https://doi.org/10.4236/pp.2014.58091.
[70] Marcu JP, Christian RT, Lau D, Zielinski AJ, Horowitz MP, Lee J, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahy-drocannabinol on human glioblastoma cell proliferation and survival. Mol Cancer Therapeut 2010;9(1):180–9. https://doi.org/10.1158/1535-7163.MCT-09-0407.
[71] Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. Future Med Chem 2009;1(7):1333–49. https://doi.org/10.4155/fmc.09.93.
[72] McKallip RJ, Nagarkatti M, Nagarkatti PS. Δ-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. J Immunol 2005;174(6):3281–9. https://doi.org/10.4049/jimmunol.174.6.3281.
[73] Zhu LX, Sharma S, Stolina M, Gardner B, Roth MD, Tashkin DP, et al. Δ-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. J Immunol 2000;165(1):373–80. https://doi.org/10.4049/jimmunol.165.1.373.
[74] Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharma-codynamics, and clinical implications. Drug Alcohol Depend 2014;144:12–41. https://doi.org/10.1016/j.drugalcdep.2014.08.005.
[75] Debruyne D, Le Boisselier R. Emerging drugs of abuse: current perspectives on synthetic cannabinoids. Subst Abuse Rehabil 2015;6:113–29. https://doi.org/10.2147/SAR.S73586.
[76] Romano B, Pagano E, Orlando P, Capasso R, Cascio MG, Pertwee R, et al. Pure delta9-tetrahydrocannabivarin and a Cannabis sativa extract with high content in delta9-tetrahydrocannabivarin inhibit nitrite production in murine peritoneal macrophages. Pharmacol Res 2016;113(Pt A):199–208. https://doi.org/10.1016/j.phrs.2016.07.045.

[77] Ke Y, Ye K, Grossniklaus HE, Archer DR, Joshi HC, Kapp JA. Noscapine inhibits tumor growth with little toxicity to normal tissues or inhibition of immune responses. Cancer Immunol Immunother 2000;49:217–25.
[78] Aneja R, Vangapandu SN, Lopus M, Chandra R, Panda D, Joshi HC. Development of a novel nitro-derivative of noscapine for the potential treatment of drug- resistant ovarian cancer and T-cell lymphoma. Mol Pharmacol 2006;69:1801–9.
[79] Aneja R, Zhou J, Vangapandu SN, Zhou B, Chandra R, Joshi HC. Drug-resistant T-lymphoid tumors undergo apoptosis selectively in response to an antimicrotubule agent, EM011. Blood 2006;107:2486–92.
[80] Aneja R, Zhou J, Zhou B, Chandra R, Joshi HC. Treatment of hormone-refractory breast cancer: apoptosis and regression of human tumors implanted in mice. Mol Cancer Therapeut 2006;5:2366–77.
[81] Aneja R, Lopus M, Zhou J, Vangapandu SN, Ghaleb A, Yao J, et al. Rational design of the microtubule-targeting anti-breast cancer drug EM015. Cancer Res 2006;66:3782–91.
[82] Landen JW, lang R, McMahon SJ, Rusan NM, Yvon AM, Adams AW, et al. Noscapine alters microtubule dynamics in living cells and inhibits the progression of melanoma. Cancer Res 2002;62:4109–14.
[83] Zhou J, Gupta K, Aggarwal S, Aneja R, Panda R, Joshi HC. Brominated derivatives of noscapine are potent microtubule interfering agents that perturb mitosis and inhibit cell proliferation. Mol Pharmacol 2003;63:799–807.
[84] Landen JW, Hau V, Wang M, Davis T, Ciliax B, Wainer BH, et al. Noscapine Crosses the blood-brain barrier and inhibits glioblastoma growth. Clin Cancer Res 2004;10:5187–201.
[85] Aneja R, Ghaleb AM, Zhou J, Yang VW, Joshi HC. P53 and p21 determine the sensitivity of noscapine-induced apoptosis in colon cancer cells. Cancer Res 2007;67:3862–70.
[86] Jackson T, Chougule MB, Ichite N, Patlolla RR, Singh M. Antitumor activity of noscapine in human non-small cell lung cancer xenograft model. Cancer Chemother Pharmacol 2008;63:117–26.
[87] Guggisberg J, Schumacher M, Gilmore G, Zylla DM. Cannabis as an anticancer agent: a review of clinical data and assessment of case reports. Cannabis Cannabinoid Res 2021 Aug 7. https://doi.org/10.1089/can.2021.0045. Epub ahead of print. PMID: 34370591.
[88] Seethalaxmi R, Saravana kumari P. In-vitro cytotoxic activity of Baliospermum Montanum leaves on cervical cancer- Hela cell lines and chemical characterization by GCMS. Int J Pharm Bio Sci 2018;9(2):213–20.
