- Review paper

Anti-Cancer Constituents from Plants: A Brief Review

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Abstract: Now-a-days, cancer is a major concern globally, for which a large number of deaths occur annually, instead of the accessibility to various treatment options. Nevertheless, the latest treatment options are principally conglomerate with many side effects. Consequently, the development of an effective and competent anticancer therapy with the lower or minimum adverse or unwanted minor effect is the prime direction of research in the fields of natural product chemistry, drug design, and drug discovery. Phytochemicals available in plants have already been proven as prospective candidates in this regard. In general, phytochemicals are non-selective in their functions and restricted due to their differential activity on cancer cells along with the normal cells. As a consequence, researchers show their interest in isolating bioactive phytochemicals from nature with potent anticancer properties and generate lead compounds based on the natural skeleton of a molecule as a synthetic approach. Several phytomolecules have already been in existence for their *in-vitro* and *in-vivo* anticancer activities. This article deals with these lead phytomolecules from fifty-two species belong to thirty-five families with their reported mechanisms of action on nuclear and cellular factors involved in the treatment of carcinogenesis.

Keywords: Cancer, Anticancer drugs, Phytochemicals, Natural product chemistry

INTRODUCTION

Generally, cancer is a state where cells can grow up and repeat uncontrollably in a particular area (*i.e.*, proliferation site) of the body. These malignant cells can invade and annihilate healthy tissues and organs nearby. Cancer cells usually commence in one part of the body and can be entrenched into a distant site by metastasis. The metastasis stage only arises when cancerous cells penetrate either the blood flow or the lymph system.[1]

Cancer proliferation includes constant altering and conversion to the cell genome carried out by both internal and external factors. Here, tumourigenesis is the process that leads to cancer cell formation, and an understanding of this procedure leads to the discovery of mutated genes (*i.e.*, oncogenes) and failure of function of tumour suppressor genes, which involves multistep processes with genetic changes at every step that direct to progressive alteration of healthy cells into tumour cells. This wild cellular propagation results in an initial heterogenic tumour followed by metaplasia, subsequent dysplasia, and anaplasia that finally results in a malignancy, which allows for invasion into the blood circulation (metastasis), followed by an incursion of a subsequent site for tumourigenesis.[2]

In 2012, Schroeder *et al*. accounted metastasis as a major cause of cancer-associated death.[3] According to Hanahan and co-workers, all types of cancer exhibit six common traits (Figure 1) that direct the transformation of normal cells to cancer cells.[4] These traits are well-known as hallmarks of cancer, with the six biological capabilities attained during the multistep progression of human tumours. The six traits include sustained proliferative signalling,

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escaping growth suppressors, resisting cell death, facilitated replicative immortality, induced angiogenesis, and activated incursion and metastasis. Two more promising hallmarks such as were listed by Hanahan and colleagues in 2011.[2] They also mentioned genome stability and mutation and tumour promoting inflammation as two enabling traits for cancer.

In accordance with the World Cancer Report 2014, cancers are the leading reasons for global morbidity and mortality. The WHO also reported that lung, prostate, colorectal, stomach, and liver cancers are prime in men and breast, colorectal, lung, cervix, and stomach cancers are predominant in women. High BMI, low fruit and vegetable intake, lack of physical exercise, and use of tobacco and alcohol were highlighted in the report as principal behavioural and dietary risk factors for one-third of cancer-associated deaths.[5] According to GLOBOCAN 2018 (reported in https://gco.iarc.fr/; extracted on 12 Feb 2020), over 18 million people are suffering from cancer, where more than 8 million are of Asia, and the projected number is 29.4 million by 2040. Thus, cancer is a disease which requires extensive attention and quicker development of new treatment weapon, new medicine.

