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SECONDARY METABOLITES AS LEAD MOLECULES FOR ANTICANCER THERAPIES: A REVIEW

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ABSTRACT: Cancer initiates from the transformation of normal living cells into malignant cells via a multistage event that usually advances from a pre-cancerous phase to a malignant tumour. Anti-metastatic drugs or anti-neoplastic drugs prevent and regulate the growth of onco cells. Based on the mode of drugs, the universally anticancer drugs market is categorized into cytotoxic, targeted, and hormonal drugs. The targeted drugs class is further divided into monoclonal antibodies, tyrosine kinase inhibitors, and others. The worldwide anticancer drugs market falls into five regions: North America, Europe, Asia Pacific, Latin America, and the Middle East and Africa. Cancer is considered the second largest cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 out of 6 deaths is due to cancer. Approximately 72% of deaths from cancer occur in developed and developing countries. Synthetic drugs and other modes of treatment are pre-existing. Chemotherapy treatments have its own limitations due to their toxic effects on non-targeted tissues and it further leads to health problems. Therefore, the demands for alternative treatments from naturally derived or plant-based anticancer agents are need of the day. Many plant-based anticancer compounds are effective inhibitors against many cancer cell lines, which make them in high demand. The Discovery of anticancer cancer compounds having specificity towards cancer cell lines via apoptotic cell death or derailment of the cell cycle in malignant cells can be considered for clinical trials. This review provides some glimpses of naturally-derived compounds from plants and their mode of action against selected cancer cell lines.

INTRODUCTION: From ancient period onwards, herbal medicines were used by the native people and are still the primary source of medicine in most parts of developing and underdeveloped countries.

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The Oldest known document of plants based drugs has been recorded on a Sumerian clay slab, nearly 5000 years old, consists of 12 recipes referring to 250 diverse plant species, like poppy, henbane, and mandrake, *etc.* [1]

There was evidence for the use of plant products in the treatment of various diseases and for revitalizing body systems from Indian, Chinese, Egyptian, Greek, and Roman civilizations. According to WHO, plant-based treatment forms the main source of medicine. India has about 4.5

million plant species, and among them, only 250,000-500,000 plant species are screened phyto-chemically for its biological or pharmacological activities. The bioactive constituents of plants extracts were used for treatment of various diseases and further, the formulation for the novel drugs in pharmaceutical industries. Researches are intended in searching the biological properties of plant extracts as potential drugs for curing many diseases including cancer [2].

There are considerable economic benefits in validating the indigenous knowledge and in the use of herbals for the treatment of many diseases. Outstanding contributions to modern therapeutics were provided by medicinal plants. Hundreds of novel plants based drugs were introduced in the USA drug market during 1950-70, which includes vinblastine, vincristine deserpidine, and reserpine, while during 1991-95 about 2% of drugs (pacitaxel, topotecan, gomishin, irinotecan *etc*.) were introduced [3]. In the middle of the 20th century, the use of medicinal plants was reduced because of the discovery of synthetic chemicals for curing diseases.

Plants produce vast and diverse types of compounds, and many of them were not directly involved in the growth and development of the species. These substances are referred to as secondary metabolites. In recent years, the commercial importance of secondary metabolites is increased. Plant secondary metabolites are usually classified according to their biosynthetic pathways. The phenyl propanoid pathway is involved in the secondary metabolite synthesis among the majority of species. Search for novel molecules of therapeutic properties within unexplored parts of biological diversity is a challenge. For the past few decades, a large number of herbals used by the tribes as ailments were exploited and experimentally evaluated. Its usage ranged from surface applications for preventing infections to internal consumption against relief from many illnesses and inflammations.

Cancer or malignant tumours represent the second-largest common disease. Evidence for cancer is increasing on a global scale. There is more than one plausible explanation for cancer initiation. Due to this, there is no effective cancer therapy available to date, and the disease can keep expanding on a global scale [4]. Cancer is a major public health issue both in developed and developing countries. It is a group of diseases characterized by unregulated division and spread of cells and also a complex genetic disease that is caused primarily by environmental factors. The carcinogens can be present in food, water, air, chemicals, and sunlight that people are exposed. More significantly, unhealthy lifestyles and the adoption of many features of the modern Western diet will increase cancer incidence.

In terms of behaviour, tumours are either ‘benign’ or ‘malignant’. Benign tumours are slow-growing, expansive masses that compress and invade surrounding tissues. Malignant tumours are usually rapidly growing, invading surrounding tissue and most significantly colonizing in distant organs. The ability of tumour cells to detach from the primary tumour and set up a metastasis *i.e.,* secondary tumour, discontinuous with the primary is the proof of malignancy. The suffix ‘oma’ usually denotes a benign tumour. Sometimes, the cancerous cells may occur in liquids (like leukemia). However most of the tumors occur as solids, originally appear in various tissues and parts of the body.

Different types of Cancers such as in Blood and lymphatic systems (Waldenstrom's disease, Hodgkin’s disease, Lymphomas, Multiple myeloma, Leukemia’s), digestive Systems (esophageal cancer, stomach cancer, liver cancer, cancer of pancreas, rectal and colon cancer, anal cancer), skin cancers (malignant melanoma), urinary system (kidney cancer, bladder cancer, testis cancer, prostate cancer), reproductive organs in women (ovarian cancer, breast cancer, choriocarcinoma, gynecological cancer), miscellaneous types (bone cancer, brain cancer, characinoid cancer, soft tissue cancer, nasopharyngeal cancer, retroperitoneal sarcomas,, thyroid cancer). Breast cancer is one of the highest forms of cancer worldwide [5].

Factors like smoking, diet, and infectious diseases as well as chemicals and radiation, along with trace levels of pollutants in food, drinking water, and air are found reasons for cancer. Some other factors which are more likely to affect are tobacco use, unhealthy diet, not enough physical activity, pollutants concentration, intensity, and exposure. The cancer risk becomes highly increased where

workers are exposed to ionizing radiation, carcinomas chemicals, certain metals, and some other specific substances or even exposed at low levels. Passive tobacco smoking increases the risk in a large population who do not smoke but exposed to exhaled smoke of smokers [6].

Over 60% anticancer agents are derived from natural resources like plants, marine organisms, and microorganisms [7]. The national cancer institute has screened around 114,000 extracts for anticancer activity [8]. Compounds that are identified and extracted from plants for their anticancer properties mainly include polyphenols. This review provides a recent outline of the ethnic plants used by the tribes, isolation of the compounds, and its validation towards anticancer potentialities.

Cancer Therapy: Cancer treatment is a combination of number of different processes, which depend on the stage and type of cancer, which includes: surgery, radiation therapy, chemotherapy, biological therapy, and hormone therapy. If the tumour is amenable to surgery, then surgery is the most effective tool for treatment. Targeted radiotherapy together with combinations of anticancer drugs is another method of treatment. Usually, conventional anticancer drugs are designed with deoxyribonucleic acid (DNA) synthesis as their target. Tumour cells are not only seen as proliferating cells in the body; they are also present in the alimentary tract, bone marrow cells, cells to fight infection, and epidermal cells, including those that generate hairs, all are highly proliferative. So the patients with cancer under-going chemotherapy commonly suffer unwanted hair loss and sometimes potentially life-threatening anaemia and proneness to infections (side effects that limit the treatment). Localized tumors can be successfully removed by surgery or irradiation with high survival rates [9]. Complementary or alternative therapies, which do not use known cancer drugs or use approaches not common in the medical community, commonly use methods to control symptoms. It is important to research and understand the risks and benefits of these therapies.