[89] Ogura M, Koike K, Cordell GA, Farnsworth NR. Potential anticancer agents VIII. Constituents of Baliospermum montanum (Euphorbiaceae). Planta Med 1978;33:128–43.
[90] Seethalakshmi R, Saravana Kumari P. In-vitro anticancer activity of Baliospermum montanum on T-cell leukemia- Jurkat cell line and Human Breast cancer MCF-7. IAETSD J Adv Sci Appl Sci Jan 2018;5(1):173–9.
[91] Renugadevi K, Aswini V, Raji P. Microwave irradiation assisted synthesis of silver nanoparticle using leaf extract of Baliospermum montanum and evaluation of its antimicrobial, anticancer potential activity. Asian J Pharmaceut Clin Res 2012;5(4):283–7.
[92] Pipatrattanaseree W, Itharat A, Mukkasombut N, Saesiw U. Potential in vitro anti-allergic, anti-inflammatory and cytotoxic activities of ethanolic extract of Baliospermum montanum root, its major components and a validated HPLC method. BMC Compl Alternative Med 2019;19:45. https://doi.org/10.1186/s12906-019-2449-0.
[93] Nandagaon VS, Kulkarni AR. In vitro antioxidant and cytotoxicity activity of Bacopa monnieri and Baliospermum. Montanum Muell Arg 2013;4:63–7.
[94] Cherian AM, Snima KS, Kamath CR, Nair SV, Lakshmanan VK. Effect of Baliospermum montanum nanomedicine apoptosis induction and anti-migration of prostate cancer cells. Biomed Pharmacother 2015;71:201–9.
[95] Nuhu H. Alakaloid content of the leaves of three Nigerian Datura species Nig. J Nat Prod Med 2002;6:15–8.
[96] Yusuf M, Begum J, Hoque MN, Chowdhury JU. Medicinal plants of Bangladesh. Chittagong, Bangladesh: BCSIR; 2009. p. 794.
[97] Ma Lei, Xie Chuan-Ming, Li Jia, Lou Feng-Chang, Hu Li-Hong, Daturametelins H. I, and J: three new withanolide glycosides from Datura metel L. Chem Biodivers 2006;3(2):180–6.
[98] Pan Y, Wang X, Hu X. Cytotoxic withanolides from the flowers of Datura metel. J Nat Prod 2007;70:1127–32.
[99] Nazeema Banu B, Julie J, Abirami J, Kumareasan R, Muthukumaran T, Rajasree S, et al. Anti-cancer activity of Datura metel on MCF-7 cell line. Asian J Pharmaceut Clin Res 2014;7(Suppl 1):181–3.
[100] Bellila A, Tremblay C, Pichette A, Marzouk B, Mshvildadze V, Lavoie S, et al. Cytotoxic activity of withanolides isolated from Tunisian Datura metel L. Phytochemistry 2011;72(16):2031–6.
[101] Xue Juan, Sun Yichun, Qing Wei, Wang Changfu, Yang Bingyou, Kuang Haixue, et al. Chemical composition and cytotoxicity of the essential oil from different parts of Datura metel L. Nat Prod Res 2015. https://doi.org/10.1080/14786419.2015.1088541.
[102] Kuriakose GC, Singh S, Rajvanshi PK, Surin WR, Jayabaskaran C. In vitro cytotoxicity and apoptosis induction in human cancer cells by culture extract of an endophytic Fusarium solani strain isolated from Datura metel L. Pharm Anal Acta 2014;5:293. https://doi.org/10.4172/2153-2435.1000293.
[103] Okhale SE, Nwanosike EM. Abrus precatorius Linn (Fabaceae): phytochemistry, ethnomedicinal uses, ethnopharmacology and pharmacological activities. Int J Pharmaceut Sci Res 2016;1(6):37–43.
[104] Chaudhari KS, Sharma Ramakant, Pawar PS, Kashikar VA. Pharmacological activities of Abrus precatorius Linn. - a review. Int J Ayurvedic Herbal Med 2012;2(2):336–48.
[105] Lochan Kanjiv. Bhaisajya Ratnavali of Govinda Dasji Bhisagratna; Volume II, chapter 44, Verse 77, 80-81, VaranasiGalaganda, editor. Chaukhamba Sanskrit Sansthan 2009;719:724–5.
[106] Sofi MS, Nabi S. Induction of caspase-3 dependent apoptosis, cell cycle arrest and cytotoxicity in breast cancer cells by Abrus precatorius. Int J Pharm Pharmaceut Sci 2018;10(8):29–35.
