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

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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 astrocytoma and other malignancies. They have various mechanisms of action including Bax upregulation, Bcl2 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.

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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), leukaemia (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
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 'Sushruta 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 encombs 15 drugs under vegetable origin, 1 drug under vegetable origin and 9 drugs under mineral origin. The listed drugs of vegetable origin are Ahipena, Arka, Bhallataka, Bhanga, Danti, Dhatura, Gunja, Jaipala, Karaveera, Langali, Parasika Yavani, Snuhi, Vatsanaabha, Vishamushthi and Shringivisha. Sarpa Visha (Snake poison) is the only drug of animal origin. The mineral origin includes Hartala (Arseno sulphide), Gauripashana, Parada, Parada (Mercury), Manahashila (Arseno sulphide), Tuttha (Copper sulphate), Rasa Karpura (Hydrargryi 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 and Acontium ferox as Papaver somniferum Linn. were 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 these, 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-(acetylmethyl)-N-(cyclopentylmethyl)-normorphine (KT-90) and NF-xB. 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 metastase 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
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(a) 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 Formula 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 Kalpaamrutha 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].

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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-SYSY, LA1-55 N, SK-N-MC, SK-N-AS, IMR32, NB1691, SK-N-SH), Ovarian (Sig C, SK-OV-3), Colon (TB4, Caco-2), Cervical (Ca Ski, Hct), 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. somniifera            | Human colorectal adenocarcinoma (HT29), human cervix carcinoma (HeLa), African green monkey kidney (Vero) and rat brain tumour cells (G3) cell lines | [14] |
| Arka                     | Papaverine                           | Human small cell lung cancer (NCI-H187), breast cancer (BC) and cervical cancer (HeLa) cell lines | [15] |
|                          | 18,20-epoxycalotropin, calactin, calotropin, 15β-hydroxycalotropin, calactin acid methyl ester and zarigenin |                                           | [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         | Ehrlich ascites carcinoma (EAC) in mice                                                 | [18] |
|                          | Of root bark’s methanol extract      |                                             | [17] |
|                          | Di-(2-ethylhexyl) phthalate          | Ehrlich ascites carcinoma (EAC) in mice                                                 | [20] |
|                          | Ethyl acetate fraction of root extract, calotropinol-A | colorectal adenocarcinoma (K562) cells                                                  | [21,22] |
|                          | Cardiac glycosides                   | breast epithelial (MCF-7) cells                                                        | [25] |
| Bhalatuka                 | Nut extracts                         | human breast cancer (T47D) cell line, human epithelial larynx carcinoma (Hep 2) cell lines | [28,31] |
|                          | Methanolic leaf extract              | cervical (HeLa), breast (MCF-7) and lung (A549) cell lines                            | [26] |
|                          | Chloroform and n-hexane fractions    | EHR(-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] |
|                          | Penatodecyl catachol I and II        | nasopharyngeal carcinoma and eagle's 9 kb cell culture system                          | [38,39] |
|                          | Oil extracted from nuts              | acute myeloid leukaemia (HL 60) and chronic myeloid leukaemia (K-562) cell lines        | [40] |
| Bhangara                 | Semecarpus lehmann (-)-trans-ð9-tetra hydro cannabinol (THC) | breast cancer (MCF-7), human glioblastoma astrocytoma (U373-MG), human lung mucoidermod (NCl-H292), androgen sensitive human prostate adenocarcinoma (LNCaP), prostate cancer (DU-1145), human pancreatic adenocarcinoma (Capan-2), pancreatic cancer (BSpc-3, MIA Paca-2 and Panc-2) cell lines | [57,63,65,66] |
|                          | Cannabidiol (CBD)                    | epithelial human breast cancer (MDA-MB-231), human glioblastoma (NCl-MG, T98G), human prostate cancer (LNCaP and PC-3) cell lines | [67,68] |
|                          | CBD + thc                            | human glioblastoma cell lines (SF-126, U251)                                            | [67,68] |
| Danti                     | Methanolic extract                   | human prostate cancer (LNCaP and PC-3)                                                   | [57] |
|                          | 12-Deoxy-5j-hydroxyphorbol 13-myristate, baliospermin, montanin, 12-deoxy-16-hydroxyphorbol-13-palmitate and 12-deoxyphorbol-13-palmitate. | cervical cancer (HeLa) cells                                                             | [88] |
|                          | Methanolic extract                   | T-cell leukaemia (Jurkat) and breast cancer (MCF-7) cell lines                          | [90] |
|                          | Silver nanoparticle made from the leaf extract | vero and Hep2 cell lines                                                                | [91] |
|                          | Ethanolic extract                    | KKKU-M156 and HepG2 cell lines                                                         | [92] |
|                          | Other extracts                       | Prostate cancer (PC-3) and human colon cancer (HT-29) cell lines                        | [93,94] |
| Dhatura                   | 7,27- dihydroxy-1-oxoithia-2,5,24-trienolide | human colorectal carcinoma (HCT 116) cell line                                          | [97] |
|                          | Withanolides (L. 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, OVCAB-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] |
|                          | Atras 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] |
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 Transient 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 TRPV1 and Transient Receptor Potential Ankyrin 1 (TRPA1) 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 cancer cells such as LNCaP [45, 46].