The step towards the development of cancer involves alterations of epigenetic processes and their deregulation. So the control of hypermethylation of tumor-suppressor genes is deregulated in cancer cells. This results in gene silencing and inactivation of tumor-suppressor genes. Drugs that can inhibit or reverse these epigenetic alterations have been in development over recent years [10]. There is many forms of cancer in the human population but share similar characteristics or genotypes. Plant-derived compounds have demonstrated properties to inhibit cancer cell activities like inhibiting the proliferation of cancer cells and inducing apoptotic cell death.

In developing countries, utilization of all plant parts, including the stem, leaf, root, and bark are included in the treatment. There are huge demands for medicinal plants in developing countries, and attention is being drawn towards food with medicinal properties like cruciferous vegetables and fruit berries [11]. Raw by-products from industries are also utilized to extract anticancer agents. For example, rape seed extract is often added in ingredients of food products due to its human health benefits. In the wine industry, grape stems are raw by-products after making wine. Its high polyphenolic content makes it advantageous for anticancer drug development and makes a profitable scheme to reduce environmental issues. Grape stem extracts have been demonstrated to have antioxidant properties, prevent DNA damage and show anti-carcinogenic potentiality against an array of cancer cell lines from cervical cancer to thyroid cancer [12].

Many studies have reported that inhibition of enzymes that stop tumor growth is mainly performed in human cell lines. Many plants play anticancer roles through their different classes of secondary metabolites. However, the study of these plants should not limit the study of a plethora of anticancer plants, some of which are still unexplored. Studies are needed to highlight the mechanism of anticancer action of many already explored and unexplored plants.

Secondary Metabolites *vs.* Anticancer Properties: Secondary metabolites (SMs) synthesized in plants mostly function as scavengers of free radicals/ reactive oxygen species, which raises the possibility of their application in food and pharmaceutical fields. The knowledge gained at the cellular and molecular levels and biological activities of SMs would be useful in planning for

future epidemiological studies and human cancer prevention trials, especially when a high dosage is not the option to deliver the active compounds into many tissues. It is well documented that cell cycle alteration by regulatory gene expression is frequently found in tumour tissues or cancer cell lines. Studies have suggested that SMs are potential targets as anticancer drugs *via* cell cycle regulations.

From time immemorial, plants have been used as a source of medicines to regulate lifestyle disorders. Many molecules were under clinical studies like flavone - favopiridol, derived from the alkaloid rohitukine was isolated from Dysoxylum binectariferum, was currently under phase I and phase II clinical trials, which shows broad activity against tumors, leukemia, lymphomas, and solid tumors [13]. Similarly, Olomucine from Raphanus sativus was designed into a synthetic agent, roscovitine, and in Europe, it is in Phase II and III clinical trials [14].

Betulinic acid (pentacyclic triterpenoid) was isolated from Zizyphus species, and they exhibited selective cytotoxic activity against human melanoma cell lines [15]. Silvesterol was isolated from the fruits of *Aglaila sylvestre*, exhibits cytotoxicity against breast and lung cancer cells. Different studies are attempted to determine the exact mechanism of action for silvesterol and other bioactive molecules [16, 17]. Phytochemical studies on roots of *Erythroxylum prvillei* has resulted in the isolation of pervilleine-A. Studies were conducted on multidrug-resistant oral epidermoid cancer cell lines using pervilleine-A (cytotoxic) along with vinblastine as preventive drugs [18]. Combretastatin was isolated from the bark of *Combretum caffrum* and has been found effective against lung and colon cancers leukemia and we presumed this was the most cytotoxic phytomolecule isolated so far [19].

Nowadays, plant-derived drugs are preferred mainly for anticancer treatment as they are natural, easily available, and can be readily administered orally as part of patient's dietary intake [20]. Being natural, the phytochemicals from plants are non-toxic to normal human cells [21]. However, there are some exceptions like lectins, saponins, lignans, cyanogenetic glycosides, and some taxanes. If plant-derived drugs are non-toxic to normal cell lines and show cytotoxicity in cancer cell lines, these drugs can be lead to clinical trials for further therapeutic developments. Epothilones are bacterial macrolides with potent antiproliferative activity, which have served as successful lead structures for the discovery of several clinical candidates for cancer treatment [22]. Major secondary metabolites from plants that have been used by the native people for anticancer therapies are listed below:

Polyphenols: Flavonoids, resveratrol tannins, curcumin, and gallacatechins are major poly-phenols having anticancer potential [23]. Resveratrol was prevalent in food items like peanuts, grapes, and red wine, while gallacatechins in green tea. The cytotoxicity of polyphenols on a range of cancer cells has been demonstrated with their antioxidant properties [24]. Fractionation of methanolic extracts of *Leucobrym bowringii* by RP-HPLC revealed a pool of phenolic acids, and further studies revealed a role in human breast cancer cell lines [25]. Polyphenols are reported to have apoptosis-inducing properties. The mechanism of action by polyphenols is mostly via apoptosis initiation by regulating the mobilization of copper ions which are bound to chromatin leads to DNA fragmentation. Another mode of action is by interfering with proteins which promotes cell growth. The structural feature of polyphenol facilitates the action via acetylation, methylation, or phosphorylation processes [26].

Tannins: These are naturally occurring water-soluble polyphenols having varying molecular weights and are the most abundant polyphenolic compounds with the capacity to precipitate proteins from solutions. In-plant cells, the tannins are located away from the proteins and the enzymes of cytoplasm, but when the tissues are damaged, tannins may react with proteins. Tannin-containing plants are used in ethnic medicine from ancient times onwards. Quercus robur is rich in tannins (gallotannins, ellagitannins, monomeric and dimeric catechins, and leucocyanidins), and has been used for its medicinal properties. Tannins may be procarcinogenic, anticarcinogenic, mutagenic, or antimutagenic. However, there is no evidence that tannins are procarcinogenic in humans [27]. Sakagami *et al.,* [28] proved that ellagitannins exhibit higher cytotoxicity against human oral squamous cell carcinoma and salivary gland tumor cell lines than against normal gingival fibroblasts.

Catechins: Catechins are a group of polyphenolic compounds, (epigallocatechin-3-O-gallate (EGCG), epigallocatechin (EGC), epicatechin-3O-gallate (ECG) and epicatechin (EC), which are abundantly present in vegetables, plant-derived beverages, and foods [29]. Chemically, they are polyhydroxylated flavonoids, which exhibit water-soluble characteristics. Being important micro-constituents of the human diet, catechins need to be taken into account when the relationship between diet and chronic diseases are to be investigated [30].

Studies indicated that EGCG can preferentially induce apoptosis in T lymphocytes of leukemia patients or cultured cancer cell lines [31]. According to them, when compared to normal controls, the transformed NIH-pATMras fibroblasts were more sensitive to EGCG at a 5 µM concentration. Anticancer activity of the catechins tested was found to be effective, and therefore they have therapeutic values.