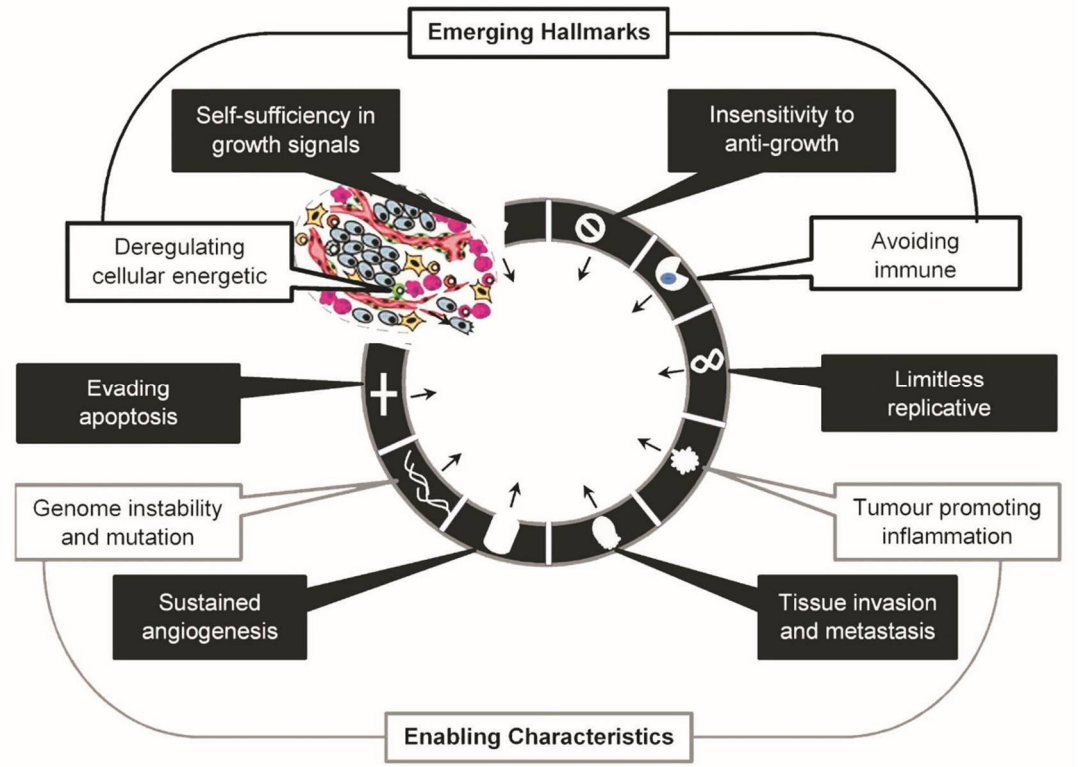

Figure 1. Imitated diagram of the six hallmarks of cancer, including two emerging traits of cancer, adapted from Hanahan and co-workers.[1]

TREATMENT OPTIONS FOR CANCER

There are many management options available for cancer, where the main approach of any treatment is to remove and/or kill carcinogenic cells to achieve inhibition of cancer cell growth. However, it is difficult to ensure either the total removal or cure of cancer cells since cancer cell propagation is caused by a variety of cell signalling pathways. Thus, researchers are investing their acquaintance to develop a single treatment approach to dodge cancer. Up to now, the key treatments for cancers are small-molecule chemotherapy, surgery, and radiotherapy.

From the beginning, chemotherapy was acknowledged as one strategy in fighting with

malignant cells and tissues. The primary theory of this approach is to kill cancer cells by treating them with chemicals that can hinder vulnerable processes linked to cell division. Chemotherapeutic agents treat cancer cells and/or suppress proliferation either by destroying essential proteins concerned in cell signalling pathways or by damaging the DNA itself.[6,7] The nitrogen mustards were the initial chemical agents with low molecular weight, which were introduced clinically in 1940 as chemotherapeutic agents. Promising improvements have been seen in the finding of new anticancer drugs during the last few decades when methotrexate and cisplatin came in front. Conversely, at the same time as chemotherapy drugs are efficient against cancer cells, they concurrently affect fast proliferating normal cells (*i.e.*, cells associated with bone marrow, immune system, GIT and hair follicles). Consequently, chemotherapy brings several unwanted side effects like alopecia, biliousness, pain, and vomiting. Due to such downsides, researchers are trying to develop site-specific small molecules, which are connected to natural product chemistry as many of established drugs are analogues of phytoconstituents.

The Vinca alkaloids (*e.g.*, vincristine and vinblastine extracted from *Vinca rosea*, Family: Apocynaceae) and taxans (*e.g.*, paclitaxel, firstly extracted from *Taxus brevifolia*, Family: Taxaceae) are the most common examples of naturally occurring chemotherapeutic agents.[8] Vinflunine, a novel fluorinated vinca alkaloid, an analogue of phytochemical, is in Phase-II clinical trials which block mitosis at the metaphase/anaphase transition and leads to apoptosis.[9]

This review compiles the fifty-two of plant species from thirty-five families that have been reported to exhibit anti-cancer activity from 1965-2018. Some of the reported structures of isolated molecules are illustrated in Figure 2, 3 and 4. It is also observed in the literature that the mode of action and dosage of administration of these plants or their parts are different from each other. This compilation will benefit future researchers to find anti-cancer principles from the plants which could be used for the treatment of cancer.

REPORTED PHYTOCONSTITUENTS AND BIOACTIVITY

Plants have been used for medicinal purposes long before the prehistoric period. Ancient Unani manuscripts, Egyptian papyrus and Chinese writings described the use of herbs. Evidence exists that Unani Hakims, Indian Vaidyas/Kabiraj, and European and Mediterranean cultures were using herbs for over 5000 years as medicine.

Acanthaceae. Kokpol and co-workers[10] have reported the isolation of octacosyl alcohol, stigmasterol (**2.1**, Figure 2), benzoxazoline-2-one (**2.2**, Figure 2) and stigmasteryl-*p*-D-glucopyranoside from the roots of *Acanthus illicifolius* L, which have shown to have activity against Friend leukemia virus in erythroleukemic Swiss mice.

Agaricaceae. In 2003, Ng and co-workers reported calcaelin, a protein, isolated from *Calvatia caelata* that has translation-inhibiting activity in rabbit reticulocyte lysate with an IC_{50} (*i.e.*, quantitative amount that specifies how much of a specific inhibitory substance is required to inhibit, *in vitro*, a given biological procedure or biological module by 50%) value of 4 nm, antiproliferative property against breast cancer cells and antimitogenic action towards mouse splenocytes. Moreover, this protein did not have hemagglutinating and antimicrobial properties.[11]

Amaranthaceae. In 1996, a short term *in-vitro* anti-tumour promoter (EBV-EA activating) test was done by Kapadia and his team members with the ethanolic extract of *Beta vulgaris* (beet) root and revealed its potential over the other extracts (*i.e.*, bell pepper, red onion skin and cranberry and long red bell pepper) and established *in-vivo* anti-tumour potential against the mice skin and lung bioassays (*i.e.*, 60% reduction of lung tumours) with a significant tumour inhibitory effect.[12]

Anacardiaceae. Bhouri *et al.*[13] confirmed the presence of digallic acid (**2.3**, Figure 2) in the fruits of *Pistacia lentiscus* L, which has prominent

antiproliferative and apoptotic activities on human lymphoblastoid TK6 cells. In their study, the initiation of apoptosis was established by DNA fragmentation and PARP cleavage and by estimating caspase events, where lymphoblastoid cell proliferation was inhibited at a dose of 8.5 µg/ml of digallic acid. The authors hypothesized that digallic acid persuades apoptosis by triggering the caspase-8 extrinsic pathway (to be noted that caspase-3 was stimulated in a dose-dependent manner too).

