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REVIEW

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Anticancer plant-derivatives: deciphering their oncopreventive and therapeutic potential in molecular terms

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Abstract

Background Over the years, phytomedicines have been widely used as natural modalities for the treatment and prevention of various diseases by different ethnic groups across the globe. Although, 25% of drugs in the USA contain at least one plant-derived therapeutic compound, currently there is a paucity of plant-derived active medicinal ingredients in the pharmaceutical industry. Scientific evidence-based translation of plant-derived ethnomedicines for their clinical application is an urgent need. The anticancer and associated properties (antioxidative, anti-inflammatory, pro-apoptotic and epithelial-mesenchymal transition (EMT) inhibition) of various plant extracts and phytochemicals have been elucidated earlier. Several of the plant derivatives are already in use under prophylactic/therapeutic settings against cancer and many are being investigated under different phases of clinical trials.

Main body The purpose of this study is to systematically comprehend the progress made in the area of prophylactic and therapeutic potential of the anticancerous plant derivatives. Besides, we aim to understand their anticancer potential in terms of specific sub-phenomena, such as anti-oxidative, anti-inflammatory, pro-apoptotic and inhibition of EMT, with an insight of the molecules/pathways associated with them. The study also provides details of classes of anticancer compounds, their plant source(s) and the molecular pathway(s) targeted by them. In addition to the anti-oxidative and antiproliferative potentials of anticancer plant derivatives, this study emphasizes on their EMT-inhibition potential and other 'anticancer related' properties. The EMT is highlighted as a phenomenon of choice for targeting cancer due to its role in the induction of metastasis and drug resistance. Different phytochemicals in pre-clinical or clinical trials, with promising chemopreventive/anticancer activities have been enlisted and the plant compounds showing synergistic anticancer activity in combination with the existing drugs have been discussed. The review also unravels the need of carrying out pan-signalome studies for identifying the cardinal pathways modulated by phytomedicine(s), as in many cases, the molecular pathway(s) has/have been randomly studied.

Conclusion This review systematically compiles the studies regarding the impact of various plant derivatives in different cancers and oncogenic processes, as tested in diverse experimental model systems. Availability of more comprehensive information on anticancer phyto-constituents, their relative abundance in crude drugs, pathways/molecules targeted by phytomedicines, their long-term toxicity data and information regarding their safe use under the combinatorial settings, would open greater avenues of their utilization in future against this dreaded disease.

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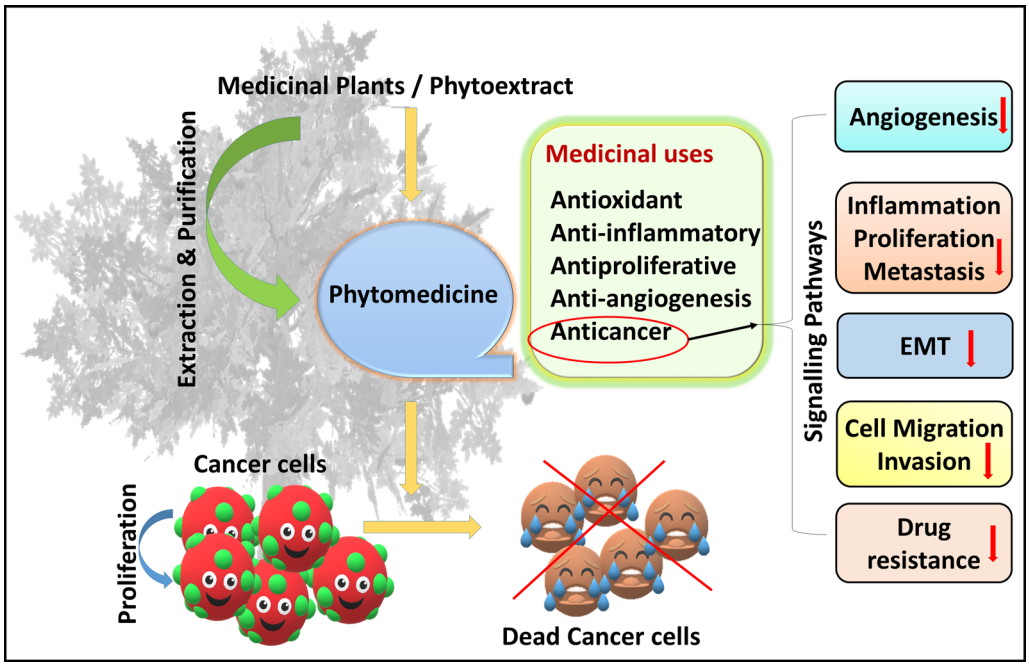
Keywords Phytomedicine, Chemo-prevention, Anticancer, Epithelial to mesenchymal transition, Metastasis, Drug-resistance

Graphical Abstract



Background

In recent years, several pharmaceutical products have been introduced into the market originally based on the leads available through the traditional knowledge. In the United States of America (USA), almost 25% of the total drug market contains at least one plant-derived constituent used in the treatment of various ailments. Traditional or herbal medicines have been widely used in the developing countries at the level of primary health care, as these have lesser side effects, are cost-effective and have better biocompatibility. In traditional culture, herbal medicines are easily accessible and most favorable therapeutic agents. Of late, the insightful knowledge related to the practice of such herbal drugs has evolved through various trials and testing during different stages of the drug development [1]. According to an estimate, almost 80% of the world's population trust the traditional medicines for the treatment of their major health problems [2]. In tropical areas of the world, people depend on the medicinal plants for the prevention and treatment of many diseases due to the abundance of such plants in their surroundings [3]. Nowadays, herbal medicines are recommended as complemetary and ocassionally as alternatives to synthetic drugs for the treatment of various health problems such as asthma, microbial infections, diabetes, inflammatory diseases, obesity, and diseases related to immune functions; moreover, against major life-threatening diseases like cancer. This became possible due to the advancement of the interdisciplinary research among life sciences, nanotechnology, proteomics, metabolomics, genomics, chemical sciences, etc. shedding light on the mechanism of actions of these compounds specifically in their purified forms. When phytomedicines are used in combination with classical and conventional therapies, an enhancement in the therapeutic effect could be seen, which in majority of cases increases the survival and quality of life of the patients. In rural communities of South East-Asia and India in particular, phytomedicines have played an important role in Ayurveda system of treatment of several diseases.

Chemically, phytomedicines consist of biologically active secondary metabolites like alkaloids, phenols, flavonoids, tannins, or terpenoids, which are isolated by different chemical extraction procedures. Several well-known drugs have been developed based on the traditional knowledge and practices of disease treatments. Historically, traditional knowledge has helped in

discovery of Artemisinin, an anti-malarial drug, which was isolated from *Artemisia annua* L. According to the World Health Organization (WHO), millions of malaria patients have been cured with artemisinin worldwide [4]. Similarly, quercetin is one of the most widely used flavonoids, which inhibits inflammation during asthma treatment by inhibiting the mast cell degranulation and histamine release [5]. Such herbal medicines are being marketed in the USA and other countries as dietary products without any much prohibition and claims. Other few examples include atropine, codeine, quinine, reserpine, digoxin, etc. having anticancerous, anti-oxidant, anti-microbial, anti-inflammatory, analgesic, and cardiotonic properties [6]. Some phytochemicals like genistein, kaempferol, resveratrol prevent inflammation via different mechanisms like inhibiting cyclooxygenase-2 (COX-2) enzymatic activity, suppressing NF-κβ pathway by decreasing TNF-α induction and thereby reducing the reactive oxygen species (ROS) level [4, 7]. Moreover, many phytoextracts stimulate the immune system and increase the phagocytosis to eliminate the pathogens/antigens.

Cancer is the second major cause of death worldwide. According to Cancer GLOBOCAN project 2012, the incidences of cancer will get doubled in India till 2035 [8]. Generally, the primary treatment for cancer includes surgery, chemotherapy, radiotherapy, and targeted therapy depending upon the extent of the disease progression. Many of these therapies are costly and have more side effects in cancer patients after treatment. However, cancer treatment using the natural compounds many in combination with the conventional treatment strategies have proven to have better prognosis with lesser side effects. Many natural compounds are being used in the treatment of the various types of cancers these days. For example-Etoposide and Teniposide, derived from the natural lignin podophyllotoxin are being used for the treatment of small lung cancer and testicular cancer. Taxanes and camptothecins are two important anticancer drugs, which were the results of collaborative research of the National Cancer Institute (NCI), of Agriculture Department, US, and Research Triangle Institute in North Carolina. Similarly, the drug Homoharringtonine, isolated from *Cephalotaxus harringtonia* (Siebold) Koidz was approved as an anticancer drug in 2012. The clinical success of these drugs generated much enthusiasm toward natural product research [6] plant-derived bioactive compounds have been established as keystone components in the therapeutic development for several diseases including cancer. Of note, natural compounds are used in the photodynamic therapy of various cancers in recent times [9].

Therefore, with an aim to comprehend the utility of phytochemicals/phytomedicines in targeting various key pathways and molecules related to cancer signaling, in this study we have reviewed the plant derivatives-mediated attenuation of oxidative and inflammatory processes, and inhibition of EMT-phenomenon. We have detailed the different plant sources of these anticancer compounds, and the chemical classes they belong to. Particularly, we have emphasized on the EMT-inhibition potential of these plant derivatives as this process induces metastasis and drug resistance in many cancers. In the methodology part we surveyed the available literature to formulate questions that are still amenable to advance research. Based on these questions, the further search of the available databases and selection of relevant articles was carried out. Of note, this study enlists the phytochemicals having anticancerous activities with promising outcomes at the preclinical and clinical trials. Moreover, we have also discussed the potential phytocompounds showing synergistic effects with the existing cancer drugs, which can be utilized for combination chemotherapy.

Phytoextracts: sources of secondary metabolites

Medicinal plants play an important role in the arena of the human health care system as a natural source of many biologically active compounds and various essential oils. These biologically active compounds are organic in nature that encompasses the primary and secondary metabolites. Primary metabolites are carbohydrates, lipids, and proteins which are essential for the growth and development of the plants. The secondary metabolites include alkaloids, phenols, flavonoids, terpenes, terpenoids, etc. which constitute nonessential parts of plants, having no fundamental role in plant growth but are used to fight microbial attack, thus are crucial in plant defense mechanisms. The diverse secondary metabolites possess numerous biological activities including antimicrobial, anti-inflammatory, antiproliferative, anti-EMT, anticancerous, etc. therefore, are useful as potential candidates for pharmacological formulations.

To date, approximately hundred thousand secondary metabolites have been discovered. Out of them, it is estimated that approximately fifty percent have been characterized structurally while the remaining are yet to be classified [10, 11]. The commercialization of some of these secondary metabolites as drugs has become possible due to their potent and widespread biological activities. Secondary metabolites present in plants are chemically very diverse as the biosynthetic pathways of secondary metabolite synthesis are mediated by several enzymes involving multiple steps.

Evidence-based ethnobotanical translation of anticancer phytochemicals in modern medicine

Investigating the traditional use of phytomedicines in any community can provide clues to direct the screening of natural compounds. This practice, commonly referred to as "reverse pharmacology," has lately come to light as a time and money saver in the drug development process since "significant knowledge of human use increases the likelihood that a cure will be successful and safe" [12, 13]. This realization sparked a resurgence of interest in the traditional applications of medicine and associated customs. Regulations governing medicinal items, to some extent, follow traditional use [14].