[107] Subba RVV, Sirsi M. Effect of Abrus precatorius L. on experimental tumors. Cancer Res 1969;29:1447–51.
[108] Siddiqi TO, Bhupinder D, Peerzada SHK, Iqbal M. Angiospermous seeds of medicinal importance. J Econ Taxon Bot 2001;25:101.
[109] Ramnath GK, Ramadasan K. Antitumour effect of abrin on transplanted tumours in mice. Indian J Physiol Pharmacol 2002;46:69–77.
[110] Sivakumar R, Alagesaboopathi C. Studies on cytotoxicity and antitumor screening of red and white forms of Abrus precatorius L. Afr J Biotechnol 2008;7(22):3984–8.
[111] Harborne JB. Phytochemical methods. 2nd ed. New York: Chapman & Hall; 1984.
[112] Manjunath Ed BL. The wealth of India – raw materials, vol. 1. New Delhi, India: CSIR; 1948.
[113] Gautam DNS, Dixit SK, Benerji R, Malhrotra S. A HPTLC study for assessment of sodhana effect on alkaloids of gunja (Abrus precatorius). Aryavaidyan 2001;14:146–53.
[114] Sivakumar R. Pharmacognostical, phytochemical and pharmacological studies on Abrus precatorius L. Ph.D. Thesis. Coimbatore, Tamilnadu, India: Bharathiar University; 2002.
[115] Subhadip M, Prashanta Kumar P, Durgesh Nandini D, Niharika S, Birendra B, Tapas Kumar M, et al. Abrus agglutinin suppresses human hepatocellular carcinoma in vitro and in vivo by inducing caspase mediated cell death. Acta Pharmacol Sin 2014;35:814–24. https://doi.org/10.1038/aps.2014.15.
[116] Gul MZ, Ahmad F, Kondapi AK, Qureshi IA, Ghazi IA. Antioxidant and anti-proliferative activities of Abrus precatorius leaf extracts - an in vitro study. BMC Compl Alternative Med 2013;13:53. http://www.biomedcentral.com/1472-6882/13/53.
[117] Gul MZ, Chandrasekaran S, Manjulatha K, Bhat MY, Maurya R, Qureshi IA, et al. Anti proliferative and apoptosis inducing effects of Abrus precatorius against Human monocytic leukaemia (THP-1) Cell line. Indian J Pharmaceut Sci 2018;80(2):307–17.
[118] Okoro EE, Osoniyi OR, Jabeen A, Shams S, Choudhary MI, Onajobi FD. Anti-proliferative and immunomodulatory activities of fractions from methanol root extract of Abrus precatorius L. Clinical Phytoscience 2019;5:45. https://doi.org/10.1186/s40816-019-0143-x.
[119] Sofi MS, M. K., Sateesh MK, Bashir M, Ganie MA, Nabi S. Chemopreventive and anti-breast cancer activity of compounds isolated from leaves of Abrus precatorius L. 3 Biotech 2018;8:371. https://doi.org/10.1007/s13205-018-1395-8.
[120] Oladimeji AO, Babatunde O, Musa RT, M'civer FA, Lawal AT, Ogunwande IA. GC-MS analysis and cytotoxic activity of essential oils from the leaves of Abrus precatorius L. Gaertn. Asian Pac J Trop Dis 2016;6(5):372–5.
[121] Patil A, Vadera K, Patil D, Phatak A, Chandra N. Phytochemical analysis, in vitro anticancer activity and HPTLC fingerprint profile of seeds of Abrus precatorius L. Int J Pharmaceut Sci Rev Res 2015;33(1):262–9.
[122] Lébri M, Tilaoui M, Bahi C, Achibat H, Akhramez S, Fofié YBN, et al. Phytochemical analysis and in vitro anticancer effect of aqueous extract of Abrus precatorius Linn. Der Pharma Chem 2015;7(8):112–7.
[123] Khalifa N S, El-Hallouty S M, Barakat H S, Salim D M, In vitro cytotoxic and antioxidant activities of some plant extracts on different human cancer cell lines, 2013, Egypt. J Exp Biol (Bot), 9(1): 137 – 144.
[124] Qiu HX. Flora of China. Beijing, China: Science Press; 1996. p. 133.
[125] Wang X, Zhang F, Liu Z, Feng H, Yu ZB, Lu Y, et al. Effects of essential oil from Croton tiglium L. on intestinal transit in mice. J Ethnopharmacol 2008;117:102–7.
[126] Glaser S, Sorg B, Hecker EA. Planta Med 1988;54:580.
[127] El-Mekkawy S, Meselly MR, Nakamura N, Hattori M, Kawahata T, Otake T. Chem Pharm Bull 1999;47:1346.
