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Anticancer potential of medicinal plants and their phytochemicals: a review

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Abstract In recent years, medicinal plants have attracted huge attention due to their diverse range of biological and therapeutic properties. Evidences have been accumulated since ages to demonstrate promising potential of medicinal plants used in various traditional, complementary, and alternative systems especially for cancer treatment. Although several medicines are available in the market to treat various types of cancers, no drug is found to be fully effective and safe as anticancer therapy. The major problem in the cancer chemotherapy is the prolonged toxicity of the well-established chemical drugs. However, plants and plant-derived products have been proved effective and safe in the treatment and management of various cancers to some extent. Many natural products and their analogs have been identified as potent anticancer agents, and anticancer properties of various plants or phytochemicals are being identified. Several plant-based anticancer agents including taxol, vinblastine, vincristine, camptothecin derivatives, topotecan, and irinotecan, as well as epipodophyllotoxins, are in clinical use all over the world. This review focuses on the application of medicinal plants and their phytochemicals as natural anticancer substances. In addition, this review will also discuss the Ayurvedic concept of using medicinal plants and their phytochemicals in traditional way for the treatment of various types of cancers. Further, a brief description will be given on the anticancer mode of action of various medicinal plants and their phytochemicals to understand the mechanisms at molecular level that alter growth and metabolism in cancer cells. Finally, this review will summarize the significance and innovative ways on using medicinal plants and their phytochemicals in anticancer therapy along with their future prospective in the treatment of cancer and related diseases.

Keywords Anticancer therapy · Ayurveda · Mechanism of action · Medicinal plants · Phytochemicals

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Introduction

Since decades, natural products especially plant-based secondary metabolites have been used for the treatment of various chronic diseases including cancer. Historically, plants as a whole or their extracted compounds have been used as medicines in Asian countries and Greece since ancient time, and an impressive numbers of modern drugs have been developed from them (Kharb et al. 2012). Several concerns on the efficacy of herbal medicines to boost immune cells of the body against cancer have been made. Accordingly, based on the reported details on complex synergistic interaction of various phytochemicals of anticancer potential, various herbal formulations have been designed to combat against cancerous cells without harming normal cells of the body (Larkin 1983; Saxe 1987). Cancer is a major public health burden in both developed and developing countries (Kharb et al. 2012). It is known to be one of the most important diseases among others, being treated by medicinal plants very frequently (Dixit and Ali 2010). Previously, an estimate of about 10.9 million new cancer cases, 6.7 million deaths, and 24.6 million persons living with cancer has been reported around the world every year (Parkin et al. 2005).

Since synthetic anticancer remedies are beyond the approach from low-income population due to high cost factor, medicinal plants and/or herbs play a significant role in primary health care system especially among rural population. The herbal medicines have played an important role in the prevention and treatment of cancer which execute their multiple therapeutic effects by inhibiting cancer activating enzymes and hormones, stimulating DNA repair mechanism, promoting production of protective enzymes, inducing antioxidant action and enhancing immunity, thus showing anticancer effect (Thakore et al. 2012). A number of medicinal herbs are being exploited in clinical trials along with vigorous investigations on plant phytochemicals to understand their anti-tumor mode of actions against various cancers (Rao et al. 2008). Cancer patients burdened with drug-induced toxicity are getting help from the complementary and alternative medicine in hope to find a better cure of cancer (Rao et al. 2008).

A number of reports have been focused on cancer drug discovery from natural sources literature in traditional material medica. A vast knowledge on the complex and synergetic understanding of different phytochemicals of plant origin may help in formulating effective candidates of anticancer potential (Merina et al. 2012). Several new chemo-preventive agents have been isolated and identified based on their ability to modulate one or more specific molecular events. The discovery of effective herbs and elucidation of their underlying mechanisms could lead to the development of an alternative and complementary method for cancer prevention and/or treatment. A number of plant-based anticancer compounds such as vinblastine, camptothecin, and taxol have been isolated and characterized from different plant species including *Taxus brevifolia*, *Camptotheca acuminate,* and *Catharanthus roseus*, respectively, which have been found to work effectively against various cancers (Cragg and Newman 2005).