In PC-3 and DU-145 cell lines expression of CPR55 was reported which mediate the effect of Lyso Phosphotidyl Inositol (LPI) [56]. Chemically induced Hepatocellular carcinoma using Diethyl nitrosoamine expressed upregulation of CD51 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].

### Table 1 (continued)

| Drug | Constituent | Activity reported against | Ref. |
|------|-------------|--------------------------|------|
| Stigmasteryl hemihydrate and b-| | breast cancer (MDA-MB-231) cell lines | [119] |
| monolinolein | | | |
| Hydroalcoholic and Petroleum ether seed extracts | | Breast cancer (Z-75-1, MCF-7) cell lines | [121] |
| Aqueous extract of leaves | | Murin mastocytoma (PB15) cell lines | [122] |
| Crude methanolic extract | | Human liver carcinoma (Hep G2), human colon carcinoma (HT-29) cell lines | [123] |
| Jaipala (Jayapala) | | Lung cancer, prostate or melanoma, colon and breast cancer, LNCaP cells | [138–142] |
| Isoguanyosine | | solid tumor and ascitic 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] |
| Phorboidieters | | 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] |
| Oleandrins and Oleandrinigen | DU145 and PC3 cells | [157] |
| NOE-4 (new leaf extract) | | human myeloma (BRO), pancreatic tumor (PANC-1) cells | [159, 162] |
| Leaf, stem and root extract | | Burkitt's Lymphoma (Raji) cells | [160] |
| Breastin, a phyto cocktail | | Leukemia (HL60, K562) 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 *Glória superba* | | CV-1, THP-1, OVCAR-5, MCF-7, HEP-2 and A-549 cell lines | [167] |
| Coded extract of *Glória superba* (GS-6) | | Lung cancer (A-549), Ovarian Cancer (IGR-OV-1), Leukemia (THP-1), Prostate cancer (A53), 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, 3-hydroxy-4-methoxy mandelic acid | | hepatic carcinoma (Hep-G2) and Squamous skin carcinoma (A431) cell lines | [170] |
| Parasika- Yavani | Grossamide, Cannabinos D and Cannabinos 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] |
| 2-oxo methyl ester, 2H-1-Benzopyran 3,5,6,8-tetrahydro, 3-hydroxy-4-methoxy mandelic acid | | Hep G2 cells | [184] |
| Vatsa-nabha | Alkaloids | leukemia and melanoma (SK-MEL-28, SK-MEL-5), MDA-MB-468, HT-29, COLO-205 cell lines | [186] |
| Aconitine | |  | |
| Vishamushi | Brucine | K562, Hela, HepG2, multiple myeloma, LoVo, HepG2, SMMC-721, HiS78-T and MDA-MB-231 | [188–190, 196, 200, 203] |
| Gemcitabine and brucine | | MCF-7 cells | [191] |
| (Logan 1) Strychnos nuxvomica fruits | | MCF-7, PA-1, WRL-68, COLO-320 and CaCo2 cell lines | [192] |
| Brucine and strychine | | 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 | Motorholic extract | Brine shrimps | [205] |
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-1a, 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 inter leukin 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 by induction of candidate of metastasis 1-Activating Transcriptor endothelial growth factor (VEGF) in prostate cells and pro in inflammation inter leukins in LPS-stimulated dermal fibrosis, which suggests its anti inflammatory properties [69].