Use of herbal medicines for treatment of various ailments have been traced back to centuries ago in Indian Ayurveda and Chinese herbal medicine systems as well as other traditional ethnic systems of disease treatment in many countries throughout the world. The unrecorded traditional knowledge of herbal medicine was imparted from generation to generation to the current civilization. However, with the advent of scientific tools and techniques reproducible experimental proofs of many potent traditional herbal medicines for treatment of different diseases have been made possible [15]. Validation of a few of these indigenous medicinal knowledge and practices through modern tools and techniques in regards to treatment of cancer and other diseases are discussed herein (Fig. 1).

Adhvaryu et al. studied the anticancer potential of four popular ayurvedic herbs: *Ocimum sanctum* L., *Curcuma longa* L., *Tinospora cordifolia* Miers ex Hook. f. & Thoms. and *Zizyphus mauritiana* Lam. For this the authors used an in-vivo Swiss Albino mice model induced with Dalton Lymphoma ascites (DLA) tumor. The study revealed varied degree of anticancer activity of these herbs. The efficacy of the herbs *T. cordifolia* Miers ex Hook. f. were found to be most effective followed by *Z. mauritiana* Lam., *C. longa* L., and *O. sanctum* L. [16].

A methylated lignans isolated from creosote bush "*Larrea tridentate,*". Tetra-O-methylnordihydroquaiaretic acid (M4N) has been elucidated to have significant anticancer potential. The long-standing traditional use of the plants by the Amerindians from South America and Native American Indian tribes in southwestern North America is evidence of the creosote bush's (*Larrea tridentate* Coult.) importance. Simple bisphenyl lignans and cyclolignans, which are tricyclic lignans, are abundant in the plant and many of the pharmacological effects of plant extracts can be attributed to these substances. Some of these actions, including the anti-inflammatory, anti-fungal, anti-herpes, and antioxidant, were known a century ago [17].

Podophyllin and podophyllotoxin isolated from rhizomes and roots of the several *Podophyllum* sp. are potent cytotoxic lignans and used as antineoplastic agents [18]. The plant has traditionally been used by North American Indians to treat skin tumors [19].

Another important powerful anticancer plant known as *Catheranthus roseus.* The herb has a long history of usage in traditional Chinese medicine, Ayurveda, and other therapeutic philosophies. During the twentieth century, western medical science started investigating

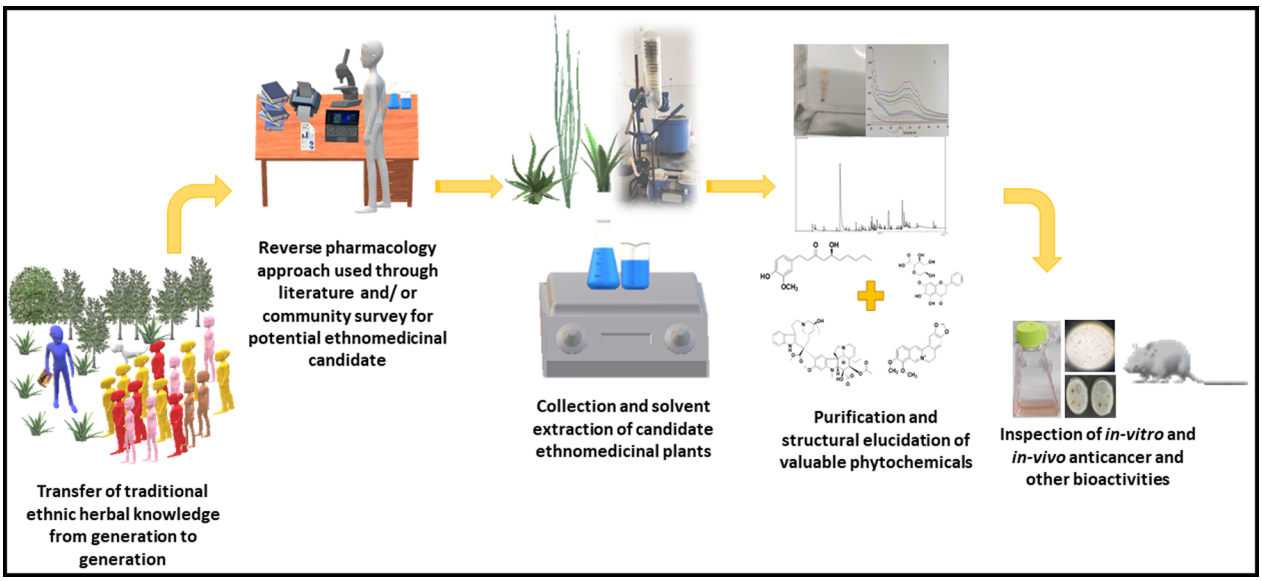


Fig. 1 Overview of experimental process involved in the translation of traditional herbal healing knowledge into modern medicine

Catharanthus roseus and its extracts, discovering various substances helpful in the treatment of cancer. Every component of the plant, including the dried root, dried leaves, dried flowers, and dry stalks, has been employed in local herbal medicine. The dried herb is used to extract the alkaloids Vincristine and Vinblastin, the potent anticancer agents that are employed in modern medicines [20].

Similarly, the medicinal Himalayan yew known as *Taxus wallichiana* Zucc., has long been used by traditional healers to treat inflammatory diseases. For the treatment of colds, coughs, respiratory infections, dyspepsia, and epilepsy, it is ingested as decoctions, herbal tea, and juice. It is also applied locally to burns and infected wounds as a poultice [21, 22]. The paste prepared from its bark is used to treat fractures and headaches, while its bark and leaves are used in steam baths to treat rheumatism. The stem is used as a decoction in Pakistan to treat tuberculosis [23]. The drug Zarnab, which is prescribed as a sedative, aphrodisiac, and a therapy for bronchitis, asthma, epilepsy, snake bites, and scorpion stings, is made from the bark and leaves of *T. wallichiana* Zucc. and is used in Unani medicine [24]. In Ayurveda, young shoots of the plant are used to make a tincture that is used to cure severe biliousness, giddiness, a weak and dropping pulse, coldness in the extremities, headaches, and diarrhoea [25]. However, the other species of *Taxus* plant are also found in many countries and used in folk medicine as well. The plant genus gained widespread attention since it was discovered that the plant's leaves and bark were the primary sources of taxol, a powerful anticancer medication used to treat breast and ovarian cancers. Taxol has the unusual ability to stop the formation of malignant cells [26]. Taxol and related bioactive taxoids have since been discovered from numerous different species of the genus Taxus after being initially extracted from the bark of *Taxus brevifolia* hort. [27–29]. Taxol is in high demand because to its excellent clinical outcomes in the treatment of many malignancies, especially resistant ovarian and breast tumors [30, 31]. It has been extracted from the leaves and bark of Taxus species including *T. brevifolia* hort., *T. wallichiana* Zucc., and others [32]. The anticancer prospects of some potent medicinal plants and their purified compounds have been discussed in the later sections of this review.

Secondary metabolites with anticancer properties

Secondary metabolites identified, extracted, and purified from medicinal plants for their anticancer properties mainly belong to one of the following classes; polyphenols, flavonoids, alkaloids, brassinosteroids, and terpenes.

Polyphenolics

Polyphenolic compounds are secondary metabolites of plants that are commonly involved in providing defense against ultraviolet radiation or belligerence by pathogens. Many evidences show that diets rich in plant polyphenolic compounds generally provide protection against cardiovascular diseases, osteoporosis, diabetes, neurodegenerative diseases, and against the development of cancers [33]. Flavonoids, tannins, curcumin, resveratrol, and gallachecine are polyphenolic compounds that are found in plants and are known to have anticancer properties. Peanuts, grapes, and red wine are rich sources of resveratrol, while gallachecine is present in green tea [34]. It has been found that polyphenols when included in a person's diet, improves health and reduces the risk of developing cancers [35]. Polyphenols modulate oxidative stress and also have ability to target cancer stem cells, thereby preventing the relapse and recurrence of the cancer [36].

Polyphenols have shown cytotoxicity against a range of cancers and also have antioxidant activity. Moreover, they can induce apoptosis. All these characteristics make them a good anticancerous agent. Polyphenols initiate apoptosis via regulating the mobilization of copper ions that are bound to chromatin, resulting in DNA fragmentation. Resveratrol causes DNA degradation in the presence of copper ion Cu (II), henceforth induces apoptosis [34]. Various cancer cell lines, when treated with curcumin have shown suppression in the expression of tumor necrosis factor (TNF) [37]. Licochalcone A (LCA), is a chalconoid—a type of natural phenol found in the root of *Glycyrrhiza glabra* L. or *Glycyrrhiza inflate*. It shows activity against a range of microbial agents such as viruses, bacteria, and protozoan parasites. Of note, it has anticancerous properties such as antioxidant, anti-inflammatory and anti-angiogenic activities. Cho JJ et al., 2014, showed that Licochalcone A can inhibit the growth of oral squamous cell carcinoma (OSCC) cells: HN22 and HSC4, in a dose dependent manner. Licochalcone A, also inhibits the Specificity protein 1 (Sp1), a well-known transcription factor and its downstream proteins leading to apoptosis of the HN22 and HSC4 cells [38].

Flavonoids

Flavonoids are a large family of naturally occurring polyphenolic compounds. Among the six major subclasses of flavonoids, namely, anthocyanidins, flavan-3-ols, flavonols, flavanones, flavones, and isoflavone; flavonols are the most widely used in the human diet. Coa et al., 2013, studied the effect of flavonoids from the fern species *Dryopteris erythrosora* (D.C. Eaton) Kuntze on human lung cancer cell line (A549).

Flavonoids showed high free radical scavenging activity and greater cytotoxicity against cancer cells [39].

Purified flavonoids have shown promising anticancer activities against many human cancer cell lines including cervical (HeLa), hepatoma (Hep-G2), and breast cancer cell line (MCF-7) [40]. Flavonoids (4'-Methoxy Licoflavanone (MLF) and Alpinumiisoflavone (AIF) extracted and purified from the stem bark of *Erythrina suberosa* Roxb. have shown cytotoxic effects when tested against human leukemia cell lines (HL-60 cells). MLF and AIF were able to induce both arms of apoptotic signaling pathways i.e., extrinsic and intrinsic pathways. Apoptosis induced by these flavonoids caused a significant decrease in the mitochondrial membrane potential, resulting in a reduction in cancer cell survival [41]. These flavonoids are also known to inhibit NF-κβ dependent signaling, which is required for angiogenesis, survival, and proliferation of cancer cells.

Astragalin, which is present in many plants, have been shown to exhibit antioxidant and anti-inflammatory potential. Yang M et al., 2021, by in vitro and in vivo studies showed that Astragalin inhibits the proliferation and migration of the human colon cancer cells via NF-κB pathway. It can induce apoptosis of cancer cells by modulation of the expression of the Bax, Bcl-2, p53, and caspases. Moreover, it can arrest cell cycle by modulating the genes involved in cell cycle regulation [42]. Centipede grass extract (CGE) composed mainly of flavonoids and its glycan derivatives, has anti-inflammatory, antioxidantive along with anticancerous properties. CGE has been shown to inhibit the growth of skin cancer cells by arresting cell cycle at G2/M phage and increasing the apoptosis of cancerous cells [43]. CGE activates effector caspases and inhibits the cellular signaling mediated by PI3K/AKT/GSK-3β pathway.