Flavonoids: Flavonoids constitute one of the large family of plant secondary metabolites with 10,000 known structures (anthocyanins, flavones, flavonols, chalcones, and many more). They are physiologically active due to their health benefits and become high scientific demand in various industries [11]. Various plants have been investigated for their flavonoid content with their mode of action in cancer cells [32]. Cao *et al.*, [33] showed that purified flavonoids with anticancer activities against human cancer cell lines such as hepatoma (Hep-G2), cervical carcinoma (Hela), and breast cancer (MCF-7).

Apigenin, quercetin, and luteolin were the major flavonoids identified by RPHPLC- PAD analysis of Marchantia linearis, a bryophyte [34]. Many studies have showed that flavonoid extracts from fern species, even at low concentrations they demonstrate a high percentage of anticancer activity [35]. As mentioned earlier polyphenols inhibit or alter the regulation of proteins and other agents, which may be contributing to the survival of cancer cells. Signal transducer and activator of transcription (STAT) proteins are anti-apoptotic and contribute to cancer cell growth [36]. Flavonoids also inhibit the expression of NF-κB, which is essential for cancer cell survival, angiogenesis, and proliferation.

Brassinosteroids: Koncz *et al.*, [37] reported brassinosteroids (BRs) as natural compounds occurring in plants that play key roles such as hormone signaling to regulate growth and differentiation of cells, resistance or tolerance against disease and stress. BRs are also used for the regulation of plant senescence. A characteristic feature of cancer cells is that they do not naturally undergo apoptosis, but they proliferate indefinitely. BRs induce responses necessary for growth inhibition and induce apoptosis by interacting with cell cycle [38]. Two natural BRs have been used in cancerous cell lines -28homocastasterone (28-homoCS) and 24-epibrassinolide (24-epiBL). BRs are used to treat a range of cancer cell lines which includes: lymphoblastic leukemia multiple myeloma RPMI 8226, CEM, cervical carcinoma, HeLa, lung carcinoma A-549, osteosarcoma HOS cell lines, breast cancer cell, and prostate cancer cells.

Alkaloids: Alkaloids have a wide distribution in the plant kingdom and mainly exist in higher plants. Several alkaloids were isolated from natural herbs exhibit antiproliferation and antimetastasis effects on various types of cancers both under *in-vitro* and *in-vivo* conditions. Camptothecin and vinblastine were alkaloids that have been successfully developed into anticancer drugs.

The first agents introduced in clinical use were Vinca alkaloids - vinblastine (VLB) and vincristine (VCR) isolated from the *Catharanthus roseus*. During experimentation, it was noted that these plant extracts reduce the white blood cell counts significantly and also caused bone marrow depression in rats. The plant extract also prolongs the life of mice bearing transplantable lymphocytic leukemia.

Further extraction and fractionation led to the isolation of two active alkaloids, namely vincristine and vinblastine. Jayakumar and Murugan [39] reported the presence of caulophyllumine A and solasodine by the fractionation of crude alkaloids from *Solanum mauritianum* having significant antiproliferation activity against cancer cell lines. Alkaloids obtained from natural herbs seem to have many targets to realize their multiple pharmacological effects.

Campothecin was first isolated from the Chinese ornamental tree, *Camptotheca acuminata*. The extract of *C. acuminata* was showed efficacy in anti- tumor activity, and the active constituents isolated was identified as camptothecin. Researches from several organizations identified effective camptothecin derivatives and topotecan (Hycamtin) (SmithvKline Beecham) were now in clinical trials. Topotecan was used for the treatment of ovarian and small cell lung cancers, while irinotecan was used for the treatment of colorectal cancers. In addition, 15 other camptothecin derivatives were in preclinical developmental trials [40].

Anthocyanin: Anthocyanin is a colouring pigment that belongs to polyphenols. They have shown significant potentiality as drugs for the treatment of diverse human diseases. Currently, attention has been focused on the antimetastatic potentials of anthocyanins. The anticarcinogenic effect of anthocyanins may be through redox status modification or interference with basic cellular functions. Many *in-vivo* and *in-vitro* studies in cancer cell lines were carried to study the antitumor efficiency of plant anthocyanins. The chemo-protective activity of anthocyanin-rich plant extracts from grapes, bilberry and chokeberry substantiate that the extracts reduce the colonic aberrant crypt foci formation in male rats treated with a colon carcinogen azoxymethane [41].

The cell suspension culture of *Bridelia retusa*, anthocyanin was extracted and purified by Aswathy *et al.,* [42], which revealed 07 fractions comprising acylated cyanidins, two peonidins, cyanidin 3-p-coumaroyl and feruloyl diglucoside-5-glucosides. Further, the cytotoxicity efficacy of anthocyanin extracts was studied in human oral squamous cell carcinoma (SCC4, SCC9, and SCC25) cells using cell adhesion and cell viability assay. Significant apoptosis was observed in the tested cell lines.

Similarly, anthocyanin was extracted, purified, fractionated by liquid chromatography-mass spectrometry (LC-MS/MS) from the *in-vitro* culture of teak and proved its potent antioxidant activity [43]. Reddivari *et al.,* [44] isolated anthocyanin fraction from potato extracts and showed its cytotoxic potency against prostate cancer cells through activation of caspase-dependent and independent pathways.

Saponins: These are glycosidic compounds of steroids or triterpenoids (sapogenin nucleus with one or more side chains of carbohydrates). Many leguminous plants of temperate areas are rich in saponins and exhibit positive and negative biological effects. Due to its amphiphilic nature and surface-active potentialities, the molecules are excellent foaming agents. The biological values of saponins are closely related to their chemical structure.

Despite the antinutritional attributes of saponins, they are known for their hypocholesterolemic, anticarcinogenic and immunostimulatory properties [45]. *Panax ginseng, P. quiquefolius, P. japonocus, P. pseudoginseng* and *Eleutheroccus senticosus* are widely employed in Chinese medicine (0.5-3%) as a tonic or adaptogenic and also for the treatment of cancer, diabetes, and hepatic and cardiovascular diseases [46]. Some of the steroidal saponins showed remarkable cytotoxicity against human oral squamous carcinoma cell lines when compared to normal human gingival fibroblasts. The tumor specificity of saponins has been reported higher than that of tannins and flavonoids, suggesting that its oxidation-mediated mechanism was not involved in the cytotoxicity activity [46].

Podophyllotoxin Derivatives: Podophyllotoxin is another plant-derived product with derivatives such as etoposide and teniposide used in therapies like cancers and venereal wart. Its structure is closely related to the aryltetralin lactone lignans that have antineoplastic and antiviral activities. These cytotoxic therapeutic constituents were first isolated in 1880. *Podophyllum peltatum* of Podophyllaceae was used by the Native Americans for the treatment of cancer. Other closely related podophyllotoxins were also isolated during 1950's and are now introduced into clinical trials [47].

Homoharringtonine: Homoharringtonine was isolated from the *Cephalotaxus harringtonia* var. Drupacea. In China, to combat acute myelogenous leukemia and chronic myelogenous leukemia, a racemic mixture of harringtonine and homo-harringtonine (HHT) was used successfully. Purified homoharringtonine has shown efficacy against various leukemias. In France, elliptinium is marketed for the treatment of breast cancer [48].