Apiaceae. Hu and co-workers reported that the ethanol extract of the roots of *Seseli mairei* showed significant cytotoxicity in different cell lines, importantly, the newly isolated cytotoxic compound, seselidiol (**2.4**, Figure 2) gave ED_{50} (*i.e.*, effective dose for 50% of the population) values of 1, 4.9 and 3.3 µg/ml against KB, P-388 and L-1210 tumour cells lines, respectively.[14]

In 1992, Zheng and co-workers isolated three monoterpene type anticancer agents, anethofuran, carvone (**2.5**, Figure 2) and limonene (**2.6**, Figure 2) from the oil of dill weed and caraway, which were mostly obtained from *Anethum graveolens L.* (also found in *Carum carvi* L.). It was postulated that these compounds induce the detoxifying enzyme glutathione *S*-transferase in several mouse target tissues, where the α,β-unsaturated ketone system in carvone has the high enzyme-inducing activity.[15]

Centella asiatica L. Urban is conventionally used for an ailment of several diseases around the globe including eastern Asia, China and India. In a study done by Heidari and co-workers, it was reported that the aqueous leaf extract of *C. asiatica* can cause the induction of spermatogenic cell apoptosis in male rats; the number of apoptotic germ cells per seminiferous tubule cross-section was significantly ($p < 0.05$) augmented in the trial group (18.11±3.5) compared to the control group (8.7±0.81). Additionally, a potential decline in serum testosterone, follicle-stimulating hormone, and luteinizing hormone levels suggested that this leaf extracts hold antifertility properties.[16]

Apocynaceae. Mokhopadhyay *et al.* isolated four indole alkaloids, vallesiachotamine (**2.7**), tetrahydrosecamine (**2.8**), polyneuridine (**2.9**), and sewarine (**2.10**), illustrated in Figure 2, from the leaves and roots of *Rhazya stricta*, where the first three alkaloids showed the anticancer property.[17] In this study, tetrahydrosecamine-diol was synthesized by reducing tetrahydrosecamine with LAH/ether, which gave the highest anticancer potential with ED_{50} values of 0.0038 and 0.33 mg/ml against KB and P-388 cell lines *in-vitro*.

It has been reported that ellipticine, an alkaloid, obtained from *Ochrosia acuminate* and its analogue, 9-hydroxyellipticine have anticancer properties in several tumour models.[18] It is also reported that ellipticine (**2.11**, Figure 2) inhibits p53 protein phosphorylation selectively in Lewis lung carcinoma and SW480 cell line at a concentration-dependent manner from 0.1-100 µM and 9-hydroxyellipticine blocks cdk2 kinase activity concentration-dependently from 1-100 µM.

Araceae. Cole and co-workers evaluated the fortified version of an extract of *Arum palaestinum* Boiss contained higher levels of isovanillin, linolenic acid, and β-sitosterol.[19] This plant is generally found in the Middle Eastern region, against tested prostate cancer cells. Additionally, 8 weeks older male NU/NU mice with xenograft tumours (*i.e.*, derived from the prostate cancer cell line) were treated every day with the suspension of fortified extract at a dose of 1000 mg/kg body weight. In the study, it was confirmed that fortified *A. palaestinum* caused a lessening in live cells within prostate cancer spheroids and blocked tumour growth from 30% to 55% (at a higher dose) in xenografted prostate tumours in mice deprived of causing toxicity.[19]

Araliaceae. In 2013, panaxadiol (**2.12**, Figure 2), a purified sapogenin, reported from *Panax ginseng*, was found to exhibits anticancer activity.[20] Flow cytometry was utilized to assay cell cycle distribution and apoptotic effects after staining with PI/RNase or annexin V/PI, where panaxadiol (10 and 20 mM) could suppress cell growth for 48 hours and expressively improved the antiproliferative effects in combination with epigallocatechin gallate (**2.13**, Figure 2) (10, 20 and 30 mM) on HCT-116 and SW-

480 human colorectal cancer cell lines. Combination therapy also effectively reduced S-phase fractions of cells.

Asteraceae. In 1968, Sorerensen reported in a review that the seeds of *Crepis rubra* contain anticancer principle whereas the flowers and fruits do not.[21] In 1980, Dhawan and co-workers found medicinal plant, *Parthenium hysterophorous* that showed anticancer property with 50% ethanol extract.[22]