Brassinosteroids

Brassinosteroids (BRs) are secondary metabolites found in plants and play an important role in hormonal signaling, control of cell growth, differentiation and development, stem cell and root cell elongation, and various other roles such as tolerance and resistance to stress and diseases [44]. Cancer cells have the characteristic of growing indefinitely and are able to escape from apoptotic cell death. BRs have been found to induce appropriate anticancerous responses against a range of cancer cells by interacting with cell cycle proteins and inducing apoptosis.

BRs have been used in studies with various cancer cell lines such as RPMI 8226 (multiple myeloma), A-549 (lung carcinoma), HOS cell line (osteosarcoma), HeLa (cervical carcinoma), and CEM (T-lymphoblastic leukemia) [45]. BRs are also effective against breast cancer and prostate cancer. Some of the major proteins like epidermal growth factor receptor (EGFR), estrogen receptor (ER), human EGFR-2 (HER-2), and androgen receptor (AR) are the main targets of BRs. They are also involved in blocking the cell cycle. Human breast cancer cell lines, when treated with 28-homoCS and 24-epiBL, show a great degree of reduction in the cyclin, a protein involved in the G1 phase of the cell cycle, thereby resulting in cell-cycle arrest. Treatment of prostate cancer cell lines (such as LNCaP and DU-145) with BRs also result in an increase in the level of proapoptotic protein Bax and a reduction in anti-apoptotic protein Bcl-2 [46].

Terpenes

Terpenes (and terpenoids) are a class of secondary metabolites produced by plants and insects. While terpenes are hydrocarbons, terpenoids are their oxygenated derivatives. In a study, Cho et al., extracted the pentacyclic triterpenes from *Perilla frutescens* (L.) Britton consisting of ursolic acid, corosolic acid, oleanolic acid, 3-epi-corosolic acid, maslinic acid, and 3-epi-maslinic acid. These compounds were found effective in preventing skin tumors by inhibiting epidermal proliferation, downstream cellular signaling, and skin inflammation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) [47]. Malla et al., reviewed role of some of the terpenoides such as ponicidin, oridonin, and curcumin against pancreatic cancer. Terpenes like monoterpenes, sesquiterpene, diterpenes, triterpenes, and tetraterpenes are already being used in cancer therapy [48]. Study of Muhseen et al., demonstrated the role of some terpenes like silvestrol, betulonic acid, and 3-*trans-p*-coumaroyl maslinic acid in retardation of cancer cell growth, which showed an inhibitory effect on the interaction of p53-MDM2 [49].

Alkaloids

Alkaloids are an important group of secondary metabolites, which play a significant role in cancer prevention and therapy. Mondal A. et al., have listed some alkaloids such as liriodenine, berberine, chelerythrine, sanguinarine, stylopine, neferine, clivorine, dibromophakellstatin, clathrodine, antofine, tylophorine, cryptolpine, β-carboline, and deoxytubulosine having promising role in cancer prevention [50]. Similarly, Masi et al., isolated the alkaloids Coccinine and Montanine from *Haemanthus humilis* Jacq. and showed that these compounds have strong growth inhibitory potential against different cancer cell lines (A549, HCT-15, MCF7, SK-MEL-28, MDA-MB-231, and Hs578T) [51]. Di Chen et al., showed the synergistic inhibitory effect of alkaloids Piperine and Piperlongumine on breast cancer cells via inhibiting the STAT3 activation [52]. The berberine alkaloids showed

the anticancer activity against the breast cancer cells via targeting Wnt/β catenin signaling pathways and EMT. It belongs to the class of isoquinoline alkaloids [53].

Honokiol is a biphenolic compound isolated from the leaves, seeds, and bark of *Magnolia* plants. Li et al., used honokiol compound to suppress A-498 metastasis, a kidney carcinoma cell line by blocking both epithelial-mesenchymal transition (EMT) and cancer stem cell (CSCs) properties [54]. Similarly, paclitaxel was isolated from the Pacific yew tree is used extensively in the treatment of cancers. Kim et al., showed the use of an exosome—based drug delivery platform for paclitaxel to treat multi-drug resistant cancer [55]. Shikonin, a phyto compound isolated from *Lithospermum erythrorhizon* Siebold & Zucc., was studied for its wound-healing activities. Interestingly, an in situ immuno-histological analysis showed that EMT regulatory molecules were enhanced in shikonin-treated epidermal tissues, and RT-PCR analyses of these tissues demonstrated that shikonin treatment down regulated the expression of around 200 families of microRNAs. These results confirmed that treatment with shikonin exhibits the potent stimulatory effect on EMT and suppresses the expression of the associated microRNAs [56]. Arrebola et al., isolated eight known anthraquinones from the ethanolic extract of *Isoplexis isabellina* (Webb & Berthel.) Mansf. from its cell suspension culture having anticancerous and antioxidant properties [57]. Diosgenin is a phytosteroid isolated from the tubers of *Dioscorea doryophora* Hance. Liu et al., showed the antiproliferative potential of diosgenin in K562 cells via cell cycle arrest in the G_2/M phase and apoptosis induction [58].

The benzophenanthridine alkaloid, Sanguinarine, found in the root of *Sanguinaria canadensis* L., and other poppy *Fumaria* species, can induce apoptosis and exhibit antiproliferative effect on tumor cells besides having anti-angiogenic and anti-invasive properties [59]. Sanguinarine also inhibits NF-κB signaling and induces apoptosis through generation of the reactive oxygen species.

The diverse secondary metabolites produced by plants have promising therapeutic potential, but their isolation, followed by identification is a tedious task. The following section provides the conventional and new strategies developed for the isolation of phytomedicinal compounds.

Phytomedicinal compounds: isolation, purification and their characterization

Approximately 20,000 plant species are found in 91 countries having medicinal values [60]. These plants are the natural source of bioactive compounds. However, the isolation, purification, characterization, and in vitro or in vivo activity evaluation of these compounds still remains a big challenge in the drug discovery field [61–63]. Therefore, ethnopharmacological knowledge is utilized to select the plant species, their parts and type of extracts for intended phytomedicinal validation [64]. There are several methodologies available for the isolation, purification, and characterization of phytomedicinal compounds. Phytoextraction is the initial step of phytomedicine preparation from traditional plants. The basic steps of phytoextraction are prewashing, shade drying of the sample, and grinding/preparing fine powder. Then, the fine powder is used to prepare the crude extract with different solvent systems. Moreover, the solvent should be selected on the basis of targeted bioactive compound's polarity [65]. The most common extraction methods generally used for the extraction are soxhlet extraction, sonication, heating under reflux, infusion, maceration or percolation methods [66], solid–solid extraction, solid–liquid extraction, microwave-assisted extraction, ultrasound-assisted extraction, high hydrostatic pressure assisted extraction, supercritical fluid extraction, and pressurized liquid extraction methods etc. [67, 68]. The purification of a particular bioactive compound after extraction and identification still remains a big challenge and is required for its subsequent characterization. To obtain pure compounds, several techniques are used; for instance, thin-layer chromatography (TLC), column chromatography, size exclusion chromatography (SEC), and high-performance liquid chromatography (HPLC) [69, 70]. These are most applicable and widely accepted techniques to analyze, identify, and often to purify specific compounds based on their retardation factor (Rf) and nature of polarity. Further structural elucidation of pure phytocompounds is generally carried out by different analytical techniques such as Liquid Chromatographic Mass Spectrometry (LC–MS), Gas Chromatographic-Mass Spectrometry (GC–MS), Nuclear Magnetic Resonance spectroscopy (NMR), and Fourier-Transform Infrared Spectroscopy (FTIR) [71]. All these techniques are used for the structural identification of bioactive compounds before their testing in the in vitro/in vivo biological assays.

Phytomedicine in cancer treatment

According to the American Cancer Society, 1,735,350 new cancer cases and 609,640 cancer deaths have been reported in the United States (US) in 2018. According to the AACR Cancer progress report (2017), the number of new cancer cases in the US will almost double by the year 2030 [72]. In 2022, the mortality data for cancer in the USA were collected by the National Center for Health Statistics. According to this study, a total of 1,918,030 cancer cases were estimated, including 609,360 cancer deaths. Moreover, 350 deaths per day were reported from lung cancer only which is the leading cause of

cancer deaths [73]. The success rate of clinical trials has been lowest for cancer therapeutics in comparison to other major diseases. Increasing tumor heterogeneity and multiple drug resistance are the major limitations to deal with the development of newer treatment modalities. Due to the scarcity of effective anticancer drugs, cancer will shortly become the main cause of death in developed countries. Therefore, the discovery/establishment of alternative therapies for the treatment of cancer is promptly required. Conventional methods available for cancer treatment include surgical resection, radiotherapy, chemotherapy, immunotherapy, and stem cell therapy. These treatments are mostly effective in treating cancer patients when used alone or in combination, but they come up with their own side effects. As some of these treatments involve the use of drugs that target cancer cells but also kills the other fast-growing normal cells of the body, for example; the cells of hair follicles, digestive tract, and bone marrow. This leads to several harmful side effects such as nervous system disorders, heart diseases, decreased production of blood cells, inflammation of the gastrointestinal tract, hair loss, nephrotoxicity, and immunosuppression, etc. Apart from the side effects, these treatments are costly and are not eco-friendly. Therefore, there is a need for alternative treatments that should be less toxic, more potent and affordable in order to treat the growing cases of cancers [74].

In traditional medicine plants and their derivatives are used as the main resource for antitumor drugs. A number of studies have been carried out to explore the cytotoxic potential of natural compounds extracted from plants. It has been reported that many of these phytochemicals have the potential to kill cancer cells without destroying the normal cells of the body [75]. This has led to the divergence of scientific interest toward medicinal plants to discover their ability to treat and prevent cancer [76]. As a result approximately 60% of cancer patients are currently using herbal medicines at least partially for their treatment [77]. These phytochemicals, more effective when given in combination with clinically proven drugs. The combinatorial treatment method increases the sensitivity of the drug-resistant cancerous cells to known drugs already being used for the treatment.

Phytomedicines target cancer at different steps of cancer cell survival pathways including cell cycle, DNA repair, apoptosis, and cellular signaling etc. These pathways are generally required for cancer initiation, progression, and metastasis. Phytomedicines target pro-inflammatory proteins and free radicals (ROS), inhibit pro-angiogenic factors (VEGF) required for angiogenesis, regulate the biotransformation of enzymes and modulate anti-metastatic proteins (Fig. 2) [78]. The following section provides a brief description of phytomedicine as chemotherapeutic agents, antioxidants, angiogenesis inhibitors, EMT inhibitors, and anti-inflammatory agents. Table 1 underlines the list of different types of phytomedicines with their mode of action on different signaling pathways of cancer cell survival and Table 2 summarizes the phytomedicines being studied in different clinical trials for cancer treatment.

Phytomedicines as chemotherapeutic agents

Approximately 35,000 plant species have been screened by the National Cancer Institute for their anticancer potential and 3,000 among them were reported to show reproducible anticancerous activity [79]. Plants with medicinal properties synthesize a wide range of secondary metabolites including lignans, anthocyanins, flavonoids, isocatechins, coumarins, and catechins. These metabolites are produced in different parts of the plant such as roots, rhizomes, flower, stigmas, embryo, leaves, seeds, bark, sprouts, fruits, and stem [80]. Presently, many cancer therapies like radiation therapy, chemotherapy, immunotherapy, photodynamic therapy, and combinational therapies have evolved. Despite the rapid development of abovementioned approaches, medicinal herbs and their phytocompounds derivatives are progressively recognized as valuable additional resources in cancer treatment. A considerable volume of clinical and scientific studies have reported a positive effect on immune modulation, survival and quality of life (QOL) in cancer patients when these phytomedicines are used in conjunction with conventional therapies [81].