[128] El-Mekkawy S, Meselly MR, Nakamura N, Hattori M, Kawahata T, Otake T. Phytochemistry 2000;53:457.
[129] Han TZ, Zhu XX, Yang RY, Sun JZ, Tian GF, LiU XJ, et al. Effect of intravenous infusions 12-O-tetradecanoylphorbol-13-acetate (TPA) in patients with myelocytic leukemia: preliminary studies on therapeutic efficacy and toxicity. Proc Natl Acad Sci Unit States Am 1998;95:5357–61.
[130] Kim CW, Moon JC, Kim JB. Cytotoxic effects of extract (cp-2) from the mixture of Coptis and Croton tiglium L. of the various tumor cell lines. Korean Cent J Med 1993;58:177–84.
[131] Kim JH, Lee SJ, Han YB, Moon JJ, Kim JB. Isolation of isoguanosine from Croton tiglium and its antitumor activity. Arch Pharm Res 1994;17:115–8.
[132] Skipper HE, Montgomery JA, Thomson, Schabel Jr FM. Structural activity relations and cross resistance observed on evaluation of a series of purine analogs against experimental Neoplasms. Cancer Res 1959;19:425–37.
[133] Li Changyou, Wu Xiao, Sun Rongli, Zhao Peng, Liu Fengjuan, Zhang Chunling. Croton tiglium extract induces the apoptosis in human lung cancer A549 cells. J Thorac Oncol 2007;12(1):S1532. https://doi.org/10.1016/j.jtho.2016.11.2120. Supplement.

[134] Huberman E, Callaham MF. Induction of terminal differentiation in human promyelocytic leukemia cells by tumor promoting agents. Proc Natl Acad Sci USA 1979;76(3):1293–7.
[135] Lotem J, Sachs L. Regulation of normal differentiation in mouse and human myeloid leukemic cells by phorbol esters and the mechanism of tumor promotion. Proc Natl Acad Sci USA 1979;76(10):5158–62.
[136] Rovera G, O'Brien TG, Diamond L. Induction of differentiation in human promyelocytic leukemia cells by tumor promoters. Science (Wash DC) 1979;204(4395):868–70.
[137] Rovera G, Olashaw N, Meo P. Terminal differentiation in human promyelocytic leukemic cells in the absence of DNA synthesis. Nature (Lond) 1980;284:69–70.
[138] Garzotto M, White-Jones M, Jiang Y, Ehleiter D, Liao WC, Haimovitz-Friedman A, et al. 12-O-tetradecanoylphorbol-13-acetate induced apoptosis in LNCaP cells is mediated through ceramide synthase. Cancer Res 1998;58(10):2260–4.
[139] Guilbaud NF, Gas N, Dupont MA, Valette A. Effects of differentiation-inducing agents on maturation of human MCF-7 breast cancer cells. J Cell Physiol 1990;145(1):162–72.
[140] Arita Y, O'Driscoll KR, Weinstein IB. Growth inhibition of human melanoma-derived cells by 12-O-tetradecanoyl phorbol 13 acetate. Int J Cancer 1994;56(2):229–35.
[141] Salge U, Kilian P, Neumann K, Elsasser HP, Havemann K, Heidtmann HH. Differentiation capacity of human non-small-cell lung cancer cell lines after exposure to phorbol ester. Int J Cancer 1990;45(6):1143–50.
[142] Salge U, Kilian P, Neumann K, Elsasser HP, Havemann K, Heidtmann HH. Differentiation capacity of human non-small-cell lung cancer cell lines after exposure to phorbol ester. Int J Cance 1990;45(6):1143–50.
[143] Powell CT, Brittis NJ, Stec D, Hug H, Heston WD, Fair WR. Persistent membrane translocation of protein kinase C alpha during 12-O-tetradecanoyl-phorbol-13-acetate-induced apoptosis of LNCaP human prostate human. Cell Growth Differ 1996;7(4):419–28.
[144] Fujii T, Garcia-Bermejo ML, Bernabo JL, Caamano J, Ohba M, Kuroki T. Involvement of protein kinase C delta (PKC delta) in phorbol ester-induced apoptosis in LNCaP prostate cancer cells. Lack of proteolytic cleavage of PKC delta. J Biol Chem 2000;275(11):7574–82.
[145] Konno S, Hsieh TC, Wu JM, Chen Y, Chiao JW, Mallouh C. Growth control of human prostate cancer cells by the phorbol ester TPA: possible involvement of protein kinases. Anticancer Res 1996;16(4A):1843–9.
[146] Zheng X, Chang RL, Cui XX, Avila GE, Lee S, Lu YP, et al. Inhibitory effect of 12-O-tetradecanoylphorbol-13-acetate alone or in combination with all-trans-retinoic acid on the growth of LNCaP prostate tumors in immunodeficient mice. Cancer Res 2004;64:1811–20.