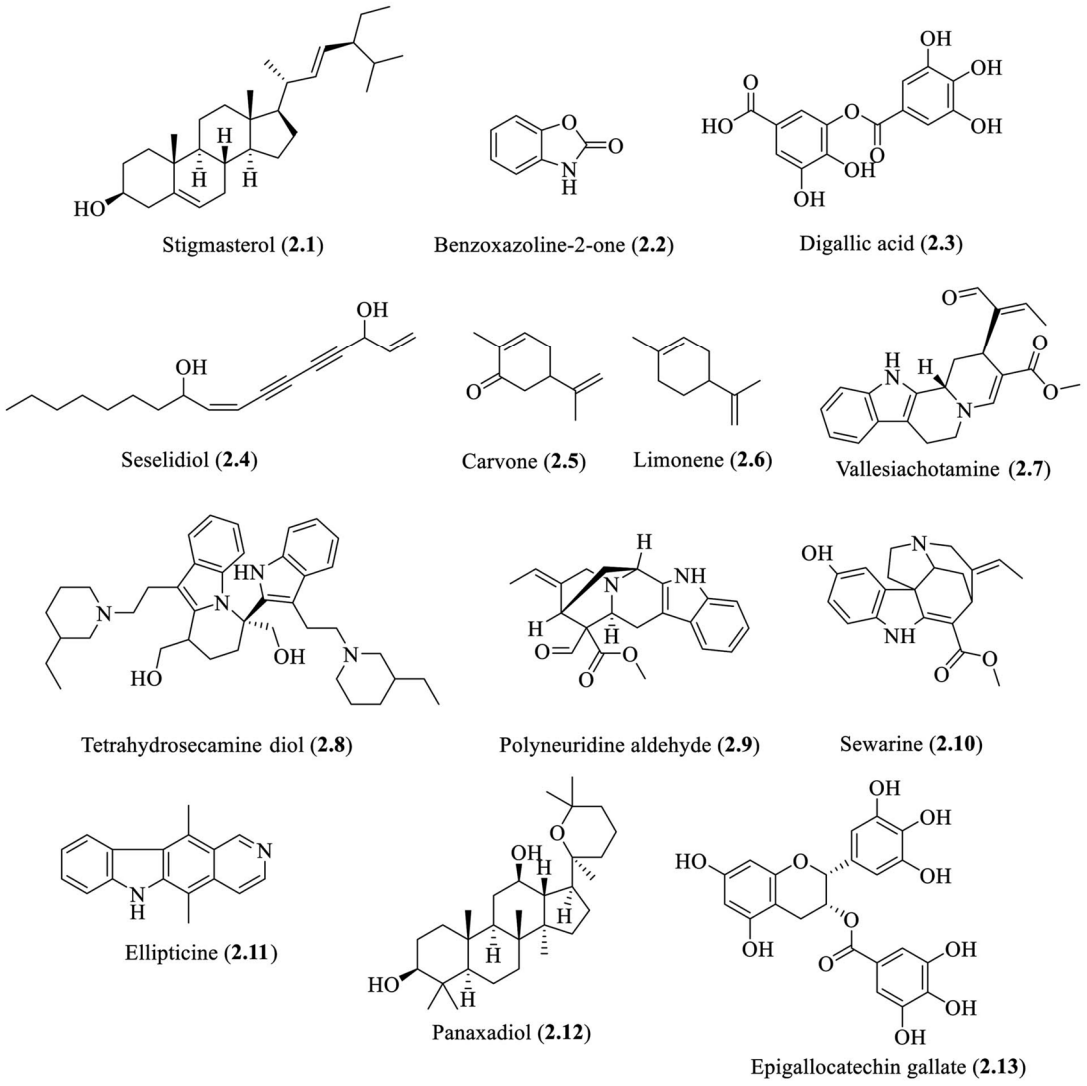

Figure 2. Some isolated antineoplastic phytochemicals reported in various published articles.

Kasai and co-workers isolated two new nor-pseudoguaianolides, microhelenin-E and -F (**3.1**, Figure 3), from Texas *Hellenium microcephalum*. Microhelenin-E demonstrated significant *in-vitro* and *in-vivo* cytotoxic and antileukemic activities against KB tissue cell culture (ED_{ao} = 1.38 Kg/ml) and P-388 lymphocytic leukemia growth in BDFl male mice (T/C = 166% at 8 mg/kg/day), respectively.[23]

Ramasamy and Agarwal reported that silymarin from *Silybum marianum* that has anti-metastatic activity along with its anti-inflammatory action. The protective effects of silymarin (**3.2**, Figure 3) and its

principal active constituent, silibinin, was studied against different tissues, which suggested its clinical application in cancer patients as an aid to recognised therapies to stop or lessen toxicity related to chemotherapy and radiotherapy.[24]

In 2018, Chaitanya and Suresh isolated astragalin (**3.3**, Figure 3) from *Anaphalis neelgerriana*, which has anticancer property that acts by stopping NF-κB pathway and plunging hexokinase-2 in cancer tissue.[25]

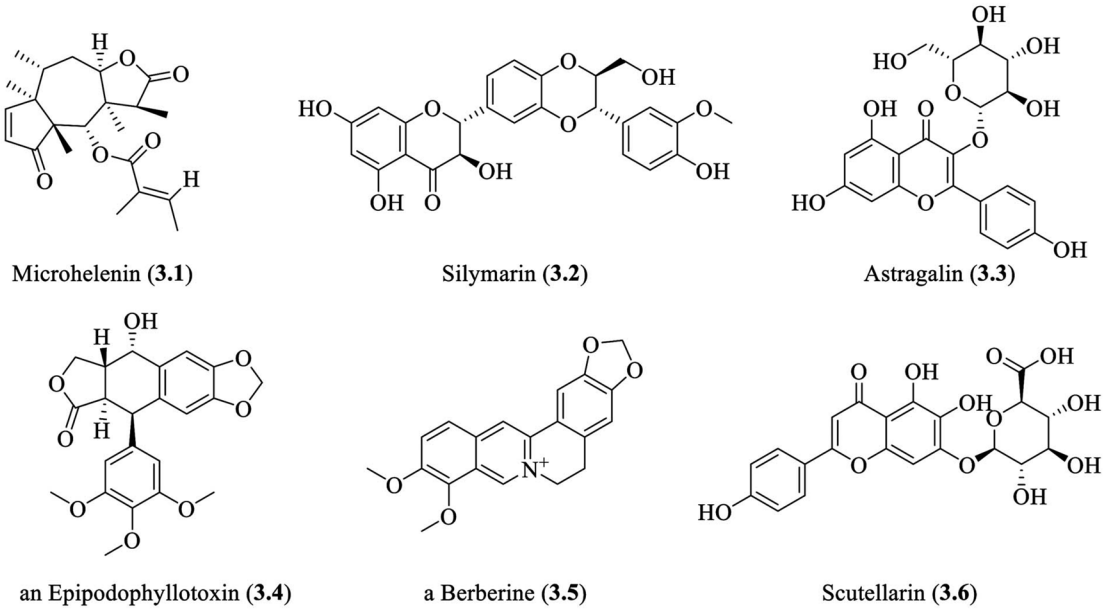

Figure 3. Some reported phytochemicals having potent anti-cancer properties.