The four clinically used and well known anticancer agents derived from plants are vinca alkaloids obtained from plant, *Catharanthus roseus* (L.) G.Don, Taxus diterpenes consisting of isoprene units are obtained from the bark of *Taxus brevifolia* Nutt., Camptotheca alkaloids isolated from the bark and stem of *Camptotheca acuminate* Decne, and Podophyllum lignans obtained from ethanolic extract of *Podophyllum peltatum* L. Globally, 60% of the total drugs that are used for the treatment of cancer are derived from natural products, which are mostly phytochemicals [82]. The total expenditure of 5 billion dollars per year is estimated alone in Europe for the production of herbal anticancerous drugs [83]. Some of the plant-derived products commonly used for the treatment of cancer are described below-

Vinca alkaloids

They are isolated from the plant *Catharanthus roseus* (L.) G. Don, commonly called 'periwinkles' belonging to the Apocynaceae family. The four different Vinca alkaloids used clinically for the treatment of different cancers are vincristine (VCR), vinblastine (VLB), vindesine, and vinorelbine. The vindesine, and vinorelbine

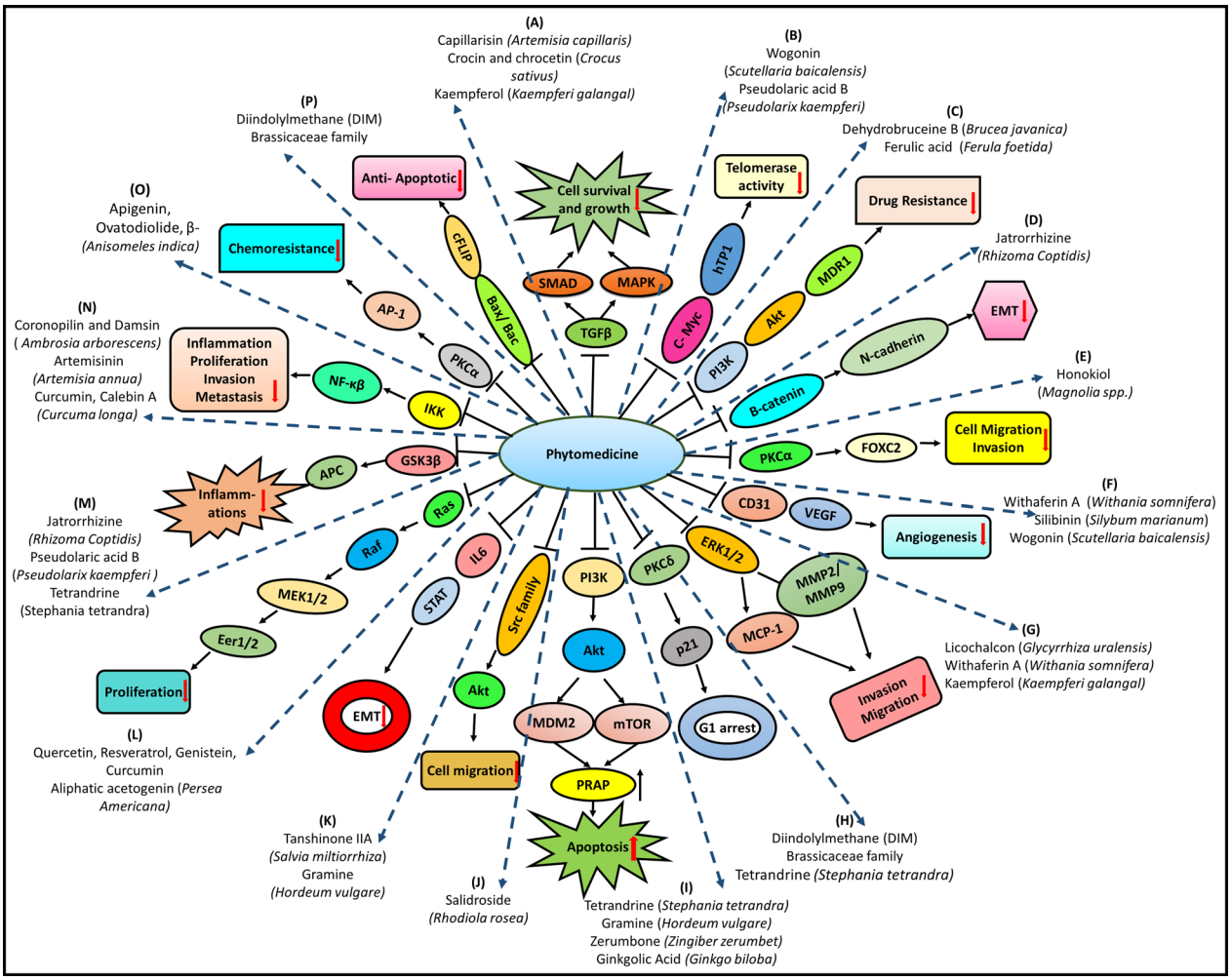


Fig. 2 Schematic diagram of different cancer cell survival signaling pathways targeted by various phytomedicinal compounds. Origin of the dotted arrow and the particular pathway being targeted by phytocompounds coincides at the center. **a** [137–139], **b** [140, 141], **c** [142, 143], **d** [144], **e** [145], **f** [141, 146, 147], **g** [137, 147, 148], **h** [103, 149], **i** [149–152], **j** [153], **k** [150, 154], **k** [78], **l** [140, 144, 149], **m** [120, 123, 155], **n** [113, 156], **o** [103], **p** [137]

are semi-synthetic analogs of vinca alkaloids [84]. While vinblastine is reported to be used for the treatment of breast cancer, lymphomas, lung cancer, leukemia, testicular cancer, and Kaposi's sarcoma; vincristine has been reported to be effective in treating leukemia in children. A study conducted by the National Cancer Institute (USA) showed that over 160 drug combinations used in almost 2069 clinical trials for cancer treatment had vinca alkaloids. These agents (vinblastine and vincristine) are reported to arrest the cell cycle at metaphase stage by hindering the functions of microtubules [85]. Vinorelbine binds to the mitotic spindle and leads to mitotic arrest, thereby causing cell death. It is also assumed to interfere with nucleic acid and lipid synthesis, cellular respiration, and metabolism of glutathione, cyclic AMP and amino acids [86].

Taxanes

Taxanes are powerful plant-derived chemotherapeutic agents. The first taxane 'paclitaxel' (also known as taxol) was isolated from the leaves and bark of *Taxus baccata* Thunb. & *T. canadensis* Marshall. Paclitaxel binds to beta-tubulin and restricts the movement of microtubules leading to mitotic arrest. It also binds to Bcl-2 protein and ceases its function, thereby leading to apoptotic cell death. Docetaxel is a semisynthetic analog of paclitaxel, which binds to microtubules and stabilizes them. This leads to inhibition of the progression of mitotic division from metaphase to anaphase. The accumulation of microtubules further initiates apoptosis resulting in the reduction of cancer cells. Paclitaxel is used for the treatment of breast cancer, NSC, lung cancer, and ovarian cancer; whereas

Table 1 Major Phytochemicals with anticancer potential and their plant source(s)

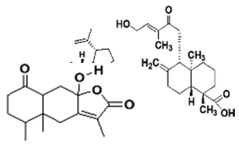
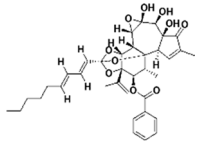
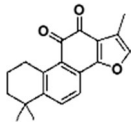
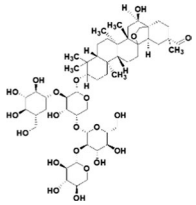
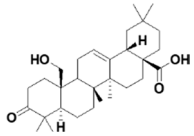
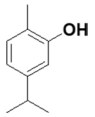
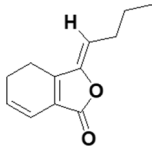
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Terpenoides				Effective for human breast cancer by Inhibiting the epithelial to mesenchymal transition via down regulation of the Runx2 activation	[157]
Lupeol, Henrilabdane, Istanbulin (terpenoids)	*Chloranthus multistachys* C.Pei	–			
Yuanhuacine (diterpenoids)	*Daphne genkwa* Siebold & Zucc	Blue Daphne & Liac Daphne		Effective for non-small cell lung cancer cell by regulation of AMPK/mTOR signaling pathways	[158]
Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Red sage or Danshen		Suppresses the growth of breast cancer stem cells by attenuation of IL-6/STAT3/NF-κβ signaling pathways	[154]
Saxifragifolin A	*Androsace umbellata* (Lour.) Merr	Umbelled Rock Jasmine		Show inhibitory effect on estrogen positive (MCF7) and negative (MDA-MB-231) receptor of breast cancer cells	[159]
Amooranin	*Amoora rohituka* (Roxb.) Wight & Arn	Amoora, Cikih		Shows anticancer potential against breast cancer (MCF-7 and HTB-126) and pancreatic cancer (Panc-1, capan1 and Mia-Paca2,)	[160]
Carvacrol	*Aromatic plants*	–		Inhibits the proliferation and migration of the non-small cell lung cancer cells by targeting the AXL	[161]
Ligustilide	*Cnidium officinale* Makino	Cheonkung		Inhibits the TNF-α induced production ROS and block the inflammatory pathways	[162]

Table 1 (continued)

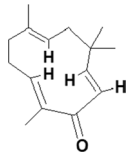
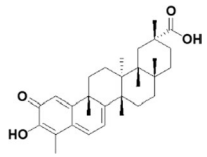
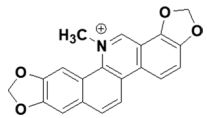
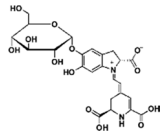
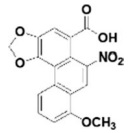
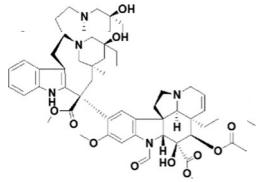
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Zerumbone	*Zingiber zerumbet* (L.) Roscoe ex Sm	Pinecone ginger, shampoo ginger or wild ginger		Inhibits the proliferation of the oral cancer cells by targeting the PI3K-Mtor and CXCR4-RohA pathways	[163]
Celastrol	*Tripterygium wilfordii* Hook.f	Thunder god vine		It targets the microRNA-24 and microRNA-181b and inhibits the proliferation of the lung adenocarcinoma cells	[164]
Alkaloids				It synergistically (combine with their derivatives) inhibits the hepatocellular carcinomas and TGF-β induced EMT, and also inhibit pro-tumorigenic processes like invasion, metastasis and angiogenesis in many cancers	[165]
Sanguinarine (SNG)	*Sanguinaria canadensis* L	Bloodwort, Redroot, Red puccoon			
Betanin	*Opuntia sp.*	–		Show modulatory effect on the EMT in renal proximal tubular cells	[166]
Aristolochic acid (AA)	*Aristolochia sp.*	–		Neurotoxin and effective for human carcinogen associated with upper urinary tract urothelial carcinoma (UUC)	[167]
Vinblastine, Vincristine	*Vinca Rosea* L	Bright eyes, Cape periwinkle		Effective against P388 leukemia and cancers of breast, ovarian, cervix, lung, stomach, colon, testis, and neuroblastoma	[168]