Phytoestrogens: These are natural phyto-metabolites comprising wide number of compounds such as isoflavones, lignans, coumestans and resorcylic acid lactones known for their estrogenic activity and were structurally or functionally similar to mammalian estradiol. Many members of Leguminosae and Poaceae are the major sources of dietary PEs. Daidzin and genistin are major isoflavonoids of soybeans [49]. Antioxidant species act *in-vivo* to prevent oxidative damage of DNA, proteins, and lipids, thus reducing the risk of coronary heart disease and cancers. Research outputs on the health-related and clinical benefits of PEs have attracted much attention from the pharmaceutical industries. Consumption of soy products with PE levels in the diet (as much as 200 mg/day), lowers the risk of hormone-dependent cancers and other chronic diseases [50]. Higher consumption of PEs was inversely correlated with the incidence and mortality rate of prostate cancer. Studies have shown that genistein inhibits prostate cancer cell growth under *in-vitro* and *in-vivo* conditions via regulating its secretion and intracellular levels of the androgen-related protein prostate-specific antigen [46].

Terpenoids: Terpenoids are secondary metabolites ubiquitously found in the plant kingdom and structurally composed of isoprenoid units. Based on structure, terpenoids are divided into monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes. The diverse array of terpenoids has increased their demand in pharmaceutical industries due to their antioxidative, anti-inflammatory, and anticancer properties. Many terpenoids have been found to exhibit anticancer property on different stages of tumor development through suppression of angiogenesis, invasion, and metastasis by regulating various intracellular signalling pathways [51]. Triterpene acids show various pharmacological activities like anti-inflammatory, antimicrobial, cytotoxic, antiviral, and cardiovascular protection [52]. Esters and their derivatives can be obtained from many natural sources. This class of compounds exhibits a variety of structural types, including aliphatic and aromatic moieties leading to broad range of biological activities like antibacterial, antifungal, inhibition of testosterone secretion, estrogenic, antiestrogenic, relaxant effect, anti-inflammatory, immunological, cytotoxic, iono-phoretic properties, vasodilatory effect and antagonist of calcium [53]. Terpenoids were extracted, purified, and fractionated by GC-MS from *Hypnea musciformis* in to hexadecane, 2, 6, 10, 14 tetramethyl, Pentadecanal, phytol isomer, 4, 8, 12, 16- tetramethylheptadecan-4-olide *etc.* [54] Phytochemical screening of *Brachythecium buchananii* revealed terpenoids with many pharmacological activities like anti-inflammatory, anti-malarial, anticancer, inhibition of cholesterol synthesis, anti-viral and bactericidal activities [55].

Taxanes are another class of diterpenes proven as anticancer drug that binds to tubulins/microtubules which have a key role in mitosis. Suppression of microtubule dynamics results in the blockade of cell mitosis, leading to apoptosis. Leaves of *Taxus brevifolia*, was used in the Ayurveda. Paclitaxel was isolated from the species and was used for the treatment of a wide variety of cancers, including breast, ovarian and non-small-cell lung cancer, and also against Kaposi sarcoma. Docetaxel, a semisynthetic derivative, was isolated and used in the treatment of breast cancer [56].

Essential Oils: Essential oils are proven for their therapeutic potentiality. Recently, essential oils (EOs) have been under study for their use in cancer therapy. EOs has been shown to possess anticancer properties through various cancer preventative mechanisms on the various tumor cell lines. Eos with therapeutic potential can act in two ways-chemoprevention and cancer suppression. EOs demonstrated to change expression levels of Bcl-2 and Bax genes, leading to the release of cytochrome C into cytosol in human oral epidermoid carcinoma cells [57]. Similarly, a study on human melanoma cells reported that EOs induces DNA damage in cancer cells which is an indicator of apoptosis [58]. Frank *et al.*, [59] studied the action of *Boswellia carteri* EO (Frankincense oil) in bladder cancer cells and observed modulation of CDKN1A, DEDD2, IER3, IL6, SGK, TNFAIP3 GAD45B, and NUDT2 genes involved in apoptosis. Chen *et al.*, [60] reported EO of Curcuma zedoaria has *in-vitro* and *in-vivo* anti-angiogenic effects, exhibited anti-proliferative activity against various cancer cell lines, and also suppressed melanoma growth and lung metastasis in mice. Girola *et al.*, [61] tested the antitumor efficacy of camphene isolated from the EO of *Piper cernuum*

in melanoma cells. By GC -FID and GC-MS analysis of essential oil from *Pogostemon benghalensis* 41 volatile compounds were reported by Pradeep and Murugan [62]. These oils mainly contained sesquiterpene and oxygenated sesquiterpene hydrocarbons having anti-cancer potentialities. Another study validated the antimetastatic mechanism of action of carvacrol, a phenolic mono terpenoid abundant in the EOs of oregano and thyme [63].

Other Compounds: Compounds including sulforaphane, isoflavones, isothiocyanates, and pomiferin are considered to inhibit histone deacetylases (HDAC), which inhibit the activity of carcinogenic proteins. According to Davidson *et al.,* [64] sulforaphane has been shown to inhibit important targets in breast cancer proliferation, *i.e.,* decreased expression of ER, EGFR, and HER-2 by HDAC inhibition in breast cancer cell lines. Plant-derived compounds which show inhibition of HDAC can enhance chemotherapeutic sensitivity in human cancers [65]. The investigations showed that the plant extracts with a combination of anticancer compounds were more reliable against cancer cells and showed no activity on normal human lymphocytes and fibroblasts. This makes plant extracts more desirable as therapeutic agents than chemically-derived compounds, which cause toxic complications in cancer treatment [66]. Discovery of anticancer cancer agents which show specificity towards cancer cells and can induce cell death and inhibit the growth of tumors may be considered for clinical trials.

With advancements and discoveries in naturally derived drugs, new technologies are emerging for the application of anticancer compounds. Administrations of new drugs are an effective alternative to current treatments like chemotherapy. The field of nanotechnology and the use of nano particles (NPs), as a delivery system for drugs to reach target sites, are developing. Some compounds that have demonstrated anticancer activities are limited in their clinical development due to the need for high dosages. Bromleain, isolated from Ananas comosus was showed more effective as an anticancer agent in formulation with NPs than free bromelain [67]. The drug's ability to inhibit the growth of tumours and reduce unwanted side effects on other tissues is much demanded in the pharmaceutical fields.

Validation of Ethnic Plants used by the Native People for Cancer Treatment: The effort of the National Cancer Institute to develop systemic and topical formulations of drugs for potential clinical trials is an ongoing event. There are many herbal databases, which provide information on anticancer compounds in plants. The WHO estimates that approximately 80% of the people rely on traditional medicine for their primary health care [68]. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened their extracts for anticancer activity [69]. Traditional types of anti-cancer plants reported were zedoary (*Curcuma zedoaria*), marijuana (*Cannabis sativa*), turmeric (*Curcuma longa*), bamboo grass (*Loathatreum gracies*), garlic (*Allium sativum*), sunflower (*Helianthus annus*), leunca (*Solanum nigrum*), and bamboo rope (*Asparagus cochinchinensis*) [70].