Berberidaceae. In 1973, Stähblin reported that *Podophyllum peltatum* contains VP 16-213 (4′-demethyl-epipodophylloloxin ethylidene-*β*-D-glucoside (*e.g*., **3.4** in Figure 3), which increases the lifespan of mouse having leukemias P-815, P-1534 and L-1210. Depending on the number of tumour cells inoculated, site of tumour implantation, treatment schedule, and route of drug injection, the glucoside upsurges lifespan in L-1210 by more than 300% or cure more than 90%.[26]

Mantena and co-workers demonstrated that the berberine (*e.g.*, **3.5**, Figure 3) of *Berberis aquifolium* can control the growth of both androgen-insensitive (*i.e.*, DU145 and PC-3) and -sensitive (LNCaP) prostate cancer cells and inhibits cell propagation and persuades cell death in a dose-dependent (10-100 μmol/l) and time-dependent (24-72 hours) manner without affecting the growth of normal cells, which can be a promising candidate for prostate cancer therapy.[27]

Xu and Zhang reported that scutellarin (**3.6**, Figure 3), an anticancer agent, originated from *Berberis vulgaris*, evidently prevents the production of HepG2 cells in a concentration and time-dependent style. Scutellarin-treated HepG2 cells were shown to have a reduced amount of ROS production compared to untreated cells.[28]

Cannabaceae. In 2018, Begum *et al.* reported the presence of anticancer agents Δ^9-tetrahydrocannabinol, myrcene (**4.1**, Figure 4), and linalool (**4.2**, Figure 4) in *Cannabis Sativa* (also widely known as Marijuana, Bhang, Ganja, and Hashish).[29-31] Galve-Roperh and colleagues showed that Δ^9-tetrahydrocannabinol, the active component of marijuana, persuades apoptosis of transformed neural cells in *in-vitro*; where, the study with two subclones of C6 glioma cells in culture confers that cannabinoids indicate apoptosis through the cannabinoid receptors-associated pathway, endured

ceramide acquisition and activation of Raf1/extracellular signal-regulated kinase.[32]

Colchicaceae. Lin and co-workers reported that costunolide (**4.3**, Figure 4) derived from *Colchicum autumnale* have potential anti-cancer properties (including causing cell cycle arrest, inducing apoptosis and differentiation, endorsing aggregation of microtubule protein, preventing the activity of telomerase, hindering metastasis and invasion, retreating multidrug resistance, limiting angiogenesis has been reported) for various types of cancer.[33] Costunolide and dehydrocostuslactone have been obtained from many species of medicinal plants named *Saussurea lappa* and *Laurus nobilis.*

Combretaceae. Pettit *et al.* (1987) isolated an antineoplastic constituent combretastatin (**4.4**, Figure 4) A-1, a new *cis*-stilbene, from the South African tree *Combretum caffrum.*[34] Chemical modification and selective hydrogenation of combretastatin A-1 afforded combretastatin B-1, a companion cell growth inhibitory constituent of *C. caffrum*. Both *in-vitro* and *in-vivo* studies suggested that combretastatin A-1 extended lifespan of 26-29% at 2.75-11 mg/kg dose with an ED_{50} of 0.99 μg/ml against the murine P-388 lymphocytic leukaemia. Additionally, combretastatin A-1 and combretastatin B-1 are effective inhibitors of microtubule assembly *in-vitro* and the most potent inhibitors of the binding of colchicine to tubulin yet reported.

Cupressaceae. Podophyllotoxin (**4.5**, Figure 4) was isolated and characterised through systematic fractionation of the alcoholic extract of *Juniperus virginiana* L. Moreover, the extract showed tumour-inhibitory activity against Sarcoma-180 in mice and human carcinoma of the nasopharynx in cell culture (KB).[35]

Fabaceae. Mehdad and co-workers reported a Bowman-Birk protease inhibitor from *Vigna unguiculata* seeds called black-eyed pea trypsin/chymotrypsin inhibitor (BTCI), potently suppresses human breast adenocarcinoma cell viability by inhibiting the activity of proteasome 20S. BTCI persuaded a negative growth consequence against a panel of breast cancer cells, with an associated cytostatic outcome at the G2/M phase of the cell cycle and causes apoptosis.[36]

Pascoe *et al.* (1986) found that seeds of *Caesalpinia bonducella* L. were used extensively in Jamaican folk medicines. Chemical examination of the defatted seed kernel has led to the isolation of a group of furanoditerpenes, and E-caesalpins, which have anticancer activity.[37]

Ginkgoaceae. Ginkgetin (from *Ginkgo biloba*) inhibited cell growth and persuaded cell cytotoxicity in osteosarcoma cells and successively triggered the apoptosis of same cells at a concentration-dependent manner, which suggested that ginkgetin (**4.6**, Figure 4) exerts growth inhibitory and apoptotic effects on osteosarcoma cells through the inhibition of STAT3 and activation of caspase-3/9.[38]

Lauraceae. Banerjee *et al.* (1995) reported that camphor (**4.7**, Figure 4) isolated from *Cinnamomum camphora* can modulate the metabolism of mutagenic and/or carcinogenic chemicals by influencing on the endogenous reduced level of glutathione concentrations and induction of liver carcinogen metabolizing enzyme systems.[39]