Table 1 (continued)

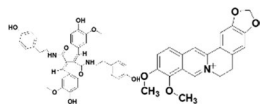
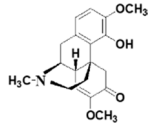
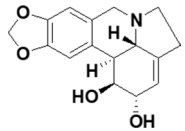
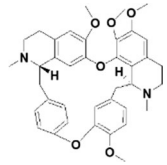
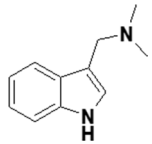
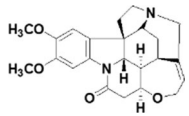
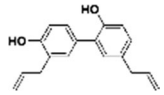
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Cannabisin-G, Berberine	*Berberis vulgaris* L	Barberry		Anti-tumor and anti-angiogenic activity against breast by reducing the expression of the HER-2 and phosphorylation on tumor cells and also effective for liver, prostate cancers and EMT of neuroblastoma cells	[169]
Sinomenine	*Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson	Orient vine stem		Suppresses the NF-κβ pathways and inhibits the breast cell invasion and migration	[170]
Lycorine	*Lycoris radiata* Miq	Red spider lily		Shows anticancer potential against the non-small cells lung cancer by targeting EMT and blocking the Wnt/β-catenin signaling pathway	[171]
Tetrandrine	*Stephania tetrandra* S.Moore	Agrimony		Modulates multiple signaling pathways such as RAS, cell cycle and apoptosis	[149]
Gramine	*Hordeum vulgare* L	Barley		Inhibits cell proliferation in oral carcinogenesis by targeting the NF-κβ and STAT3 pathway and also attenuate the EGFR-mediated inflammation	[150]
Brucine	*Strychnos nux-vomica* L	Nux vomica, semen strychnos		Inhibits breast cancer metastasis by inhibiting the EMT and matrix metalloproteinases	[172]
Phenols				Suppresses renal cancer cell's metastasis via inhibiting EMT and cancer stem cell properties by modulating the miR—141/ZEB2 Signaling	[54]
Honokiol	*Magnolia sp.*	–			

Table 1 (continued)

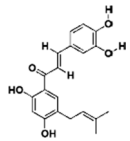
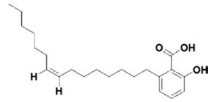
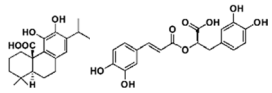
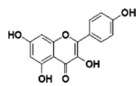
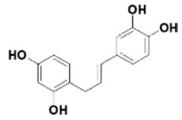
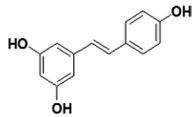
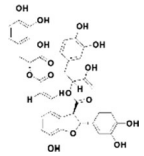
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Broussochalone	*Broussonetia papyrifera* L	Paper mulberry		Anticancer potential via FOXO3 activation	[174]
BRM270	*Saururus chinensis* (Lour.) Baill., *Arnebia euchroma* (Royle) I.M.Johnst., *Scutellaria Baicalensis* Georgi, *Citrus unshiu* Markow, *Portulaca oleracea* L., *P. vulgaris,* and *Aloe vera* (L.) Burm.f	Lizard's tail, Pink Arnebia Chinese skullcap, Baikal Cold hardy mandarin, Common purslane, Aloe	(cocktail of extract)	Inhibits the hepatocellular carcinoma cell proliferation by inducing apoptosis and G2/M phase cell cycle arrest	[174]
Ginkgolic acid	*Ginkgo biloba* L	Ginkgo		Effective for lung cancer by inhibiting the invasion, migration and TGF-β induced EMT through inhibiting the PI3K/Akt/mTOR pathways	[151]
Carnosic acid and Rosmorinic acid	*Rosmarinus officinalis* L	Rosemary		Show inhibitory effect on the growth of human cancer cell line (small cell lung carcinomas, human breast and prostate adenocarcinomas)	[175]
Kaempferol	*Spinacia oleracea* L., *Brassica oleracea var. sabellica* L., *llium schoenoprasum* L., *Anethum graveolens* L., *Artemisia dracunculus* L	Spinach, Cauliflower, wild–cabbage, Chives, Dill, Tarragon		Suppresses the EMT and metastatic-related behaviors of MCF-7 breast cancer cells	[137]
Butein (3,4,2′,4′-Tetrahydroxychalcone)	*Rhus verniciflua* Stokes	Lacquer tree		Effective for bladder cancer by inhibition of invasion through the ERK1/2 and NF-κβ signaling pathways	[176]
Resveratrol	*Vitis vinifera* L	Grape vine		Suppresses the EMT in prostate cancer and colorectal cancer by suppressing the TGF-β1/Smads signaling pathways by mediating Snail/E-cadherin expression	[178]
Salvianolic acid B	*Salvia miltiorrhiza* Bunge	Red sage		Prevent EMT by inhibiting TGF-β and Smads pathways	[178]

Table 1 (continued)

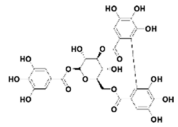
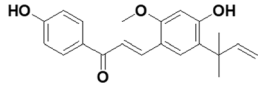
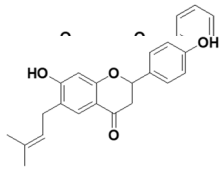
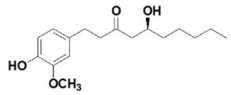
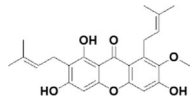
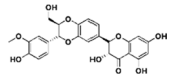
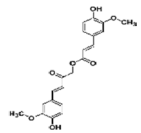
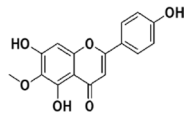
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Corilagin	*Phyllanthus niruri* L	Bhui aonla, Jaramla		Inhibit ovarian cancer cell growth by inhibiting the TGF-β pathways	[179]
Licochalcone A	*Glycyrrhiza uralensis* Fisch	Licorice		Effective for bladder cancer cell lines and mice models by decreasing the proliferation and reduction of the proliferation of ERK1/2 in carcinoma cells	[148]
Bavachanin, Corylfolinin	*Psoralea corylifolia* L	Babchi		Show cytotoxicity on KB, KBv200, K562/ADM cancer cells of human leukemia	[180]
6-gingerol	*Zingiber officinale* Roscoe	Ginger, Adrak		Effective for the human cervical adenocarcinomas by modulating the cell cycle and apoptotic pathways	[181]
α-Mangostin	*Garcinia mangostana* L	Gamboge, Mangusta Mangustan		Effective for the viability and growth of spheroids derived from the human breast cancer cell lines	[182]
Flavonoids				Attenuates pro-angiogenic response and EMT in prostate cancer	[146]
Silibinin	*Silybum marianum* (L.) Gaertn	Milk thistle			
Calebin A	*Curcuma longa* L	Termeric		Suppresses NF-κβ pathways, inhibit cell metastasis and invasion	[155]
Hispidulin	*Saussurea involucrata* Matsum. & Koidz	Snow lotus		Prevent EMT in human colon carcinoma cells by inhibiting the mRNA and protein expression of HIF-1α via modulation of PTEN/PI3K/Akt pathways	[183]

Table 1 (continued)

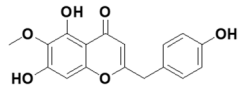
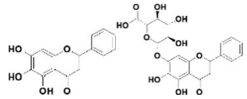
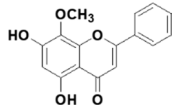
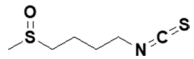
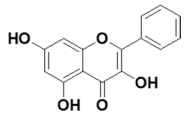
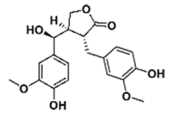
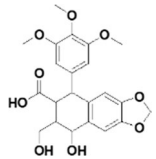
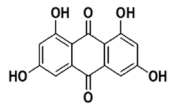
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Capillarisin (CAP)	*Artemisia capillaris* Thunb	Capillary wormwood		Attenuates muscle damage by modulating MAPK and NF-κB signaling	[138]
Baicalin &Baiclein	*Scutellaria baicalensis* Georgi, *Oroxylum indicum* (L.) Kurz	Chinese skullcap, Indian trumpet flower		Inhibits inflammatory disorders by which also arrested cell cycle against tumor cells and induced apoptotic signaling pathways	[184]
	Scutellaria baicalensis Georgi	Chinese skullcap		Anti-tumor activity by regulating the Akt/AMPK/apoptosis signaling pathways, also inhibits growth of drug resistance of malignant cells and their invasive, migration and metastasis	[141]
Sulforaphene	*Rhapanus sativus*	Radish		Inhibit proliferation of the human breast cancer cells by inducing the G2/M cell cycle arrest and apoptotic pathways	[185]
Galangin	*Alpinia officinarum* Hance	Greater galangal		It prevents the invasion in A172 glioma cells by decreasing the ADAM9 expression and increasing the ERK1/2 phosphorylation	[186]
Lignans				Suppresses tumor necrosis factor-α by blocking the MAPK/NF-κβ and activation of the Nrf2/ HO-1	[188]
(-)-7(S)-hydroxylmatairesinol	*Picea abies* (L.) H.Karst	Common spruce			
Podophyllin	*Podophyllum peltatum* L	Mayapple, wild mandrake		Show strong antineoplastic activity against breast, liver, brain and bladder cancers	[152]
Anthraquinones				Inhibit TWIST-induced EMT in head and neck squamous cell carcinomas cells by blocking the β-catenin and Akt pathways	[188]
Emodin	*Rheum palmatum* L	Chinese rhubarb			

Table 1 (continued)

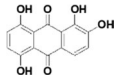
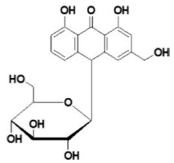
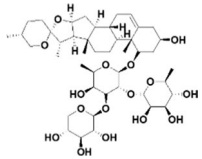
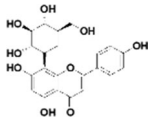
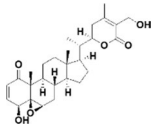
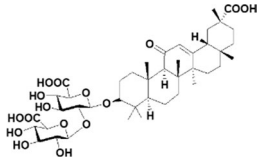
Phytomedicinal compounds	Plant source	Common name	Structure	Evidences in cancer prevention and treatment	References
Quinalizarin	–			Targets the Akt, MAPK, STAT3 and p53 signaling pathways in lung cancer A549 cells	[189]
Glucosides				Effective against hepatocellular carcinoma	[190]
Aloin A	*Aloe vera* (L.) Burm.f	Aloe			
Ophiopogonin D	*Ophiopogonin japonicas*	Mondo Grass		Suppresses the proliferation and chemosensitization of human lung cancer cells and also modulate the multiple signaling pathways	[191]
Vitexin	*Passiflora species; Pennisetum glaucum* (L.) R.Br	– Pearl millet		Effective for human glioblastoma cells by targeting Akt/mTOR pathway and also induce the apoptosis and G2/M phase arrest	[192]
Steroid lactone				Suppresses the growth of the ovarian cancer metastasis by targeting putative cancer stem cells and also effective for cancer of breast, colon, nasopharynx, cervix and malignant melanoma	[147]
Withaferin	*Withania somnifera* (L.) Dunal	Ashwagandha			
Saponins				Target apoptotic and ROS mitochondrial pathway in breast cancer	[193]
Glycyrrhizic acid	*Glycyrrhiza glabra* L	Liquorice			