Since conventional therapeutic strategies have shown negative outputs to fulfill the essential requirements for successful cancer therapy, alternatives on anticancer molecules from plant origin have gained huge attention, which are cost effective and safe in use due to being of natural in origin. Hence, effective utilization of plant formulation or herbal extracts can be exploited to certain extended levels in anticancer therapy, especially in India. India has vast diversity of thousands of plant species known for their tremendous medical potential since decades. From the last few decades, universal acceptance has been made on the use of herbal medicines showing an impact on both world health care system and international trade of herbal medicine. It has been confirmed that medicinal plants have played an important role in the healthcare system of a large number of the world's population (Akerele 1988). Recently, use of plants and plant-based phytomedicines has increased dramatically in the USA due to their being less toxic and natural origin. In fact, there are several medicinal plants all over the world, including India, which are being used traditionally for the prevention and treatment of various cancers. In this review, we focused on the application of medicinal plants and their phytochemicals as natural anticancer substances. This review will also provide information on the Ayurvedic concept of using medicinal plants and their phytochemicals in anticancer therapy. A brief description has also been given on the anticancer mode of action of various medicinal plants and their well-known biologically active phytoconstituents to visualize their effect on the metabolism of cancer cells. Finally, this review will summarize the significance and importance of using medicinal plants in anticancer therapy along with their bioactive components with updated information on their clinical efficacy and optimum doses in cancer prevention.

Cancer-causing genes and their action

There are four main types of gene involved in cell division. Most tumors have faulty copies of more than one of these genes which include the followings:

Oncogenes (OG): Ontogenesis genes, under normal conditions, play a role encouraging the cells to start dividing. On the activation of oncogenes, they speed up the growth rate of cells. Cancer is occurring when one of the oncogenes got damaged. It works as an accelerator stacking down the cell along with daughter cells, going to be instructed permanently to divide the cell (Dhanamani et al. 2011).

Tumor suppressor genes (TSG): TSG was co-discovered in 1979 by a UK scientist David Lane. TSG make proteins whose normal function is the opposite to that of ontogenesis. P53 is called one of the most important tumor suppressor genes in cancer disease (Dhanamani et al. 2011).

Suicide genes (SG): Apoptosis or cell suicide is considered to be a highly complex and hugely important process. In usual, cells have the ability to commit suicide when something happens wrong in order to prevent damage to their neighbors. A number of SG are associated in cancer diseases. Upon damage of SG, a faulty cell can keep dividing and becomes cancerous (Dhanamani et al. 2011).

DNA repair genes (DRG): The DNA present in the every cell of the body is under constant assault from a variety of directions (Dhanamani et al. 2011).

Causes of cancer

It has been reported that the most common cause of cancer is caused by genetic disorders and inheritance, and the

incidences are higher among the patients with positive family history. Exposure to radiation is considered another cause of cancer in which nearly all tissues are susceptible to tumor induction with variable sensitivity. Tobacco smoke inhalation is known to be the principle carcinogenic agent in the environment, responsible for lung cancer with higher percentage rate in smokers than non-smoker population. Cancer is also induced by variety of factors in oral cavity, esophagus, kidney, bladder, and pancreas. In addition, dreadful cause of cancer induction includes occupational exposure in working sectors. Although there have been extensive researches on virus oncology, they are linked to occurrence of various organ-specific cancer inductions in varied critical situations including Hepatitis B infection and are correlated with hepatocellular carcinoma. Moreover, the ultimate cause regardless of above-mentioned points is the frequent exposure to carcinogenic agent (Harrison 1998). Major causes of cancer include (i) environmental and occupational exposure such as ionizing, UV radiation, and exposure to chemicals including vinyl chloride, benzene, and asbestos; (ii) life style factors such as high fat, low-fiber diets, tobacco, and ethanol; (iii) medication such as alkylating agents and immunosuppressants; and (iv) genetic factors such as inherited mutations, cancer-causing genes, and defective tumor suppressor genes.

Ayurvedic concept of cancer

In Ayurveda, equivalents of cancer are described as "granthi" and "arbuda" (Prakash et al. 2013). Granthi and arbuda can be inflammatory or devoid of inflammation, based on the doshas involved (Kapoor 1990). Three doshas including vata, pitta, and kapha are responsible for disease in the body, and the balanced coordination of these doshas in body, mind, and consciousness makes the real definition of health in Ayurveda (Balachandran and Govindarajan 2005). Tridoshicar budas are usually malignant because all three major body humors lose mutual coordination, leading to a morbid condition (Singh 2002). In Ayurveda, neoplasm can be classified into following groups depending upon various clinical symptoms in relation to tridoshas:

Group I consists of diseases that can be named as clear malignancies, including arbuda and granthi, as well as mamsarbuda (sarcomas), raktarbuda (leukemia), mukharbuda (oral cancer), and asadhya vrana (malignant ulcers) (Prakash et al. 2013).