Lamiaceae. Prakash *et al.* (1979) isolated three new diterpenes named calyone, calyenone, and precalyone from the aerial parts of *Roylea calycina*, where precalyone was reported to have antitumour properties against P-388 lymphocytic leukaemia.[40]

Imai and co-workers evaluated that the proliferation of a human colon carcinoma cell line, COLO 201 in the presence of ethanolic extract from *Vitex agnus* and reported that flavonoids within the extract were effective to suppress the apoptosis.[41] Further investigation reported in the same study showed that the initiation of apoptosis was not reserved due to presence of N-acetyl-L-cysteine, while HO-1 gene expression levels augmented among other distinctive oxidative stress-related genes examined after treating with the extract, which suggested that *Vitex* could activate pathway linked to HO-1 gene activation and subsequent induction of apoptosis in COLO 201.

Liliaceae. In 1999, Takezaki and co-workers reported that there is a truncated risk zone for gastric

cancer in Jiangsu Province, China, where people regularly consume raw allium vegetables (*e.g.*, *Allium cepa*) and it is believed that regular intake of such vegetables along with other anticancer diets influence in low death occur due to gastric cancer.[42]

Kang *et al.* reported that capsaicin (**4.8**, Figure 4), the *trans*-8-methyl-*N*-vanillyl-6-nonenamide, a major pungent ingredient in red pepper, contains anticarcinogenic, antimutagenic or chemo-preventive activities.[43] Capsaicin selectively induces apoptosis in H-Ras transformed MCF10A human breast epithelial cells but not in their normal cell counterparts. In H-Ras MCF10A cells, capsaicin treatment triggered the JNK1 and MAPK, whereas it switched off the ERKs. The authors postulated that capsaicin selectively persuades apoptosis through variation of Ras-downstream signalling molecules in Ras-activated MCF10A cells, where unrestrained Ras activation is a plausible most common genetic defect in human cancer cells.

Moringaceae. It has been reported that the leaves of *Moringa oleifera* and its crude extract have antileukemic properties. The *in-vitro* study showed that the ethanolic extract of *M. oleifera* killed about 36% of abnormal cells among primary cells harvested from three patients with acute myeloid leukaemia and hepatocarcinoma cells HpG2, indicating its antileukemic efficacy.[44]

Moraceae. Two isoquinoline alkaloids, illustrated in Figure 4 isolated from *Broussonetia papyrifera* (L.), were characterized as N-norchelerythrine (**4.9**) and dihydrosanguinarine (**4.10**). The total alkaloids and seven distinct alkaloids gave higher activities on BEL-7402 and Hela cell lines with low IC_{50} values od 6.61–47.41 mg/ml and 5.97–40.17 mg/ml, whereas, among other compounds, nitidine, broussonpapyrine and chelerythrine showed robust toxicity on non-cancer cells with IC_{50} values 18.01, 19.91, and 22.31 mg/ml, respectively.[45]

Myrtaceae. Spooner and co-workers reported that the fruits of *Syzygium cumini* have anticancer activity. The methanolic fraction of ethanol extract of seeds of *S. cumini* when tested for anticancer properties on several human cancer cell lines indicated its effectiveness as anticancer agent.[46]

Nyctaginaceae. Mishra *et al*. (2014) reported an overview of *Boerhavia diffusa* Linn, where it was stated that chemical analysis of *B. diffusa* confirmed the presence of variable phytoconstituents, namely, rotenoids, flavonoids, xanthones, purine nucleoside, lignans, and steroids. Further ethnopharmacological studies supported that the plant has medicinal values in reproductive system, GI system, respiratory system, urinary system, hepatic system/jaundice, cardiovascular system, and melanoma.[47]

Olacaceae. Polyacetylene(-)-17-hydroxy-9,11,13,15-octadecatetraynoic acid, isolated from the stem bark of *Minquartia grtiannrtis*, was found to be cytotoxic on P-388 murine lymphocytic leukaemia (ED_{50} of the pure compound is 0.18 µg/ml).[48] The compound was also shown to be active in the brine shrimp lethality bioassay (LC_{50} = 5.06 µg/ml).

Oxalidaceae. In 2007, Guruvayoorappan and Kuttan evaluated evaluate the immunomodulatory and antitumour potentials of the alcoholic extract of *Biophytum sensitivum*. The extract showed 100% toxicity at 0.5 mg/ml concentration to Dalton's lymphoma ascites (DLA) and Ehrlich ascites carcinoma (EAC) cells, which was also found to be cytotoxic towards L929 cells at a concentration of 0.1 mg/ml. It was reported that administration of *B. sensitivum* extract (500 µg/dose/animal) can obstruct the growth of solid tumour in DLA cell-induced mice and upsurge the lifespan of mice bearing EAC tumours by 93.3%.[49]

Piperaceae. Duh and co-workers isolated cytotoxic pyridone alkaloids namely N-(3-methoxy-4,5-rnethylenedioxydihydrocinnamoyl-Δ^3-pyridin-2-one, *N*-(3-methoxy-4,5-methylenedioxy-cinnoyl)-Δ^3-pyridin-2-one, piplartine (**4.11**, Figure 4) and piplartine dimer-A, from the leaves of *Piper aborescens*, which were tested against A-549, HT-29, KB, and P-388 cell lines. In their study, piplartine demonstrated the most significant results against all cell lines (*i.e.*, ED_{50} values were 0.60, 0.45, 1.80, 0.90 µg/ml for A-549, HT-29, KB, and P-388, respectively).[50]