[147] Mizokami A, Gotoh A, Yamada H, Keller ET, Matsumoto T. Tumor necrosis factor-α represses androgen sensitivity in the LNCaP prostate cancer cell line. J Urol 2000;164(3 part 1):800–5.
[148] Witcher M, Ross DT, Rousseau C, Deluca L, Miller Jr WH. Synergy between all transretinoic acid and tumor necrosis factor pathways in acute leukemia cells. Blood 2003;102:237–45.
[149] Chambaut-Guerin AM, Costa SL, Lefrancois T, Fages C, Gauthereau X, Tardy M. Effects of retinoic acid and tumor necrosis factor-α on GL-15 glioblastoma cells. Neuroreport 2000;11:389–93.
[150] Changyou Li, Xiao Wu, Rongli Sun, Peng Zhao, Fengjuan Liu, Chunling Zhang, Croton tiglium extract induces apoptosis via Bax/Bcl-2 pathways in human lung cancer A549 cells, Asian Pac J Cancer Prev APJCP, Vol 17, 4893-4898.
[151] Zhang XL, Wang L, Li F, Yu K, Wang MK. Cytotoxic phorbol esters of Croton tiglium. J Nat Prod 2013;76(5):858–64.
[152] Junfeng Wang, Li Qin, Biqing Zhao, Liang Cai, Zhenping Zhong, Yonghong Liu, et al, Two rare tigliane diterpenoid derivatives against K562 cells from Croton tiglium, Org Biomol Chem. DOI: 10.1039/c8ob02519c.
[153] A brief history of the wondrous oleander plant-Part 3 of the oleander series. 2013. Available from: http://www.naturalnews.com/022949_Oleander_health_history.html# [Last cited on 2013 Feb 11].
[154] Nerium Biotechnology, Inc.. 2013. Available from: http://www.Neriumbiotech.com/research.htm [Last cited on 2013 Feb 2].
[155] Sharma PV. Susruta-Samhita; Volume II Chapter XVII, Verse 37-42. In: Cikitsasthana Ashtadashosadhyayah, editor. Varanasi: Chaukhamba Visvabharathi; 2010. p. 444–5.
[156] Ali HFM, El-Ella FMA, Nasr NF. Screening of chemical analysis, antioxident antimicrobial and antitumor activity of essential oil of oleander (Nerium oleander) flower. Int J Biol Chem 2010;4(4):190–202.
[157] Smith JA, Madden T, Vijjeswarapu M, Newman RA. Inhibition of export of fibroblast growth factor-2 (FGF-2) from the prostate cancer cell lines PC3 and DU145 by Anvirzel and its cardiac glycoside component, oleandrin. Biochem Pharmacol 2001;62(4):469–72. https://doi.org/10.1016/s0006-2952(01)00690-6.
[158] Afaq F, Saleem M, Aziz MH, Mukhtar H. Inhibition of 12-O-tetradecanoyl-phorbol-13-acetate-induced tumor promotion markers in CD-1 mouse skin by oleandrin. Toxicol Appl Pharmacol 2004;195(3):361–9.
[159] Newman RA, Yang P, Hittelman WN, Lu T, Ho DH, Ni D, et al. Oleandrin-mediated oxidative stress in human melanoma cells. J Exp Therapeut Oncol 2006;5(3):167–81.
[160] Ghoneum M, Ozel HZ, Gollapudi S. Nerium oleander leaf extract sensitizes human burkett cell lymphoma (Raji) to human cytotoxicity mediated by natural killer cells. Clin Immunol 2006;119(SUPP):S188.
[161] Turan N, Akgün-Dar K, Kuruca SE, Kiliçaslan-Ayna 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 Therapeut Oncol 2006;6:31–8.
[162] Newman RA, Kondo Y, Yokoyama T, Dixon S, Cartwright C, Chan D, et al. Autophagic cell death of human pancreatic tumor cells mediated by oleandrin, a lipid-soluble cardiac glycoside. Integr Cancer Ther 2007;6(4):254–64.
[163] Fiebig HH, Kelter G, Maier A, Metz T, Rashan LJ. Breastin a natural product from Nerium Oleander exhibits high activity in a panel of human tumor cell lines. Cancer Res 2013;73(8 Suppl):5572. https://doi.org/10.1158/1538-7445.AM2013-5572.
[164] Simon SE, Jayakumar FA. Antioxidant activity and anticancer study on phytochemicals extract from tubers of Gloriosa superba against human cancer cell (Hep-G2). Res Rev: J Pharmacogn Phytochem 2016;4(4):7–12.