Group II consists of diseases that cannot be considered real cancers; however, they can be considered probable malignancies such as ulcers and abnormal organ or tissue growths. The most reported cases of group II diseases include mamsaja oshtharoga (growth of lips), asadhya galganda (incurable thyroid tumor), tridosaja gulmas, and asadhya udara roga (abdominal tumors like carcinomas of the stomach and liver or lymphomas) (Prakash et al. 2013).

Group III diseases include possible cases of diseases which can result in malignancy, such as visarpa, asadhya kamala (incurable jaundice), and asadhya pradara (intractable sinusitis) (Prakash et al. 2013).

Important plants clinically used for the treatment of cancer

Commonly used herbal decoctions reported in Ayurveda are made of multiple herbs possessing great potential for a cancer cure; scientifically, these formulations work effectively through multiple biochemical pathways and influence different organ systems and nourish the body as a whole by supporting body's deference systems. Medicinal plants and herbs improve healing process, and reduce the adversary effects and cancer-associated complications (Ganguly 2014). Each medicinal plant or herb contains multiple active compounds that work synergistically producing therapeutic benefits and lowering the risks of adverse effects, and avoids the need for supplemental therapy to manage cancer cachexia. This has made significantly needed to promote the use of natural Ayurvedic therapies for curing variety of cancers and suggest an integrated approach in tumor management and treatment (Patel et al. 2010). A number of important plants of medicinal values have been used for the treatment of various cancers which include the followings:

Allium sativum has been used for the treatment of number of diseases including cardiovascular atherosclerosis, HIV drug-induced lipid disorders, cancer prevention, cold, flu, and prevention of tick bite (Bloch 2000) which seems to be acting affectively against erythroleukemia as well as breast and prostate cancer cells (Zhang et al. 1998). Anticancer potential of *A. sativum*-derived hydroalcoholic extract displayed dose-dependent anti-proliferative effects on human liver carcinoma cell line (HepG2) (Chaudhary et al. 2012). The two major compounds in garlic such as *S*-allylcysteine and *S*-allylmercapto-L-cysteine have been found to be potent antioxidant molecules (Thomson and Ali 2003). In addition, some organosulfur compounds derived from *A. sativum*, including *S*-allylcysteine, have been found to retard the growth of chemically induced and transplantable tumors in several animal models (Thomson and Ali 2003). Epidemiological and animal studies have suggested that extractives of *A. sativum* and its organosulfur constituents, such as *S*-allylcysteine and *S*-allylmercaptocysteine, have anti-carcinogenic effects. Further, a preliminary double-blind, randomized clinical trial using high-dose AGE (AGE 2.4 ml/d) as an active treatment and

low-dose AGE (AGE 0.16 ml/d) as a control was performed to confirm these effects in humans with colorectal adenomas-precancerous lesions of the large bowel (Tanaka et al. 2006). Shirzad et al. (2011) also reported that in a preclinical trial, BALB/c mice were injected with WEHI-164 tumor cells and divided into six groups. The treatment group received boiled garlic extracts at 20 mg/kg/0.2 ml. Three weeks following tumor inoculation, the mean tumor size in garlic extract-treated groups was reduced with significant reductions compared with the control group (Shirzad et al. 2011).