Plumbaginaceae. Plumbagin (**4.12**, Figure 4), the 5-hydroxy-2-methyl-1,4-naphthoquinone, initially reported from *Plumbago zeylanic* was also found in the plants of Droseraceae, Ancestrocladaceae, and Dioncophyllaceae families. It was proven that plumbagin can inhibit the activation, proliferation, cytokine production, and graft *versus* host disease in lymphocytes and to inhibit the growth of tumour cells by suppressing NF-κB. Additionally, it was also reported to have inducing potential for ROS generation in tumour cells, although the mechanism is still undefined.[51]

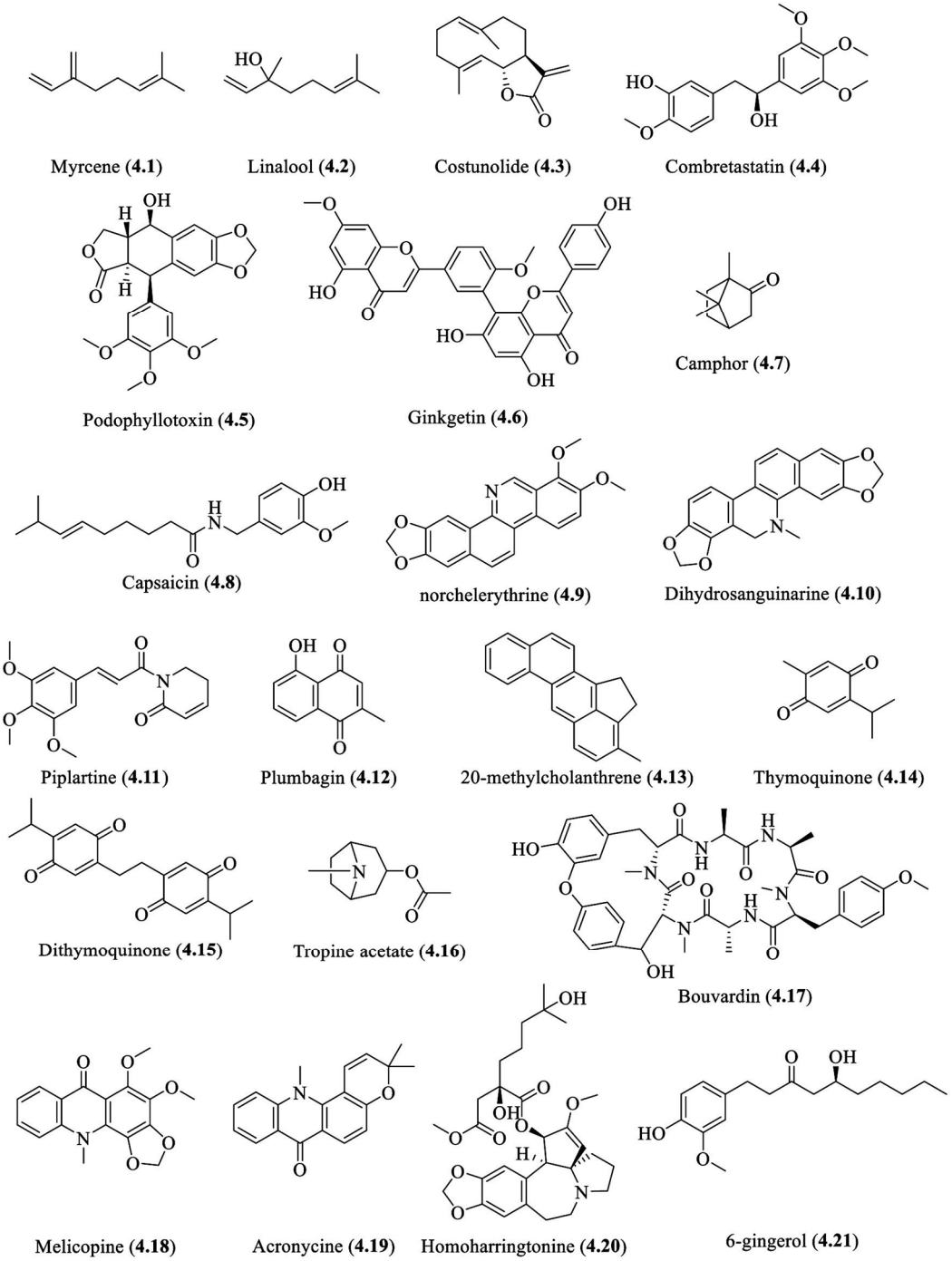

Figure 4. Phytoconstituents isolated from different species with anticancer efficacy.

Ranunculaceae. Salomi and co-workers reported that topical application of *Nigella sativa* and *Crocus sativus* (Family- Iridaceae) extracts inhibited two-stage initiation and promotion of skin carcinogenesis in mice. In this study, it was shown that the onset of papilloma formation and mean number of papillomas per mouse can be deferred by 33.3% and declined by 10%, respectively, at a dose of 100 mg/kg body wt. of these extracts (intraperitoneal administration of *N. sativa* and oral administration of *C. sativus* for 30 days followed by subcutaneous administration of 20-methylcholanthrene (**4.13**, Figure 4) at 745 nmol for 2 days).[52] It is hypothesized that these extracts can inhibit the action of 20-methylcholanthrene-induced soft tissue sarcomas.