Table 2 Phytomedicinal compounds in pre-clinical and clinical trials

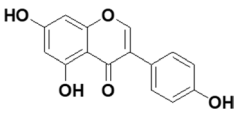
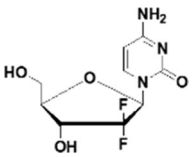
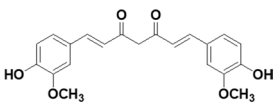
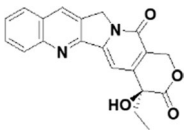
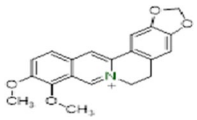
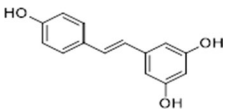
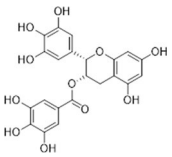
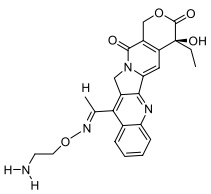
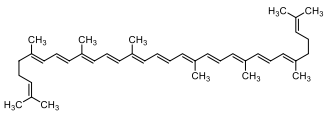
Phytomedicinal compounds	Source	Animal model	Pre-Clinical evidences	References
Quercetin, coumarin	*Melilotus indicus*	Mice	Significant anticancerous effect were seen in quercetin-coumarin combination treated animals against skin cancer	[203]
Hexadecanoic, Octadecanoic acid	*Raphanus sativus*	Chicken-chorioallantoic membrane	Down-regulates the expression of iNOS, TNF-α, ROS, and NF-kβ with significant anti-angiogenic effects	[204]
Carvocrol, trans-caryophyllene	*Wedelia chinensis*	C57BL/6 mice	Target lung cancer by scavenging free radicals	[205]
Polyphenols (plant methanol extract)	*Sphagneticola calendulacea*	Swiss albino mice	Strong antineoplastic activity against Ehrlich ascites carcinoma by inhibiting the proliferation, decreasing tumor weight and by increasing the apoptosis	[206]
Triptolide	*Tripterygium wilfordii*	Balb/c-nu mice	Shows Antitumor activity by inducing apoptosis and regulating MMP-2, Sorcin and vascular endothelial growth factor expression	[207]
Deoxyelephantopin	*Elephantopus scaber*	Male swiss albino mice	Reduced tumor volume in Murine ehrlich ascites carcinoma	[208]
B-sitosterol, palmitic acid	*Nitraria retusa*	Balb/c mice	Antitumor activity by inhibiting the tumor growth	[209]
Isoegomaketone	*Perilla frutescens*	Tumor-xenograft nude mice	Suppressed Hepatocellular carcinoma tumor growth via blocking PI3K/Akt signaling pathway	[210]
Oridonin	*Rabdosia rubescens*	Athymic nude mice	Inhibited growth of xenograft in athymic nude mice	[211]
Phytomedicinal compounds	**Structure**	**Nature of compound**	**Clinical evidences**	**Clinical Trials. Govt. No**
Genistein		Flavonoid	The last update of this study was posted September 10, 2019. Study results are still awaited	NCT01126879
Polyphenols (green tea)	Compounds Mixture	Phenolic	No study results posted for clinical evidence and still work is going on in prostate cancer treatment	NCT01912820
Lycopene		Terpene	Study results still awaited for clinical evidence against prostate cancer	NCT00006078
Mistletoe	Compounds Mixture	Alkaloid	Study is not completed, and last update posted June 6, 2018 and no result posted	NCT02948309
Gemcitabine		Flavonoid	Total participants were 548 and after treatment of NSCLC patients with gemcitabine + cisplatin, the overall survival time were 9.9 months and *P* value of overall survival time were 0.0120	NCT00981058
Curcumin		Polyphenol	No result posted yet against prostate cancer	NCT01917890
Panax ginseng	Water extract	Saponin	Study is in progress for breast cancer treatment	NCT00631852

Table 2 (continued)

Phytomedicinal compounds	Structure	Nature of compound	Clinical evidences	Clinical Trials. Govt. No
Camptothecin		Alkaloid	Study results awaited for clinical evidence against unspecified adult solid tumor	NCT00059917
Berberine		Alkaloid	Overall status is still not known against Colorectal adenomas	NCT03281096
Resveratrol		Stilbenoid	This study was carried out against against Notch-1 signaling of Gastrointestinal tumors, results still awaited	NCT01476592
Epigallocatechin Gallate (EGCG)		Flavonoid	This study was carried out against the colorectal cancer patients, but the results is still not posted	NCT02891538
Namitecan		Alkaloid	Study have been completed against solid tumors but result not posted	NCT01748019
Lycopene		Carotenoid	Study being carried out against Colorectal cancer	NCT03167268

docetaxel is used primarily for treating breast cancer [87].

Podophyllotoxin

They are lignan derivatives and are isolated from *Podophyllum peltatum* L. They form complex with topoisomerase II enzyme and DNA hence prevents the ligation of broken DNA strands. The breaks in the DNA are accumulated over the time leading to cancer cell death. Etoposide and teniposide are semi-synthetic analogues of podophyllotoxin. Etoposide is used as a chemotherapeutic drug for the treatment of lung cancer, glioblastoma multiforme, testicular cancer, lymphoma, Kaposi's sarcoma, Ewing's sarcoma, and nonlymphocytic leukemia [86].

Camptothecin derivatives

Camptothecin is inhibitor of topoisomerase I which is isolated from the stem and bark of *Camptotheca acuminate* Decne. Topotecan and irinotecan are derived from camptothecin. Topotecan is used for the treatment of lung and ovarian cancer; irinotecan treats colorectal cancer [88]. Their mode of action involves inhibiting the function of topoisomerase I enzyme. The camptothecin derivatives bind to DNA and topoisomerase I, forming a ternary complex. This complex halts the DNA replication and produces lethal double-stranded breaks in DNA. This damage is not repaired efficiently by the cancer cells, thereby leading to their apoptosis [89].

The Food and Drug Administration (FDA), has approved various drugs, out of which dacarbazine was the first clinically approved alkylating chemotherapeutic drug used for metastatic cancer treatment [90]. Similarly, cisplatin, doxorubicin, paclitaxel, and fluorouracil are the most common types of chemotherapeutic agents, used by numerous oncology laboratories for combinatorial studies (including their additive and synergistic effects) [91]. Phenolic compounds like kaempferol, resveratrol,

curcumin, quercetin, etc. and many alkaloids have proven to be very effective against different types of cancers [92–94]. Many studies have reported the use of alkaloids in combination with some well-known cancer drugs used in clinical settings. Xieet al., reported the synergistic effects of alkaloids with paclitaxel against cervical cancer [95]. Terpenoids like retinoic acid, lycopene, and β-carotene are also effective against cancers [96].

In addition to the phytochemicals described above, which are utilized in cancer treatment, many more are being discovered. *Centella asiatica* (L.) Urban derived phytochemical, Asiatic acid has been shown to have anticancerous effect on Cholangiocarcinoma (malignant tumor of the epithelium of the bile duct) besides its antioxidant and anti-inflammatory effects [97]. Sakonsinsiri C et al., 2018, have shown by in vitro assays that Asiatic acid induces apoptosis in Cholangiocarcinoma cells and suppresses the expression of BCL2 and Survivin/BIRC5, anti-apoptotic genes. With the increasing cancer-associated mortality rates, phytomedicines have become focal point for pharmaceutical industries [97].

Phytomedicines as antioxidants

Splitting of oxygen inside a cell leads to the generation of free radicals. Free radicals (reactive oxygen species; ROS) are unstable molecules due to the presence of unpaired electrons. Generally, they are involved in the regulation of different physiological processes but dysregulation of free radicals gives rise to several pathological conditions (aging, inflammation, cancer, etc.) by damaging lipids, nucleic acids, proteins, and various cellular organelles. Antioxidants are compounds that play an essential role in regulating and maintaining the proper balance of the level of free radicals inside a cell. In this process, they donate their own electrons and stabilizes the free radicals [98]. Excessive accumulation of free radicals inside the cell leads to oxidative stress and antioxidants are the potent defense system of the body that confronts these free radicals. Overproduction of reactive oxygen species (ROS) alters metabolic pathways and induces chronic inflammation which leads to carcinogenesis [99].

Numerous studies have shown that phytomedicines have antioxidant potential. Noelia et al., studied the antioxidant potential of compounds (iridoids, monoterpenoids, lignan, and glycosylated phenylpropanoids) isolated from *Lemon verbena* extract through semi-preparative high-performance liquid chromatography approach (HPLC). These compounds were examined for their antioxidant activities through Trolox equivalent antioxidant capacity (TEAC), oxygen radical absorbance capacity (ORAC), Ferric reducing antioxidant potential (FRAP). Their results suggest that out of the different compounds isolated, phenylpropanoids exhibited the strongest antioxidant activity [100].

Kicel et al., investigated the antioxidative potential of fourteen unsaturated fatty acids, two triterpenoid acids, twenty-six polyphenolic compounds, and three Phytosterol isolated from *Cotoneaster* fruit. The antioxidant potential was assayed through FRAP, DPPH, and Thiobarburitic acid reactive substances (TBARS) assays. Out of these compounds, polyphenols exhibited the highest antioxidant activity [101]. In 2016, Chang et al., reviewed the various phenolic and flavonoid compounds isolated from dried fruits for their antioxidant activities. The compounds included caffeic acid, ferulic acid, vanillic acid, syringic acid, cyanidin, delphinidin, kaempferol, protocatechuic acid, rutin, and quercetin, phytoestrogen like genistein, daidzein, lariciresinol, pinoresinol, secoisolariciresinol, and carotenoids having moderate to good antioxidant activity [102]. Lee et al., in their study explored the antioxidant potential of phytochemicals (lycopene, curcumin, resveratrol, catechin, mulberry leaves) isolated from *Echinacea purpurea* (L.) Moench and *Toona sinensis* (Juss.) M. Roem, and investigated their role in modulating the oxidative status in an animal model [103]. According to Barros et al., the publications related to in vivo and in vitro antioxidant potential of phenolic compounds obtained from medicinal plants increased significantly from 2000 to 2014 [104].

Phytomedicines as 'epithelial to mesenchymal transition (EMT)' inhibitors

The change in epithelial cell phenotype to mesenchymal phenotype is defined as epithelial to mesenchymal transition (EMT). It plays a key role in embryonic development, development and remodeling of tissues/organs, wound healing and in carcinogenesis [105]. It also contributes in fibrosis and tumor metastasis [106]. The important difference between the embryogenic and tumorigenic EMT process is that the tumorigenic EMT process involves emergence of abnormal cells and erroneous cellular signaling. It also imparts cell death resistance and development of multi-drug resistance phenotype in tumors. Therefore, for the inhibition of the tumorigenic EMT process, currently, phytomedicine in combination with well-known anticancer drugs/therapies are being recommended. In recent scientific reports (2015–2019), researchers and pharmaceutical industries focused on the development of new anticancer drugs from natural products. In a study, Dai et al., reported that TGF-β/Smad signaling is responsible for the induction of EMT and progression of colorectal cancer (CCR). They studied the compound ginsenoside Rb2 for its anti-EMT potential in colorectal cancer. The results showed that ginsenoside Rb2 was effective

in downregulating EMT markers (Vimentin, Snail, and N-cadherin) in HCT116 and SW620 cells by inhibiting TGF-β/Smad signaling [107]. Chenxia et al., 2018, reported the EMT inhibitory effect of curcumin isolated from the rhizome of *Curcuma longa* L. against breast cancer. This study showed the antiproliferative potential of curcumin and suppression of migration and invasion in breast cancer cell lines. Curcumin also affected cellular phenotype by upregulating the epithelial marker E-cadherin and downregulating the mesenchymal marker, vimentin and inhibited the EMT and metastasis processes [108]. Naveen et al., 2016, showed that the phyto-alkaloid berberine, plays an important role in attenuating cancer stemness. They showed the decreased expression of cancer stemness markers n-myc, notch2, β-catenin, sox2, CD133, and nestin, increased neuronal differentiation, which was marked by the expression of MAP2, NCAM, and β-III tubulin. Berberine reduced the expression of neural cell adhesion molecule (NCAM) and the polysialylated form of NCAM (PSA-NCAM), thereby reducing EMT. Berberine also increased the expression of Hsp70, an inhibitor of EMT, confirming its role in the reversal of EMT [109].