[165] Luc, Amerikalei, Sandra, Heide, Rica, Hondstraat, et al. Extracts, compositions and use thereof, International Application Published Under The Patent Cooperation Treaty (PCT), WO 2016/146562 Al. World Intellectual Property Organization; 22 September 2016.
[166] Khan Haroon, Khan Murad Ali, Hussan Iqbal. Enzyme inhibition activities of the extracts from rhizomes of Gloriosa superba Linn (Colchicaceae). J Enzym Inhib Med Chem 2007;22(6):722–5. https://doi.org/10.1080/14756360601164853.
[167] Budhiraja A, Nepali K, Sapra S, Gupta S, Kumar S, Dhar KL. Bioactive metabolites from an endophytic fungus of Aspergillus species isolated from seeds of Gloriosa superba Linn. Med Chem Res 2013;22:323–9. https://doi.org/10.1007/s00044-012-0032-z.
[168] Shah Kautuk Kumar, Vidya Sagar G. Phytochemical and pharmacological evaluation of Gloriosa superba. J Drug Deliv Therapeut 2015;5(4):27–42.
[169] Budchart Prapaphan, Khamwut Ariya, Sinthuvanich Chomdao, Ratanapo Sunanta, Poovorawan Yong, Nattanan Panjaworayan, et al. Partially purified Gloriosa superba peptides inhibit colon cancer cell viability by inducing apoptosis through p53 upregulation. Am J Med Sci 2017;354(4):423–9.
[170] Jayakumar FA, Simon SE, Yan YW, Yap PW. Characteristic and optimized use of bioactive compounds from Gloriosa superba and albizia amara with apoptotic effect on hepatic and squamous skin carcinoma. Int J Pharmaceut Sci Res 2018;9(5):1769–78.
[171] Srikanth Murthy KR, Cikitsita Vata Vyadhi, Stana Cikitsita. Vag Bhata's Astanga Hridayam, vol. 508. Varanasi: Chaukhamba Krishnadas Academy; 2012. p. 58–61. Volume II, [Chapter 21], Verse.
[172] Ma Cui-Ying, Liu Wing Keung, Che Chun-Tao. Lignanamides and non-alkaloidal components of Hyoscyamus Niger seeds. J Nat Prod 2002;65(2):206–9.
[173] Turker AU, Yildirim AB, Karakas FP, Turker H. In vitro anti-bacterial and anti tumor efficiency of some traditional plants from Turkey. Indian J Tradit Knowledge 2018;17(1):50–8.
[174] Ismeel AO. Cytogenetic and cytotoxic studies on the effect of phytoinvestigated active compounds of Hyoscyamus Niger (in vivo and ex vivo). PhD thesis. Iraq: Al-Nahrain University- College of Science; 2011.
[175] Deniz U, Hatice G, Fatma G, Ramazan M. Cytotoxic activities of certain medicinal plants on different cancer cell lines. Turk J Pharm Sci 2017;14(3):222–30. https://doi.org/10.4274/tjps.80299.
[176] Sharma PV. Classical uses of medicinal plants. Varanasi: Chaukhamba Visvabharathi; 2004. p. 397.
[177] Bigoniya P, Rana AC. Radioprotective and in-vitro cytotoxic sapogenin from Euphorbia neriifolia (Euphorbiaceae) leaf. Trop J Pharmaceut Res 2009;8(6):521–30.
[178] Patil S B and Magdum C S, Determination of LC50 values of extracts of Euphorbia hirta Linn and Euphorbia neriifolia Linn using brine shrimp lethality assay, Asian J Res Pharm Sci 1(2): April-June 2011; Page 42-43.
[179] Upadhyaya C, Kumar A, Sathish S. A study on anti-cancer activity of Euphorbia neriifolia (milk hedge) latex. Int J Adv Sci Eng Technol 2017;5(2):5–7. Spl. Issue-2.
[180] Pracheta, Sharma V, Paliwal R, Sharma S, Singh L, Janmeda BS, et al. Chemoprotective activity of hydro-ethanolic extract of Euphorbia neriifolia Linn leaves against DENA-induced liver carcinogenesis in mice. Biol Med 2011;3(2):36–44. Special Issue.
[181] Janmeda P, Sharma V, Singh L, Paliwal R, Sharma S, Yadav S, et al, Chemopreventive effect of hydroethanolic extract of Euphorbia neriifolia leaves against DENA-induced renal carcinogenesis in mice, Asian Pac J Cancer Prev APJCP, 12, 677-683.
[182] Li JC, Feng XY, Liu D, Zhang ZJ, Chen XQ, Li RT, et al. Diterpenoids from Euphorbia neriifolia and their related anti-HIV and cytotoxic activity. Chem Biodivers 2019;16:e1900495.