TABLE 1: SOME ETHNIC PLANTS USED BY TRIBES OF KERALA FOR PREVENTION AND TREATMENT OF CANCER

S. no.	Name of the species	Tribal / Native community	Phytochemical	Reference
1	*Hypnea musciformis, Kappaphycus alvarezii* & *Gracilaria dura*	Mukkuva	Terpenoids	Sumayya *et al.,* [71]
2	*Marchantia linearis*	Kanni	Flavonoids	Remya Krishnan and Murugan[72]
3	*Leucobryum bowringii*	Kanni	Secondary metabolites	Manoj *et al.,* [25]
4	*Brachythecium buchananii*	Kanni	Terpenoids	Greeshma and Murugan[55]
5	*Bridelia retusa*	Koragas	Anthocyanins	Aswathy *et al.,* [42]
6	*Pogostemon benghalensis* & *P. cablin*	Marattis and Malavettuvas	Essential oil	Pradeep and Murugan[62]
7	*S. mauritianum*	Mavilan	Alkaloids	Jayakumar and Murugan [39]

Ethnic plants in Kerala used by the tribals or native locals for the prevention and treatment of cancer were given below and validated scientifically **Table 1**. The data also gives information regarding the active anticancer components of the plants.

Sea Weed Terpenoids: Shelar *et al.,* [73] documented the ethnic knowledge of native Mukkuva community regarding the usage of selected sea weeds as tumour protective. This information was validated by Sumayya *et al.,* [71]. Seaweeds are rich in bioactive compounds that had a broad range of biological activities, including anticancer potential. *Hypnea musciformis*, *Kappaphycus alvarezii* and *Gracilaria dura* are marine algae. Anticancer potentiality of these sea weeds against three human cancer cell lines (A549, HeLa, and HepG2) with purified terpenoid extracts was analyzed by Sumayya *et al.* [71] The cytotoxicity studies were carried out using an MTT assay. All the purified terpenoid extracts revealed antiproliferative potential against the three cancer cell lines in a dose and duration-dependent manner. G. dura terpenoids fraction showed significant inhibition when compared to the other red algae.

The phase-contrast microscopic visuals showed significant morphological anomalies on the treated cell lines. The extracts were subjected to column chromatography followed by GC-MS analysis revealed the presence of 17 peaks of terpenoids in *H. musciformis* (hexadecane, eicosane, pentadecanal, octadecane, tetradecanoic acid, heneicosane, 2-pentadecanone, 6,10,14-trimethyl-2-pentadecanol, phytol isomer, hexadecanoic acid methyl ester, isophytol, n-hexadecanoic acid, behenic alcohol, octadecanoic acid metyl ester, 4, 8, 12, 16-tetramethylheptadecan-4-olide, 3, 4, 8, trimethyl-2-noneal and 9,19 cyclolanostan-3-ol-24-methylene), 10 peaks in K. alvarezii (hexadecane, octadecane, tricosane, nonadecane, hexadecanoic acid methyl ester, eicosane, heneicosane, stigmast-5-en-3-ol, gamma sitosterol and β- amyrin) and 4 major peaks in *G. dura* (hexadecanoic acid, n-hexadedcanoic acid methyl ester, octadecanoic acid methyl ester and phytol).

The cytotoxic effect was further validated by lactic acid dehydrogenase assay, apoptosis, cell cycle arrest, and caspase activities. *Capsosiphon fulvescens* (Cf) is a green marine alga used as sea-food as well as a potential drug. Cf glycoprotein (Cf GP) exhibits antitumor activity against several cancer cells via inducing different pathways. Analysis of Frizzled receptor, Wnt 1 signaling proteins Axin, LRP, β catenin, APC and GSK-3 beta reports the suppression of Wnt 1 signaling, β catenin, and transcription factors in AGS cells by Cf-GP. RT-PCR and Western blotting experiments of transcription factor Tcf/LEF also proved the decrease level of Wnt-1 signaling pathway and arrested the G0/G1 phase of AGS cells by Cf-GP [74]. According to Kim *et al.,* [75] Cf-GP treatment not only stimulated the release of cytochrome C and apoptotic protease activating factor-1 from mitochondria to the cytosol but also inhibited the growth of AGS cells through induction of sub-G1 phase arrest, which decrease in the expression of cyclin D, E, Cdk2, Cdk4, and Cdk6 and an increase in the protein levels of p21 and p27.

Chlorella is an important genus among green algae. Chlorella marina has been reported to exhibit potential anti-proliferative and apoptotic effect on prostate cancer cell lines. Exposure of PC-3 and DU-145 cell lines to algal lycopene (AL) at a dose of 20 and 50 μM significantly down regulated the growth and colonisation of cancer cell lines, and the percentage of inhibition was higher than total lycopene (TL)-treated groups. Stronger apoptosis signal was induced at higher concentrations (50 μM) of algal lycopene. Increased DNA damage was observed in AL- and TL-treated cells which were confirmed in the comet assay. Flow cytometry results indicated that AL treatment caused PC-3 cells to accumulate in the G0/G1 phase and to undergo apoptosis. Thus, it can be summarized that algal lycopene showed significant anti-proliferative and apoptotic effect in human prostate cancer cell lines [76].

Sargassum heterophyllum has anti-proliferative activity against MDA-MB-231 breast cancer cells. Sargaquinoic acid (SQA) induces apoptosis, while polihalogenated monoterpene RU015 induce necrosis in breast cancer cells. To investigate the *in-vitro* cytotoxic activity, methanol extract of S. swartzii were used against HT-29, Ca co-2, T47D, MDA-MB468 and /NIH 313 cell lines and resulted selective cytotoxicity against proliferation of Caco-2 cell77. Alcoholic extract of *S. ilicifilium* was tested against human cancer cell lines MCF-7, MDA-MB-231, HeLa, HepG2, and HT-29; the

extract showed an anti-proliferative effect against all the five cancer cell line in a dose-dependent manner [78].

Bryophytes: Remesh and Manju [79] reported the ethnobryological information from the Western Ghats, India, related to bryophytes therapeutic usage. Remya Krishnan and Murugan [72]; Manoj *et al.*, [25] and Greeshma and Murugan [55] analyzed scientifically in selected species regarding its antimetastatic potentials.

Plagiochila beddomei, *Leucobryum bowringii* and *Octoblepharum albidum* were screened for anticancer study as per the ethnic knowledge of Kanni tribes. Bryophytes are a group of plants devoid of true vascular tissues. Being small and insignificant, bryophytes have been neglected in scientific investigations. With the advent of modern techniques and methods, it has been possible to isolate and structurally elucidate bioactive molecules in bryophytes.