Hypoxia is a common feature in the tumor and its surroundings; it imparts cell death resistance, invasion and metastasis [106]. HIF-1α regulates the oxygen signaling in the cells and itself is regulated by the oxygen level of the tissue micro-environment. Its level is upregulated under hypoxic conditions and can directly or indirectly modulate the level of Snail leading to EMT [110]. Curcumin has been shown to suppress HIF-1α expression and EMT process in HepG2, human hepatoma cells [111]. Curcumin also inhibited the proliferation and migration of tumor by inactivating the HIF-1α. Similarly Allicin also reverses the EMT process via ERK1/2-TGF-β signaling pathway [106].

A phytocompound chrysotobibenzyl, isolated from *Dendrobium pulchellum* Roxb. ex Lindl showed the inhibitory effect on the migration of lung cancer cells by suppressing caveolin-1, integrin, and EMT process [112]. Likewise, ovatodiolide inhibited nasopharyngeal cancer by inhibiting EMT via altering the expression of epithelial and mesenchymal markers. It has been shown that ovatodiolide can suppress breast, pancreatic, and oral carcinomas by modulating the EMT process [113]. It is reported that triple-negative breast cancer cells are more aggressive cancer cells with mesenchymal phenotype and could be responsible for increasing breast cancer rates worldwide [114]. Ophiobolin A (OpA), a sesterterpenoid produced by the fungi as secondary metabolite. Genera of *Aspergillus, Bipolaris, Cephalosporium, Cochliobolus,* and *Drechslera* produces this compound. It has sensitizing effect on breast cancer cells leading to their death due to its suppressive role on the miR-200c [115]. Literature survey reveals that diverse phytomedicines isolated from plants have the potential to suppress EMT process and thus carcinogenesis via targeting inflammatory pathways. The EMT modulating effect of a range of natural compounds has been also reviewed earlier [116].

Phytomedicines as inhibitors of inflammation

Several factors like microbial infections, allergic reactions, and chemical injury induces inflammation in cells and tissues. Inflammation causes pain, redness, swelling, and irritation in the affected area. During inflammation, infiltration and extravasation of immune cells, leukocytes and neutrophils increases at the affected site. Inflammation is a complex process, categorized into two types: acute inflammation and chronic inflammation. Acute inflammation exists for a short period, while chronic inflammation persists for a longer duration. Pathologically, prolonged persistence of chronic inflammation is life-threatening, resulting in heart disease, arthritis, Alzheimer's, AIDS, cancer, and many other diseases. Lwalewa et al., 2009, reviewed the anti-inflammatory potential of various phytocompounds like flavonoids, phenolics, alkaloids, tannins, and terpenoids [117]. Sharman et al., in 2019 reviewed the effect of phytomedicine or natural products on inflammatory pathways in Alzheimer's disease. The phytocompounds like resveratrol, Cinnamaldehyde, lipoic acid, omega-3-fatty acids, cannabidiol, luteolin, genistein, curcumin, and ginsenosides are well reported for the treatment of Alzheimer by targeting the inflammatory pathways [118]. Similarly, ethyl p-coumarate has been reported as an anti-inflammatory agent, it decreases the migration rate of leukocytes, carrageenan-induced paw edema in mice and level of pro-inflammatory interleukins [119]. Sesquiterpene lactones-coronopilin and damsin are secondary metabolites isolated from *Ambrosia arborescens* Mill, which inhibit various inflammatory pathways including NF-κβ signaling, level of p65 and proinflammatory cytokines MCP-1 and IL-6 in human skin cells [120]. Ibrahim et al., used the extract of *Triticum aestivum* and determined its anti-inflammatory and analgesic activity in Swiss albino mice. Their results showed that the plant extract significantly inhibited the edema (19.023%) compared to standard Ibuprofen and showed thrombolytic activity [111]. Another study demonstrated the anti-inflammatory potential of herbal plants like *Curcuma longa* L., *Camellia sinensis* (L.) Kuntze, *Gardenia jasminoides* J. Ellis, *Zingiber zerumbet* (L.) Roscoe ex Sm., and *Polygonum tinctorium* Aiton in mouse and rat animal models [122].

Some herbal medicines isolated from plants like *Artemisia absinthium* L., *Aloe vera* (L.) Burm.f., *Plantago*

ovate, Triticum aestivum L., and *Boswellia serrate* Roxb. ex Colebr., have been used in clinical trials, for patients having inflammatory diseases. Their use have rendered significant improvements and fewer side effects in the patients [122]. The different parts of these plants are used as powders, seeds, gels, and extracts. These phytomedicines also act as anticancer drugs by inhibiting chronic inflammatory pathways. Many studies have shown that overexpression of the components of the inflammatory pathways play a major role in causing cancer by inducing EMT. Therefore, phytomedicines having anti-inflammatory activity could eventually play a role in targeting EMT and inhibiting cancer metastasis. Thus, phytomedicines are used as a source of ethnic and alternative medicines and have become a relevant source for new drug discovery [123, 124].

Phytocompounds as angiogenesis inhibitors

The formation of new blood vessels from pre-existing blood vessels is known as angiogenesis [125]. It is an important physiological process but also plays an important role in the development of cancer. Oxygen and nutrients are required for tumor development. Blood is the main supplier of oxygen and nutrients to the whole body and to the tumor cells; therefore the process of angiogenesis is increased several folds in cancer cells. For the invasion of the tumor, excessive oxygen and blood is needed; in this way angiogenesis plays an important role in tumor invasion [126]. Angiogenesis is commenced by tumor-derived proteolytic enzymes and pro-angiogenic factors, which enhances the proliferation of endothelial cells (ECs), migration of ECs toward tumor cells, and formation of a functional vasculature.

Libra et al., studied the correlation between enhanced production of MMP-2 and MMP-3 with invasiveness, metastasis, and angiogenesis of cervical cancer [127]. Their study suggests that angiogenesis could be an attractive target for cancer therapy. Among the well-studied phytochemicals, phloretin, a dihydrochalcone flavonoid, is an active component in the peel and root skin of vegetables and fruits, including apples and strawberries, and has many pharmacological activities such as antioxidant [128], anti-inflammatory [129], and anticancer effects [130]. There are many studies which explored the anti-angiogenic potential of phytochemicals including resveratrol, rhaponticin, curcumin [131], and ethanol extracts of *Nona atemoya* [132], *Lophatheri herba* [133], and baked *Gardeniae fructus* [134]. Zhang et al., reported the inhibitory potential of tumor-induced angiogenesis in a zCDX model of SGC-7901 by Para-coumaric acid methyl ester (pCAME) [135]. They demonstrated that tryptanthrin exerts an anti-angiogenic effect by downregulating the expression of apelin in HUVECs [136].

Clinical studies of various phytocompounds against different cancers

Current developments in the field of phytomedicine research have provided new ways for cancer treatment. In recent years, oncologists and researchers have done noteworthy work for the early detection, treatment, and prevention of cancer, which has resulted in extended survival of cancer patients. Cancer treatment faces tough challenges and requires the experience of experts from associated and distinct fields. Uniting extant methods with innovative ones could help in undertaking this challenging health problem, for the development of new anticancer drugs from plants to halt disease progression, and prolonging the life expectancy of patients. Phytomedicines are less expensive and have no serious side effects on human health. In combination with known drugs, phytomedicines have shown their better therapeutic effect on drug-resistant cancers. Many research groups are working on herbal medicines, investigating their mode of action and target signal pathways and have got success in clinical trials. Various steps are involved in discovering medicinal plants (identification of plants, isolation, extraction, and purification of biologically active compounds, testing of compounds) and clinical trials of isolated drugs from them. These steps include drug identification and in vivo-based bioassays and drug optimization by chemical and combinatorial studies [194].

Prior to entering clinical trials, the isolated phytocompounds are characterized and screened by researchers for their pharmacological potential, mechanism of action, molecular targets and pathways, efficacy, and toxicity through pre-clinical study. Over the past decades, numerous phytochemicals have been shown to possess extraordinary anticancer effects and many of them as a single agent or combined with existing anticancer drugs have progressed from pre-clinical to clinical practice. Phytocompounds like allicin, apigenin, 6-shogaol, baicalein, curcumin, and many others are pre-clinically approved as anticancer drugs and also are used in the clinical practice [195]. Similarly, 6-gingerol, Vitexin, nimbolide, ursolic acid, withaferin A, Sulforaphane, and emodin were also pre-clinically tested against lung cancer and further approved for the preliminary stage of clinical trials; although berberine, curcumin, epigallocatechin gallate, quercetin, and resveratrol are already under clinical trial [196]. Many other phytochemicals like angelicin, apigenin, chrysin, coumarins, curcumin, eupafolin, etc., have also been recognized for the prevention and treatment of renal cell carcinoma by preclinical and clinical evidences [197]. Table 2 enlists some of the pre-clinical studies of the phytocompounds for cancer treatment.

According to a study, more than 100 plant-derived natural compounds are under the clinical process [198].

Richardson et al., discussed the use of complementary or alternative medicine (CAM) for cancer patients. The study insisted on improving awareness among cancer patients, passing on reliable information to patients and initiate research to determine the best possible synthetic drug-herbal medicine-vitamins interactions [199]. However, there is a need for standardizing approaches to isolate, synthesize, and administer these herbal compounds. Furthermore, the different active components from a medicinal plant might have synergistic activities. The biologically active constituents of medicinal plants show significant differences in their activity due to changes in temperature, moisture, soil, and genetics. Many medicinal plants have shown their promise in phase II or phase III trials [200]. Ryan et al., evaluated the activity of curcumin to reduce radiation dermatitis severity (RDS) in 30 breast cancer patients by conducting a randomized double-blind, placebo-controlled clinical trial. Their results showed that curcumin reduces RDS compared to placebo at the end of the course of treatment. They showed that, 6.0 gm of oral curcumin reduced the RDS in breast cancer patients during radiotherapy [201]. The anticancer effect of curcumin has also been observed in other clinical trials, mainly as a chemopreventive agent in pancreatic, cervical, and colon cancer treatment. When curcumin along with gemcitabine was administered in patients with advanced pancreatic cancer, an unbiased response was found in less than 10% of patients with minor effects on survival [202]. Similarly, European mistletoe (*Viscum album* L.) phytochemicals (Iscador and aviscumine) have undergone 23 clinical trials, out of which 19 trials have shown enhanced efficacy of the drugs against cancer, increased survival rates, improvement in quality of life, etc. Clinical trials-based evidence for some major phytomedicines are listed in Table 2.