Crocin, isolated from *Crocus sativus* (commonly known as Kashmiri saffron), has been reported to inhibit the growth of xenograft both *in vitro* and *in vivo*. Moreover, crocin can decrease cell viability in DLA cells in a concentration- and time-dependent manner. A substantial upsurge in the lifespan of Dalton's lymphoma bearing animals was observed by 37% and 44%, respectively. Additionally, animals when given treatment before the introduction of cancer exhibited 58% rise in lifespan and 95.6% drop of solid tumour in crocin treated animals on the 31st day after tumour inoculation were reported in study.[53] Worthen *et al.*[54] assayed the crude gum, fixed oil, and two purified components, thymoquinone (**4.14**, Figure 4) and dithymoquinone (**4.15**, Figure 4) isolated from *Nigella sativa* seed for their cytotoxic potential and to evaluate parental and MDR against human tumor cell lines. Both thymoquinone and dithymoquinone showed cytotoxic effect for different cell lines with IC_{50} values ranging from 78 to 393 μM. It was also observed that both parental cell lines and their corresponding MDR variants, were over 10-fold more resistant to the standard antineoplastic agents, doxorubicin and etoposide, compared to their corresponding parental controls and were equally sensitive to thymoquinone and dithymoquinone.

Rhizophoraceae. In 1969, Loder and Russell revealed that the extracts of *Bruguiera sexangula* bark had activity against two tumours cell lines Sarcoma 180 and Lewis Lung carcinoma. Tropine and tropine esters of acetic (**4.16**, Figure 4), propionic acid, *n*-butyric acid, isobutyric acid, α-methylbutyric acid or isovaleric acid, and benzoic acids have been reported in crude alkaloid mixtures from the bark of *B. sexangula and B. exaristata*, where a new alkaloid, brugine, (+)-tropine 1,2-dithiolan-3-carboxylate is the key component from both species.[55]

Rubiaceae. Jolad and co-workers reported Bouvardin (**4.17**, Figure 4) and deoxybouvardin, from the methanol extract of *Bouvardia ternifolia*, with prominent antitumour activity in the 3PS, B1 and KB systems.[56]

Polyindoline alkaloids, namely quadrigemine A, quadrigemine B, psychotridine, and isopsychotridine C have been reported from the leaves of *Psychotria forsteriana* by Roth and co-workers. These alkaloids were shown to have greater toxicity on HTC cells compared to the standard antitumour chemotherapeutic agent vincristine, a *bis*-indole alkaloid.[57]

Morita *et al.*[58] reported a hexapeptidic glucoside, RA-XII, from *Rubia cordifolia* which has antitumour activity similar to bouvardins.

Rutaceae. In 1966, Svoboda and co-workers isolated a common triterpene, lupeol and three alkaloids namely melicopine (**4.18**, Figure 4), acronycine (**4.19**, Figure 4) and normelicopidine, from the bark of *Acronychia baueri* Schott (*Bauerella australiana* Borzi). It was postulated that the possible antitumour activity was ascribed to acronycine, a previously reported potential antitumour alkaloids. Thus, the study signifies a new lead in the search of chemotherapeutic agents.[59]

Two new amides clausenalansamide-A and clausenalansamide-B were reported from *Clausena lansium* seed extract along with three known compounds. During evaluation of their anticancer potential against three human cancer cell lines namely KB, MCF7, and NCIH187, clausenalansamide-B showed cytotoxicity against KB and

NCI-H187 cancer cell lines with IC_{50} value ranging from 26.75 and 28.48 µg/ml, respectively, whereas the compound was inactive towards MCF7 cell line.[60]

Simaroubaceae. In 2018, Prajapati and co-workers reported that methanolic extract of *Simarouba glauca* leaves has significant anticancer activity against MOLT-3 and K-562 cell line with IC_{50} values of 69.69 µg/ml and 74.21 µg/ml.[61]

Solanaceae. *Withania somnifera* (L.) Dunal was assessed for its tumour prevention properties against urethane-induced lung adenomas in adult male albino mice. It was observed that concurrent oral administration of *W. somnifera* extract, at a dose of 200 mg/kg daily, together with urethane protected animals from the tumour-inducing effect of urethane.[62]

Taxaceae. Feldman *el al.* (1996) found that *Cephalotaxus harringtonia* contains homoharring-tonine (**4.20**, Figure 4), a novel cephalotaxime alkaloid, which shows antileukemic activity.[63]

Zingiberaceae. In 2015, Rastogi and co-workers confirmed that the polyphenolic alkanone, 6-gingerol (**4.21**, Figure 4), present in the extract of *Zingiber officinale* has potent antitumourigenic and pro-apoptotic properties.[64] In this study, the authors further established that 6-gingerol effectively inhibited the proliferation of HPV positive cervical cancer cells and confirmed that the molecule inhibits the chymotrypsin activity of proteasomes, induces reactivation of p53, increases levels of p21, induces DNA damage and G2/M cell cycle arrest alters expression levels of p53-associated apoptotic markers (*e.g.*, cleaved caspase-3 and PARP) and potentiates the cytotoxicity of cisplatin both *in-vitro* and *in-vivo.*

CONCLUSION

Cancer, an atypical malignant growth of body tissue or cell, is a key health burden worldwide, which requires specific, efficacious and non-toxic treatment option and global traditional systems of medicines can bring the solution with the phytoconstituents. Since plants are loaded with phytomolecules, several chemo-protective consti-tuents can be brought in light for the mankind. To be noted, some of them have already been proven to have potent activities and are undergoing clinical trial. Medicinal plants maintain the well-being and vitality of individual and can cure numerous diseases including cancer without causing toxicity. From the review work, it may be concluded that a greater number of plants possess anti-cancer constituents. These reports also emphasize the mode of action, dose, and relative activity against the cancer cells which differ from each other. Plants are abundant sources of chemically unique and biological interesting compounds in the world. Still now, the medicinal values of numerous plants are not known. This paper will also help the researchers to investigate more potent anticancer agents from the plant sources.

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