[183] Chodoeva A, Bosc J-J, Robert J. Aconitum alkaloids and biological activities. Natural Products 2013:1503–23. https://doi.org/10.1007/978-3-642-22144-6_191.
[184] Feng HT, Zhao WW, Lu JJ, Wang YT, Chen XP. Hypaconitine inhibits TGF-β1-induced epithelial–mesenchymal transition and suppresses adhesion, migration, and invasion of lung cancer A549 cells. Chin J Nat Med 2017;15(6):427–35.
[185] Chodoeva A, Bosc JJ, Guillon J, Costet P, Decendit A, Mérillon JM, et al. Hemisynthesis and antiproliferative properties of mono-[O-(14-benzoylaconine-8-yl)]esters and bis-[O-(14-benzoylaconine-8-yl)]esters. Eur J Med Chem 2012;54:343–51.

[186] Chodoeva A, Bosc JJ, Lartigue L, Guillon J, Auzanneau C, Costet P, et al. Antitumor activity of semisynthetic derivatives of Aconitum alkaloids. Invest N Drugs 2014;32(1):60–7. https://doi.org/10.1007/s10637-013-9986-z.
[187] Bensky D, Gamble A. Chinese herbal medicine. Seattle: Eastland Press; 1986. p. 646.
[188] Cai BC, Wang TS, Kurokawa M, Shiraki K, Hattori M. Cytotoxicities of alkaloids from processed and unprocessed seeds of Strychnos nux-vomica. Acta Pharmacol Sin 1998;19:425–8.
[189] Deng X, Yin F, Xiaoyu L, Cai B, Yin W. The apoptotic effect of brucine from the seed of Strychnos nux-vomica on human hepatoma cells is mediated via Bcl-2 and Ca2+ involved mitochondrial pathway. Toxicol Sci 2006;91:59–69.
[190] Rao PS, Ramanadham M, Prasad MN. Anti-proliferative and cytotoxic effects of Strychnos nux-vomica root extract on human multiple myeloma cell line-RPMI 8226. Food Chem Toxicol 2009;47:283–8.
[191] Serasanambati M, Chilakapati SR, Manikonda PK, Kanala JR, Chilakapati DR. Anticancer effects of brucine and gemcitabine combination in MCF-7 human breast cancer cells. Nat Prod Res: Formerly Nat Prod Lett 2014. https://doi.org/10.1080/14786419.2014.951932.
[192] Khan M, Garg A, Srivastava SK, MDarokar MP. A cytotoxic agent from Strychnos nux-vomica and biological evaluation of its modified analogues. Med Chem Res 2012;21:2975–80.
[193] Rao PS, Ramanadham M, Prasad MN. Anti-proliferative effects of Syrychnos nux-vomica root extract on human multiple myeloma cell line- RPMI 8226. Food Chem Toxicol 2009;47(2):283.
[194] Eldahshan OA, Abdel-Daim MM. Phytochemical study, cytotoxic, analgesic, antipyretic and anti-inflammatory activities of Strychnos nux-vomica. Cytotechnology 2015;67:831–44.
[195] Anajwala CC, Patel RM, Dakhara SL, Jariwala JK. In vitro cytotoxicity study of Agave americana, Strychnos nuxvomica and Areca catechu extracts using MCF-7 cell line. J Adv Pharm Technol Res (JAPTR) 2010;1(2):245–52.
[196] Zheng L, Wang X, Luo W, Zhan Y, Zhang Y. Brucine, an effective natural compound derived from nux-vomica, induces G1 phase arrest and apoptosis in LoVo cells. Food Chem Toxicol 2013;58:332–9.
[197] Rao PS, Prasad MNV. Strychnos nux-vomica root extract induces apoptosis in the human multiple myeloma cell line—U266B1. Cell Biochem Biophys 2013;66:443–50.
[198] Agrawal SS, Saraswati S, Mathur R, Pandey M. Cytotoxic and antitumor effects of brucine on Ehrlich ascites tumor and human cancer cell line. Life Sci 2011;89:147–58.
[199] Saraswati S, Agrawal SS. Brucine, an indole alkaloid from Strychnos nux-vomica attenuates VEGF-induced angiogenesis via inhibiting VEGFR2 signaling pathway in vitro and in vivo. Cancer Lett 2013;332(1):83–93. https://doi.org/10.1016/j.canlet.2013.01.012.
[200] Shu G, Mi X, Cai J, Zhang X, Yin W, Yang X, et al. An alkaloid from seeds of Strychnos nux-vomica Linn., represses hepatocellular carcinoma cell migration and metastasis: the role of hypoxia inducible factor 1 pathway. Toxicol Lett 2013;222(2):91–101. https://doi.org/10.1016/j.toxlet.2013.07.024.