Crude methanolic extracts isolated from the liverworts and mosses (*Plagiochila beddomei* Steph. (Plagiochilaceae), *Leucobryum bowringii* Mitt. and *Octoblepharum albidum* Hedw. (Leucobryaceae)) showed the presence of rutin, quercetin, and kaempferol (flavonoids) and a pool of phenolic acids. *P. beddomei* revealed the presence of phenolic acids such as gallate (199.4 µg/g), vanilate (75.3 µg/g), chlorogenate (200 µg/g), cinnamate (212.2 µg/g), protocatechol (16121.7 µg/g), coumarate (289.7 µg/g), ferulate (232.7 µg/g), sinapic (222 µg/g) and caffeate (322.4 µg/g). Fractionation of phenols in *L. bowringii* revealed the presence of phenolic acids such as gallate (10.4 µg/g), vanilate (11.3 µg/g), chlorogenate (11.2 µg/g), cinnamate (11.1 µg/g), protocatechol (13.4 µg/g), coumarate (114 µg/g), ferulate (34.8 µg/g), sinapic (87.4 µg/g) and hydroxyl benzoate (0.65 µg/g). Similarly, the total phenols in *O. albidum* revealed the presence of phenolic acids such as gallate (11.5 µg/g), vanilate (12.4 µg/g), chlorogenate (12.3 µg/g), caffeate (48.6 µg/g), protocatechol (14.7 µg/g), and ferulate (19.8 µg/g). *Plagiochila beddomei*, *Leucobryum bowringii* and *Octoblepharum albidum* were screened for their cytotoxic activity on cancer cell lines such as pharyngeal squamous carcinoma (KB), leukemia HL-60, K562, MDR K562/ A02, breast ductal carcinoma (MDA-MB-435), P-388 murine leukemia tumor, glioma A172 cells, T98G, U87 glioma, liver hepatoblastoma (HEP-G2), lung carcinoma (A549), colon adenocarcinoma (LOVO) cell lines, osteosarcoma U2OS and MCF-7 breast cancer cell lines (Abhijit and Anuradha, 2015). MTT assay revealed cytotoxicity only in *Leucobryum bowringii* as compared to others. Further, the mode of action was confirmed in terms of apoptosis and necrosis induction such as DNA fragmentation, nuclear condensation, proteolysis of poly (ADP-ribose) polymerase (PARP), activation of caspases, inhibition of antiapoptotic nuclear transcriptional factor-kappa B and activation of p38 (mitogen-activated protein kinase). Hoechst 33342 staining assay reveals massive chromatin condensation and subsequent cleavage of structural components of the nucleus. The results indicate that methanol extracts inhibit the growth of human breast cancer cells partially through the inhibition of metallo proteinases MMP-2 and MMP-9 activities [80]. *Leucobryum bowringii* alone confirmed the knowledge of the tribal people.

Marchantia linearis Lehm & Lindenb., a bryophyte, was commonly used in folklore medicine by tribals for curing many diseases. *In-vitro* cell suspension culture of M. linearis yielded remarkable levels of flavonoids. RPHPLC- PAD fractionation of flavonoids revealed the presence of apigenin, quercetin, and luteolin as major constituents. The study of anticancer potentialities against SW 480 colon cancer cell lines reflected significant anti-proliferation activities and was substantiated by cell apoptosis, cell cycle, and growth kinetics. Activities of quinone reductase, glutatione-S- transferase, and cytochrome P450 were correlated with reduced glutathione content and lipid peroxidation. The results of MTT assay showed that 50 µg/mL of flavonoid remarkably reduced the growth kinetics of cells coupled with induced cell apoptosis. The xenobiotic metabolic enzyme CYP 2A1 showed a marginal decrease whereas, QR and GST revealed increased activities. Caspases such as 3/7, 2, 6, 8, and 9 showed a significant level of expression [72].

Brachythecium buchananii, yellowish-green coloured moss, grows as dense mats belong to Brachytheciaceae was used by the native people for curing tumours. The initial phytochemical analysis

of *B. buchananii* confirmed the presence of alkaloids, tannins, flavonoids, terpenoids, triterpenoids, and cardiac glycosides in varying levels. The moss contains essential amino acids such as isoleucine, phenylalanine, and tyrosine. Terpenoid showed a significant level compared to other phytochemicals. Subsequently, the terpenoids was purified with column chromatography and eluted with different combinations of PE: EA solvent system. The 90:10 (PE: EA) purified fraction revealed the presence of terpenoid-related components such as dodecanal, hexadecane, tetradecanal, heptadecane, and 6, 4, 10-trimethyl-2-pentadecanone (sesquiterpenoid). Cytotoxicity of purified terpenoid of *B. buchananii* against the HeLa, MDA-MB-231 and MG 63 cell lines (0, 6.25, 12.5, 25, 50, and 100 µg/ml) *vs.* different time spans (24 and 48 h) revealed a concentration and duration-dependent impact. Cancer cells exhibited significant morphological anomalies at 50 and 100 µg/ml terpenoid extracts. Significant inhibition of MG 63 invasion in a dose-dependent manner was observed. The mode of action was *via* apoptosis, cell cycle arrest, and DNA fragmentation [55].

Similarly, the 100% PE eluted fraction of *Thuidium tamariscellum* revealed 15 compounds in GC-MS analysis such as α-cubebene, caryophyllene (sesquiterpenoids), dodecanal, 1-tetradecene, tetradecane, pentadecane, heptadecane, hexadecane, octadecane, eicosane, nonadecane, heneicosane, pentacosane, docosane, and hexacosane. Further, the antimetastatic analysis of purified terpenoid from *T. tamariscellum* displayed the efficacy against HeLa cell lines only.

Spjut *et al.,* [81] screened species of bryophytes as antitumor agents; interestingly 43 species were found to be active, and 75 species were toxic to mice. The most significant activities was noted in the following families like Thuidiaceae, Brachytheciaceae, Hypnaceae, Grimmiaceae, Mniaceae, Dicranaceae, Neckeraceae, and Polytrichaceae. Petroleum ether, ethyl acetate, and n-butanol leaf extracts of Marchantia convoluta showed cytotoxic effects to lung carcinoma (H1299) and liver carcinoma (HepG2) and it was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Crude extracts of the *Mastigophora diclados* and Frullania species showed cytotoxic activity against HL-60 and KB cell lines [82].

Ferns are one of the oldest divisions of the Pteridophyta and comprise over 12000 species [83]. The biomedical system and Ayurvedic systems of medicine suggested the use of some ferns in the Samhita Texts. Pteridophytes were also used by physicians in the Unani system of medicine. Recently, ethnobotanical and pharmacological studies have been carried out on ferns and their allies by several investigators. According to Lee *et al.,* [84] *Asplenium polyodon*, *Asplenium nidus*, A. capillus- veneris, *Ophioglossum gramineum*, and *H. arifolia* have anti-cancer, antidiabetic, and antiviral activity. Yang *et al.,* [85] reported inhibition of stomach cancer, prostate cancer, malignant melanoma, and mouse fibroblasts by crude extracts and several isolated compounds of Cyrtomium fortunei.

Pteris semipinnata showed *in-vivo* and *in-vitro* anticancer activity in human liver adenocarcinoma cell line (HePG II), human lung adenocarcinom a cell line (SPC-A-1), human gastric adenocarcinoma cell line (MGC-803) and human nasopharyngeal carcinoma cells by MTT assay [86]. Uma and Pravin [87] reported *in-vitro* cytotoxic activity of *Marsilea quadrifolia* on MCF-7 cancer cell lines. *In-vitro* MTT assay of *Blechnum orientale* extracts against human colonic adenocarcinoma HT-29, human colonic carcinoma HCT-116, human breast adenocarcinoma MCF-7 and human leukemia K562 cancer cells were carried out by Lai and Lim [88]. Dicranopteris linearis showed significant anti-metastatic potentiality under *in-vitro* MTT assay on MCT-7, HeLa, HT-29, HL-60, K-562, and MDA-MB-231 cell lines [86].