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]. Nocapine, a nonselective 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 monoeccious leafy undershrub medicinal plant. It is distributed throughout India, Malaya and Burma. In a study, presence of 14 different compounds including toptocan 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 montanum 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 12.7% 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. Dhatura (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-arthritis, anti-fertility, nephroprotective, anti-seratonergetic, anti-inflammatory, anti-oxidant activity etc [103,104]. Traditionally an Ayurvedic preparation named Gunajada tailam which has gunja and arka as two of the ten ingredients was used topically to treat anti-hill like tumors [105]. Abrus precatorius showed significant apoptosis against cancer which was confirmed by Sub G0/G1 (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 Asctes 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 Asctes (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 agglutin 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
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 *Euphorbiaceae*. 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-tetradecanoylphorbol-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 tumorgenesis. 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 anticancer 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 *Apocynaceae*. *Nerium oleander*, common oleander and *Nerium odorum* were considered to be the synonyms of *N. indicum*. The plant is being 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 oleandrogenin 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 β 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-Fluorouracil 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 lipoproteinase, acetyl cholinesterase, butyryl cholinesterase and urease. Among them the chloroform fraction expressed highest inhibition (90%) of lipoproteinase. 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-lipoproteinase 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-lipoproteinase 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 ghrita 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 tumefaciens 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 Hede, Thohar and Shehund. 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 (Aconitum ferox Wall. Ex. ser)

_Aconitum ferox_ Wall. Ex. ser 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 pseudoaconitine, aconitine, hycapontine, 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_. Hapaconitine (Hpa), a diterpene alkaloid isolated from _Aconitum ferox_ have expressed inactivation of the NF-kB signaling pathway. Through p53 activation, ERK1/2 and p38 MAPK signaling cascade, the alkaloids have shown protective autophagy [183]. Hapaconitine 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 aconite. Among them a compound named bis[O-(14-benzoylaconine-8-yl)] suberate (BBAS) was found to be most active [185].

BBAS showed the G50 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. Vishamushhti (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 apoptosis 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 (Aconitum chasmanthum Stapf ex 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 boydii, 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 be 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 Schedules 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 documentation 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 Ghanu) 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 practised 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 categories 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 ghtra which has Yavani, warmed wet pack made with stem of Snuhi, N. tallim which has Langali and G. tallim 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 [59], 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 remarkable 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. Tetrahydrocannabinol isolated from the Bhang is active against breast cancer, glioblastoma, astrocytoma, lung mucopidermoid carcinoma, prostate adenocarcinoma & pancreatic adenocarcinoma. 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 calotropisid-A have shown synergistic properties with 5-fluorouracil 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-fluorouracil 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 anticancer 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, navitaxal, 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 Burkitt’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 Hipenpa 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 Rhabdomysarcoma [215], Logannin 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-fluorouracil, hydroxycarbamide act by causing cell death at S-Phase by interfering 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, calotropisid A (G2/M phase), against colon cancer methanolic extract of Dunali (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 G0/G1 phase) against Breast cancer, oleandrin isolated from Karaveera (G2/M phase) against pancreatic cancer, BBAS from Vatsanabh (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 caspses that is caspase-1 to caspase-10 and caspase-14 [216]. Calotropisid 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-Fluorouracil 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, astrocytoma 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 PH11 are the newly developed principles from Gunja that act by caspase 3/7 and PARP cleavage. Brucine an active phytoconstituent from Vishamushti 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 tri-dosha 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 *Punarnava*, *Snuhi*, *Vatsanabhana*, *Shringvisha* 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 drugs 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.

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