[201] Saraswati Sarita, Alhaider Abdulqader, Sunder Shyam. Anticarcinogenic effect of brucine in diethylnitrosamine initiated and phenobarbital-promoted hepatocarcinogenesis in rats. Chem Biol Interact 2013;206:214–21. https://doi.org/10.1016/j.cbi.2013.09.012.
[202] Deng XK, Yin W, Li WD, Yin FZ, Lu XY, Zhang XC, et al. The anti-tumor effects of alkaloids from the seeds of Strychnos nux-vomica on HepG2 cells and its possible mechanism. J Ethnopharmacol 2006 Jun;106(2):179–86. https://doi.org/10.1016/j.jep.2005.12.021.
[203] Li M, Li P, Zhang M, Ma F. Brucine suppresses breast cancer metastasis via inhibiting epithelial mesenchymal transition and matrix metalloproteinases expressions. Chin J Integr Med 2018;24(1):40–6. https://doi.org/10.1007/s11655-017-2805-1.
[204] Li S, Wang XP. In vitro and in vivo evaluation of novel NGR-modified liposomes containing brucine. Int J Nanomed 2017;12:5797–804.
[205] Anwar S, Ahmad B, Subhan M, Gul W, Islam NU. Biological and pharmacological properties of Aconitum chasmanthum. J Biol Sci 2003;3(11):989–93.
[206] Maurya SK, Seth A, Laloo D, Singh NK, Gautam DN, Singh AK. Śodhana: an Ayurvedic process for detoxification and modification of therapeutic activities of poisonous medicinal plants. Ancient Sci Life 2015 Apr-Jun;34(4):188–97. https://doi.org/10.4103/0257-7941.160862. PMID: 26283803; PMCID: PMC4535066.
[207] WHO. Guidelines on the prevention of toxic exposures education and public awareness activities international programme on chemical safety UNEP. Int Program Chem Saf 2004;1–116.
[208] Series-i G. Guidelines series-I general Guidelines for drug development of ayurvedic formulations. New Delhi: Central Council For Research In Ayurvedic Sciences, Ministry of AYUSH, Government o f India; 2018.
[209] Ventola CL. Current issues regarding Complementary and Alternative Medicine (cam) in the United States - Part 2: regulatory and safety concerns and proposed governmental policy changes with respect to dietary supplements. P T 2010;35:514–22.
[210] Ramadoss Malathi Seshasayee Konda, Koumaravelou Kailasam. Regulatory compliance of herbal medicines – a review. Int J Res Pharm Sci 2019;10:3127–35. https://doi.org/10.26452/ijrps.v10i4.1609.
[211] List of banned or restricted herbal ingredients for medicinal use. Guidance-Banned and restricted herbal ingredients. Medicines and Healthcare products Regulatory Agency. https://www.gov.uk/government/publications/list-of-banned-or-restricted-herbal-ingredients-for-medicinal-use/banned-and-restricted-herbal-ingredients; 2014.
[212] Institute NC. Drugs approved for different types of cancer. 2021. https://www.cancer.gov/about-cancer/treatment/drugs/cancer-type.
[213] Institute NC. Topotecan hydrochloride n.d. https://www.cancer.gov/about-cancer/treatment/drugs/topotecanhydrochloride.
[214] García-Aranda M, Pérez-Ruiz E, Redondo M. Bcl-2 inhibition to overcome resistance to chemo- and immunotherapy. Int J Mol Sci 2018;19:3950. https://doi.org/10.3390/ijms19123950.
[215] Martino E, Casamassima G, Castiglione S, Cellupica E, Pantalone S, Papagni F, et al. Vinca alkaloids and analogues as anti-cancer agents: Looking back, peering ahead. Bioorg Med Chem Lett 2018;28:2816–26. https://doi.org/10.1016/j.bmcl.2018.06.044.
[216] Li J, Yuan J. Caspases in apoptosis and beyond. Oncogene 2008;27:6194–206. https://doi.org/10.1038/onc.2008.297.
[217] Singh RH. An assessment of the ayurvedic concept of cancer and a new paradigm of anticancer treatment in Ayurveda. J Alternative Compl Med 2002 Oct;8(5):609–14. https://doi.org/10.1089/107555302320825129. PMID: 12470442.
[218] Gundeti Manohar Saheb, Rammanohar Puthiyedath, Bhat Sulochana G, Narayanam Srikanth. Ayurveda in cancer care in India: scope, challenges, and suggested approaches. J Alternative Compl Med 2018;24(9–10):1023–4. https://doi.org/10.1089/acm.2018.0161.