Angiosperms: Nisha and Sivadasan [89]; Raji and Raveendran [90] and Udayan *et al.,* [91] documented the ethno medicinally significant plants used by traditional healers of Wayanad District, Kerala and Namakkal district, Tamil Nadu. In this part, we analyzed such species connected with cancer therapy.

In 2018, Aswathy *et al.,* [42] isolated, purified, fractionated and analysed the anti-metastatic potentiality of anthocyanin from *Bridelia retusa* against oral squamous carcinoma cells. Anthocyanin production at pH 4.4 – 4.6, HCl-ethanol extraction for 90 min yielded the maximum anthocyanin content, and fractionation of anthocyanin using

HPLC coupled with mass spectrometry revealed 07 fractions such as acylated cyanidins, two peonidins, cyanidin 3-p-coumaroyl and feruloyl diglucoside-5-glucosides. The cytotoxicity effect of *B. retusa* anthocyanin extracts on human oral squamous cell carcinoma (SCC4, SCC9, and SCC25) cells using cell adhesion and cell viability assay was analyzed. The morphological alterations in SCCs cells after treatment with *B. retusa* anthocyanin and apoptotic cells as revealed by Hoechst staining. Flow cytometry revealed arresting of SCC25 cells mostly in the G0/G1 and S-G2/M stages with a concomitant up-regulation of sub-G1 fraction, indicating cell death by apoptosis. Apoptosis was further substantiated by the activation of caspase-3 expression in the SCC25 cells treated with *B. retusa* anthocyanin. *In-vitro* cytotoxic screening of *Glycyrrhiza glabra* belonging to Fabaceae showed glycyrrhetic acid in the chloroform extract and is a potential natural anticancer component. The study was carried using three different extracts (chloroform, methanol, and water) by the MTT method. Cell viability of glycyrrhetic acid in the three different extracts was also determined by trypan blue method using two different cell lines MCF7-cancerous and Vero-normal cell lines. The percentage viability of two different cell lines was 45.71% for the Vero-normal cell line and 78.78% for MCF7cancerous cell line [92].

Oroxylum indicum is a member of Bignoniaceae and was widely used by the Keralites for the treatment of various ailments. The decoction of the bark was taken for curing gastric ulcers and the paste of the bark to mouth cancer, scabies, tonsil pain and other diseases [93]. Cytotoxic assay of a leaf extract from Annona muricata on WRL-68 (normal human hepatic cells), MDA-MB-435S (human breast carcinoma cells) and HaCaT (human immortalized keratinocyte cells) lines by MTT assay, revealed that the extract at its lower doses exhibited a significant cytotoxicity on MDA-MB-435S and HaCaT cells with the IC_{50} values of 29.2 and 30.1 µg respectively. Meanwhile, it exhibited only a moderate cytotoxicity towards WRL-68 with a comparatively higher IC_{50} value *i.e.,* 52.4 µg, indicating the differential cytotoxicity dosage levels among the cells [94]. Essential oils from medicinal plants are proven for their therapeutic potential. Anti-proliferative effects of of EOs from *Pogostemon benghalensis* and *P. cablin* on human colon cancer cell lines (SW 480) and human breast cancer (MCF-7) was studied by Pradeep and Murugan [95]. The essential oil was extracted from the fresh leaves of the plants using the Clevenger apparatus and the components were fractionated by gas chromatography-mass spectroscopy. GC-MS analysis revealed 41 and 36 volatile compounds from the essential oil of *Pogostemon benghalensis* and *P. cablin* respectively. Cytotoxic and viability of the oil against SW 480 and MCF-7 tumor cell lines were analyzed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and Trypan blue dye exclusion method. *P. beghalensis* showed cytotoxicity of 58.42% and 59.22% against SW480, MCF 7 respectively at concentration of 100 µg, while 57.47 and 58.77% cytotoxic effect was noticed with the oil from *P. cablin*. Significant reduction of the viability among SW 480 and MCF-7 cells was also noticed in a concentration-dependent manner.

Achyranthes aspera, a common weed along the road sides throughout India. The methanol extract of A. aspera, possess alkaloid, non-alkaloid, and saponins. A crude dose of 100 µg exhibited significant inhibitory effects on the Epstein-Barr virus antigen activation induced by the carcinogen 12-O-tetradecanoylphorbol-13-acetate in Raji cells (ATCC number CCL-86) under *in-vitro* conditions [96]. Solanum is known for its alkaloid contents. *Solanum mauritianum* is commonly known as bugs weed. Tribes use the plant to cure skin-prone diseases. Anti-proliferative effect of *S. mauritianum* alkaloids against MCF 7 breast cancer cell lines was reported by Jayakumar and Murugan [39]. Purification and fractionation of alkaloids from *S. mauritianum* yielded blue-colored caulophyllumine A and yellow-colored solasodine, both of which inhibited proliferation of MCF 7 cancer cell lines. The results were further substantiated by flow cytometry and V-FITC/ PI analysis. 25 and 50 µg/ml solasodine displayed an increase in the G1 phase and decreased S phase. V-FITC/ PI analysis revealed a concentration and time-dependent increase in the percentage of apoptotic and necrotic cells [39].

Fagonia indica, known as dhamasa is a flowering plant belongs to Zygophyllaceae. Members of Fagonia re-known for their use in traditional medicine and are found effective in curing many

skin problems [97]. The aqueous extracts of F. indica have been found effective against different types of cancer cell lines. Waheed *et al.,* [98] reported bioactivity-guided fractionation to isolate the active and potent compounds of the F. indica extract. The activity assessed against three cancer cell lines: MCF-7 breast cancer, MDA-MB-468 estrogen-independent breast cancer, and Caco-2 colon cancer cells related to apoptosis.

The fruit extract of *Garcenia indica* was used by Hong *et al.,* [99] for the isolation of garcinol. The garcinol showed positive activities in the experimental HT-29 and HCT-116 colon cancer cells along with normal immortalized intestinal cells (IEC-6 and INT-407). The garcinol at IC_{50} values (3.2–21.4 μM) for 72 h treatment showed strong inhibitory properties in all the intestinal cells. The anticancer properties were higher in the cancer cells as compared to normal immortalized cells. Liao *et al.,* [100] also observed a high tumor-inhibiting activity of *G. indica* in the human colorectal cancer cell line (HT-29).