Synergistic and/or additive effect of phytomedicines

Combinatorial strategy involving administration of certain phytochemicals along with known anticancer drugs tends to produce synergistic and/or additive effects and enhance the effect of other administered drug. Additionally, some of the herbal medicines also have been found to mitigate the side effects of anticancer drugs in system. For instance, patients with kidney cancer receiving cisplatin have shown nephrotoxicity. But patients consuming chinese herbal medicine (CHM) decoction along with cisplatin showed positive results with reduced nephrotoxicity by decreasing the levels of creatinine, beta-2-microglobulin, blood urea nitrogen, and urea N-acetyl-beta-glucosaminidase [212]. Six phytochemicals have been examined in combination to combat the breast cancer cells in vitro, including indol-3-carbinol, C-phycocyanin, resveratrol, curcumin, isoflavone, and quercetin. The results showed suppression of tumour cell motility and invasion with cell growth inhibition, and cell cycle arrest thereby promoting apoptosis. Various studies have also shown significant enhancement in anticancer activities by combining two or more phytocompounds. When combined with quercetin, cisplatin, tamoxifen, vincristine, and doxorubicin have shown enhancement in their efficacy against oral squamous cell carcinoma, breast cancer, cervical cancer, lymphoma, and gastric cancer. Resveratrol along with temozolomide, doxorubicin showed drug efficacy against malignant glioma and melanoma. Genistein when used in combination with 5-FU, photofrin and estradiol also showed increased efficacy of these anticancer drugs in pancreatic cancer, ovarian cancer, and thyroid cancer. The natural compound emodin when used with sorafenib, afatinib, cisplatin, paclitaxel, gemcitabine, endoxifen also showed improved outcome of anticancer activities against hepatocellular carcinoma, pancreatic cancer, lung adenocarcinoma, non-small cell lung cancer, and breast cancer. These studies demonstrate that use of phytocompounds in combination with other anticancer medications that are clinically used can significantly improve the treatment outcomes [213]. Galangin, a non-toxic phytochemical is known to have strong anticancer potential as a single component while in combination with berberine showed the strong synergistic activity against the oesophageal carcinoma cells by increasing the cell cycle arrest [214].

Currently, chemotherapies are the most useful treatment methods for cancer while having critical side effects and unavoidable challenges. A combination of natural products with chemotherapeutic compounds; have the potential to synergistically enhance the effectiveness of treatments while minimizing their side effects. The *Ficus carica* plant extract was studied with and without therapeutic modalities against rhabdomyosarcoma (RD) cells lead to conclusion that the phytoextract with combination of therapeutic modalities enhances the treatment efficacy of RD metastasis [215]. Curcumin and resveratrol are well-known strong chemotherapeutic agents that show a synergistic effect in combination with clinically known anticancer drugs such as docetaxel, paclitaxel, doxorubicin, and cisplatin and also reduce the chemotherapy-associated toxicity by modulating the apoptosis and autophagy cell death pathways [216]. In most studies, curcumin itself was found to be an effective anticancer drug, nevertheless, curcumin with arctigenin showed a synergistic effect against human prostate adenocarcinoma, and curcumin in combination with epigallocatechin gallate again found synergism against breast cancer [217]. Similarly, resveratrol with phenyl isothiocyanate showed synergistic effect against pancreatic cancer cells

[218]. Curcumin in combination with cisplatin exhibited the anticancer activity by inhibiting the ERK signaling pathways, similarly, with oxaliplatin inhibits the proliferation of NF-kβ signaling pathways in colorectal cancer cells [219, 220]. Numerous in vitro and in vivo studies demonstrated that the phytomedicine resveratrol in combination with temozolomide induces apoptosis and inhibits the ROS/ERK pathways [216]; and in combination with paclitaxel shows synergistic effect in breast cancer treatment [221]. Another study demonstrated the synergistic effects of phytocompounds anethole and doxorubicin against triple negative breast cancer cells by enhancing the cytotoxic effect, which was evaluated by various parameters including cell proliferation, cell cycle analysis, DNA damage and apoptosis [222]. These combinatorial studies have enhanced the therapeutic efficacy of several anticancer drugs and raises hope to overcome the challenges in the current cancer drug development programs.

Phytochemicals in reducing the side effects and drug resistance during chemotherapy

Besides surgery and radio-therapy, chemotherapy is one of the most relied methods for the cancer treatment. However, it comes with debilitating side effects and multiple health issues due to their cytotoxic nature. Use of plant-derived natural products has been shown to ameliorate the chemotherapy induced side effects. Tamoxifen is used in the treatments of all stages of the hormone dependent breast cancers. But it has multiple side effects including hepatic and renal toxicity. Tamoxifen induces hepatorenal toxicities through induction of oxidative stress, inflammation, and cellular apoptosis. Chlorogenic acid, which is a polyphenolic compound, is found in *Hibiscus sabdariffa* L. leaves, egg-plant, prunes, peaches and coffee beans. Use of Chlorogenic acid has been shown to reduce the Tamoxifen associated hepatic and renal injuries in the experimental rats and acts as a chemoprotective agent [223].

Phytochemicals not only help in reducing the side effects caused by the various chemotherapeutic agents as they can sensitize cancer cells to these drugs [202]. Luteolin is one such phyto-flavonoid which suppresses the EMT process and helps in overcoming the Paclitaxel resistance in ovarian cancer cells [225]. Similarly, Apigenin supplementations tame the Adriamycin resistance in breast cancer cells [226]. It has been shown that the fungus derived OpA increases the sensitivity of breast cancer cells to the chemotherapy by Paclitaxel and doxorubicin used in conventional treatments [115]. Thymoquinone (TQ) derived from seeds of *Nigella sativa* L. have anticancerous and chemopreventive properties [227]. It induces death of the cancerous cells by inducing apoptosis and modulating the redox system. Besides these, TQ has anti-inflammatory properties, modulates the epigenetic markers and immune responses during cancer development [227].

Phytochemicals also have ability to overcome the multiple drug resistance (MDR) in various cancers [202]. The phytochemicals including capsaicin, quercetin, curcumin, and resveratrol alone and in combination with gemcitabine have shown the down regulation of MDR markers such as ATP binding cassette subfamily C member 2 (ABCC2), deoxycytidine kinase (DCK), and Thymidine kinase (TKs) in bladder cancer cells. Capsaicin has shown to have synergistic effects in T24-GCB cells in combination with gentamycin which provides adjuvant therapy for overcoming MDR in bladder cancer [228]. The plant-derived phytochemicals show the suppressive effect on p-glycoprotein by modulating the numerous signal transduction pathways including ABCB1 gene expression, and aid to overcome the MDR during cancer chemotherapy [229]. Curcumin suppresses the STAT3 and NF-κB pathways, thereby enhances the Cisplatin (CP) sensitivity, and prevents the drug resistance. Curcumin also increases the CP cytotoxicity against cancer cells and reduces the CP-mediated side effects [230]. Phytochemicals thereby are being well appreciated as complementary therapy for cancer treatment, which reduces the side effects and enhances the efficacy of chemotherapy [231].

Epigenetic alterations in carcinogenesis: phytochemicals as redeemer

Epigenetic changes such as methylation, acetylation, and histone modifications play pivotal role in maintaining cellular homeostasis. However, aberrant epigenetic changes are associated with the carcinogenesis. In instances of generation of excessive reactive oxygen/ nitrogen species, long lasting damage to the DNA/ proteins/ lipids may occur. This leads to the deregulation in the expression and activities of the various tumor suppressor genes and oncogenes leading to cancer [232].

Polyphenols regulate epigenetic modulation, hence are important agents in preventing cancer development and its progression [36]. This modulation of epigenome by the polyphenols is due to their ability in rescuing the redox balance as well as their ability to modulate chromatin remodeling [233]. Some of the polyphenols with the ability to harmonize epigenetic changes are genistein, phenethyl isothiocyanate, curcumin, sulforaphane, and resveratrol.

The epigenetic alteration are also caused by other factors such as toxic chemicals and heavy metals. The arsenic metalloid is one of the most common environmental pollutants that induces epigenetic alteration like acetylation, histone methylation as well as miRNAs modulation and promotes cancer development. Some flavonoid-rich phytochemicals

have shown to be a potential halt marker of carcinogenesis by preventing these epigenetic alteration. Catechins are the most active flavonoids present in green and black tea, which have been reported as epigenetic modulators by their chemopreventive attributes against arsenic-induced carcinogenesis [234]. The polyphenolic compounds of Green tea such as epigallocatechin-3-gallate acts as an epigenetic regulators to prevent cancer [235]. Irshad et al., reviewed several natural products like berberine, parthenolide, apigenin, sulforaphane, curcumin, genistein, quercetin, and resveratrol that showed their great potential in targeting and modulating the epigenetic markers and regulating carcinogenesis [236]. Cinnamaldehyde (CA), is a well-known anticancer bioactive phytocompound, present in *Cinnamomum cassia* (L.) J.Presl. In gastric cancer cells, CA induces cell death by inducing the Beclin-1, ATG5, and LC3B expression and inhibits p62 expression by epigenetic modifications [237].

Key challenges in phytomedicine-based cancer therapy

Phytomedicine has been proven to be an alternative medicine for the treatment of cancer. Some of the challenges related to the use of phytomedicine in cancer treatment are as follows-

- The screening and standardization of phytomedicinal compounds prior to their use in the cancer treatment is a complex process.
- Usually, phytomedicine-based treatment requires a longer time compared to synthetic medicine.
- Cancer is a complex genetic disorder, therefore phytomedicine may not be enough to root out this disease completely.
- Limited sustainability of plant sources harboring the potent anticancer agents could also affect the availability of anticancer phytomedicines.
- Lack of financial resources for scientific researches related to phytomedicine-based cancer treatment can also contribute to the key challenges

Conclusion

Owing to their lesser side effects, affordability, accessibility, and possibly better cultural acceptability, herbal medicines constitute the backbone of primary health care for about 75–80% of the world population. At the front of cancer treatment, traditional medicines have been using plants as the main resource for antitumor drugs. Various studies have been carried out to explore the cytotoxic potential of phytochemicals and many of them have shown marked anticancer activity without significantly harming the normal cells of the body. Based on their remarkable pre-clinical results, many of the plant-derived drugs have advanced into clinical trials (Table 2) and a few of them could be envisaged to make their place in the treatment modalities against different kind of cancers in near future. For instance, analogs of plant-derived chemicals such as podophyllotoxins, taxol, vinca alkaloids, like vinblastine, and vincristine have been advanced from preclinical to clinical practices. Additionally, several newer compounds have shown excellent preclinical results against different cancers and are expected to be in clinical trials in the due course. Till date the 'EMT inhibiting potential' of different phytochemicals seems to be underutilized in clinical practice, though many of the phytochemicals have shown synergistic activity in combination with the existing drugs. The EMT inhibition is known to sensitize the tumors toward different anticancer drugs and reduce their metastatic potential as well. Therefore, the combinatorial therapeutic approach for the treatment of drug-resistant cancer based on phytomedicine (for EMT inhibition) and conventional treatment methods (for cytotoxicity etc.) could be the most sought of option in the future.

Different clinical trials along with pre-clinical results indicate that multiple molecular aspects as well as numerous phytochemicals are being explored to take them from bench to bedside, and in the future several valuable and novel therapeutic options based on phytomedicines would be available to the public for the treatment of different diseases including cancer.

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