Morus alba (white mulberry), is cultivated throughout the world. Extracts from M. alba are traditionally used to cure cough, edema, insomnia, bronchitis, asthma, nose bleeding, wound healing, eye infections, and diabetes. Devi *et al.,* [101] reported that the plant contains many pharma-ceutically important compounds like moranoline, morusin, calystegin kuwanol, hydroxymoricin, albafuran and albanol. The leaves contain some active compounds like quercetin, rutin, apigenin, 1-deoxynojirimycin. Chon *et al.,* [102] analysed the anti-proliferative power of methanolic extracts on different human cell lines like pulmonary carcinoma (Calu-6), colon carcinoma (HCT-116) and breast adenocarcinoma (MCF-7). Kikuchi *et al.,* [103] reported apoptosis-inducing, cytotoxic activity (IC_{50} = 1.7 μM) in HL-60 cell line. It induced topoisomerase II (IC_{50} = 22.8 μM) and clearly reduced the levels of pro-caspases [3, 8, and 9]. Wedelia Chinensis is an indigenous species of India, South-East Asia, and China. It is one of the important anticancer plants belonging to Asteraceae and was rich in secondary metabolites like phenol, flavonoids, and tannin.

The essential oils of W. chinensis showed a positive effect on lung cancer cells under an *in-vitro* study. The GC-MS analysis recorded the presence of two important compounds carvacrol and trans-caryophyllene. The study of B16F-10 melanoma metastatic cell line showed regulation of antioxidant enzymes (including catalase, superoxide dismutase, and glutathione peroxidase) in the treated cells. The amount of glutathione also increased, while the lipid peroxidation and nitric oxide levels decreased. The histopathology studies further corroborated with analytical results [104].

Schischkinnin and montamine were alkaloids isolated from the seeds of *Centaurea schischkinii*, and Centaurea montana belongs to the family Asteraceae. Both alkaloids exhibited significant cytotoxicity against human colon cancer cell lines [8]. According to Ayurveda Digitalis lanata and Digitalis purpurea of Plantaginaceae have anticancer activity [105].

Brucea fruit extract is used for the treatment of carcinomas of the liver, breast, thyroid, uterine cervix, rectum, anus, oesophagus, lung, skin and colon when topically applied [70]. Psoralea fruit extract is used for the treatment of heart failure, coronary heart disease, leukoderma, urine bladder atonia, prostatitis and night bed-wetting. Seeds of this herb contain psoralen which is a photo-sensitizer, which damages membrane of normal cells and tumor cells. It also binds to DNA of cells and induces apoptosis and death of normal cells, diseased cells and tumor cells. Glossy Privet fruit is also used for treatment of cancer *i.e.*, 20 to 30% anti-cancer efficacies in patients with leukemia or lymphoma and also caused some adverse effects. Similarly, when mixed with Milkvetch root herb it attains 90% anti-cancer efficacy and brings about 10% or minimal side-effects [106].

Artemisia capillaries, a medicinal plant found in Korea. The methanol extracts of *A. capillaries* were used for the evaluation of DPPH (2,2-diphenyl- 1-picrylhydrazyl), hydroxyl radical (OH) scavenging, reducing power assay connected with antioxidant activity and also trailed the anticancer activities using MTT assay. The extracts exhibited potential antioxidant activity and anticancer activity under *in-vitro* condition [107]. *Rosa roxburghii* is another beneficial species used for improving immune responses, enhancing digestive ability, and demonstrating anti-aging effects. Evidence showed that herbal medicine soups containing extracts of

this plant shows efficacy in malignant tumors. The studies were undertaken to evaluate anticancer potential against three carcinoma cell lines like human esophageal squamous carcinoma CaEs-17, human gastric carcinoma SGC-7901, and pulmonary carcinoma A549 by MTT assay and flow cytometry. The combination of *Rosa roxburghii* and *Fagopyrum cymosum* showed significant inhibition of cell growth and increased apoptosis. The mRNA and protein expression levels of Ki-67 and Bcl-2 were regulated by the extracts [108].

Goniothalamus macrophyllus of Annonaceae showed the presence of goniothalamin, a natural compound. Apoptosis induction by goniothalamin in the Hela cervical cancer cell line was observed by MTT assay method [109]. The ethanolic extract of Derris scandens showed potent radiosensitizer potency against human colon cancer HT29 cells. D. scandens extract in combination with gamma irradiation synergistically sensitizes HT-29 cells to cell lethality by apoptosis and mitotic catastrophe [110]. *Atractylis lancea* a medicinal herb in Asia, has been reported to have anti-tumor effects on cancer cells. *In-vitro* studies on the proliferation of the Hep-G2 liver cancer cell line by MTT test revealed effective inhibition in a concentration- and time-dependent manner [111].

Phyllanthus emblica is known to have various pharmacological properties. Cytotoxicity to human fibrosarcoma cells, HT1080, was assessed by viability assay using the 3-(4,5-dimethylthiazol,2-yl)-2,5-diphenyltetrazolium bromide. The results showed that *P. emblica* extract reduces cell proliferation, migration, invasion, and adhesion in both dose- and time dependent manners, especially growth arrest with low IC_{50} value [112]. Ethanol extract of *Boerhaavia diffusa* (Punarnava) showed cytotoxic effect against Hela cell lines and inhibited the S-phase of the cell cycle. It also inhibits the growth of cancer cells in DMBA-induced cancer carcinogenesis in mice through free radical scavenging [113]. *In-vivo* methanol extract of Cucurbita maxima was studied for anticancer activity against Ehrlich ascities carcinoma cells in mice. Oral administration of the methanol extract of the *C. maxima* at a dose of 200 mg/kg and 400 mg/kg showed the cytotoxicity in mice in a dose-dependent manner [114].

Calotropine, is a glycoside present in Calotropis procera, has shown anti-tumor activity against human epidermoid carcinoma cells of rhino pharynx under *in-vivo* conditions. They also inhibited the growth of cells and mitotic activity in a dose-dependent manner [115]. The methanol and acetone extract of the flowers of *Parthenium hysterphorus* were showed *in-vitro* anticancer activity against the A-549 (Lung adenocarcinoma) cell lines by MTT and Trypan blue exclusion assay [116]. The methanol extract of the leaves of the Citrus maxima displayed anticancer activity (at a dose 200-400 mg/kg), against *Ehrlich Ascities* carcinoma cell lines in Swiss albino mice in a dose-dependent manner [117]. *Azadirachta indica*, *Boesenbergia pandurata*, and *Coscinium fenestratum* were tested for their cytotoxic effects. The results showed that the three plants have high cytotoxic potentiality against the Hep2 cell lines with a minimum concentration of 0.05% [118 & 119].

CONCLUSION: There are studies on the *in-vivo* and *in-vitro* analysis of anticancer drugs and plants. It was generally established that the drugs, including the anticancer compounds, require clinical research trials for marketing permissions. Except for some exceptional circumstances, all the drugs need to go through all the phases of trials according to the guidelines of international agencies like the FDA and EMA. Plant-based compounds have shown less toxicity than conventional synthetic compounds. Insufficient data available regarding the quality, safety, and efficacy of herbal drugs lead to side effects, which is a major problem nowadays. The process of oncological drug development and marketing is regulated through the involvement of experts and advisory authorities. There are several regulatory framework models for prescribing such drugs, and there is a need for harmony among regulating. It is evident from studies that plants of the same species grown in different areas vary in their medicinal compound profile, which calls for the need to focus on the production of uniform and high-quality plants with a uniform metabolite profile and it is achieved through the advancement of biotechnology and bioinformatics. The current review comprehensively highlights the mechanism of antitumor action of important plants. It generates awareness regarding the usage of these herbs and exploring their properties.

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