Aronia melanocarpa, a rich source of polyphenols and anthocyanin can stimulate circulation, protect urinary tract, and strengthen heart function ability. Due to its potent antioxidant ability, it is considered to be a highly active molecule against the degenerative diseases caused by free radicals or oxygen reactive species as a dietary preventative. A number of researches have been reported on therapeutic efficacy of *A. melanocarpa* to treat colorectal cancer, colon cancer, cardiovascular disease, chronic inflammation, gastric mucosal disorders (peptic ulcer), eye inflammation, and liver failure (Malik et al. 2003; Han et al. 2005; Ohgami et al. 2005; Lala et al. 2006). Recent studies on *A. melanocarpa* have confirmed that anticancer potential of *A. melanocarpa* is associated predominantly with its bioactive components such as chlorogenic acids, some cyanidin glycosides, and derivatives of quercetin (Sharif et al. 2012). *A. melanocarpa* juice has also been found to induce apoptosis of different human lymphoblastic leukemia cells (HSB-2, Molt-4, and CCRF-CEM). In addition, recent research confirmed that *A. melanocarpa* juice containing several polyphenols displayed strong pro-apoptotic effect in human primary lymphoblastic leukemia cells but not in human normal primary T-lymphocytes (Sharif et al. 2012), exhibiting anticancer activity through a redox-sensitive mechanism in the p53-deficient Jurkat cells (Sharif et al. 2012). Another model study conducted by Bermudez-Soto et al. (2007) demonstrated that prolonged exposure to *A. melanocarpa* juice exerted potent anti-proliferative effect toward the human colorectal cancer cell line Caco-2 which might be mediated through arrest of the cells at the G/M checkpoint. Further, changes in the mRNA levels of several tumor markers typical for colon cancer and of proteins involved in proliferation and cell cycle as confirmed by gene expression analysis confirmed the role of *A. melanocarpa* in cancer treatment. In a study performed by Sueiro et al. (2006), anthocyanins (25 μg/ml) derived from *A. melanocarpa* remarkably inhibited the generation and release of superoxide radicals by human granulocytes, and some of the sub-fractions extracted from *A. melanocarpa* showed >90 % inhibitory effect on L1210 leukemia cells at 50 μg/ml. Results of Lala et al. (2006) showed a protective effect of *A. melanocarpa* extract in colon carcinogenesis and hypothesized multiple mechanisms of action. Moreover, the extract from *A. melanocarpa* has also shown anticancer effects through mediating the increase of tumor suppressor genes as well as by reducing oxidative stress eventually resulting in DNA damage important for the proliferation of cancer cells. Recently, Thani et al. (2014) also reported the effect of *A. melanocarpa* extract alone (IC_{75} value; 1 μg/ml) or in combination with gemcitabine to assess the growth of the AsPC-1 cell line. Gemcitabine in combination with *A. melanocarpa* extract was found more effective than gemcitabine alone. TUNEL assays showed apoptosis to be a mechanism occurring at 1 μg/ml concentration of *A. melanocarpa* extract, with apoptotic bodies detected by both colorimetric and fluorometric methods.

Camellia sinensis also known as green tea is used in the treatment of prostate, colon, and gastric cancers by preventing blood vessel growth in tumors (Taylor and Wilt 1999). Efficacy of green tea has also been confirmed to cure skin cancer caused by ultraviolet radiation (Katiyar et al. 2000). Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in green tea (Cao and Cao 1999). Epidemiological studies have been confirmed that epigallocatechin-3-gallate (EGCG), a potent polyphenol present in green tea, has been found to play an important role on inhibiting the invasion and migration of human colon and oral cancer cells which can be correlated with the decreased production of MMP-2, MMP-9, and uPA (Ho et al. 2007). In addition, EGCG has not only been found to inhibit the growth of cancer cell lines including hepatocellular carcinoma through induction of cell cycle arrest (Nishikawa et al. 2006), but it also inhibits growth of ovarian carcinoma cell lines HEY and OVCA, human colon, and rectal cancer cell lines HT-29 and HCA-7 (Spinella et al. 2006a, b). Apart from EGCG, other flavonoid compounds such as rutin and quercetin have also been found to contribute with anti-carcinogenicity through inhibition of oxidative activation (Hu et al. 2005). Recently, it has been reported that *C. sinensis* extract remarkably inhibited the proliferation of HT-29 cells with an IC_{50} of 87 μg/ml (Hajiaghaalipour et al. 2015). The extract increased the levels of caspase-3, -8, and -9 activities in the HT-29 cells. DNA damage in 3T3-L1 normal cells was detected using the comet assay. The extract protected 3T3-L1 cells against H_2O_2-induced DNA damage. The results of this study confirmed that white tea has antioxidant and anti-proliferative effects against cancer cells, but protect normal cells against DNA damage. In addition, epidemiological studies suggested that *C. sinensis* exhibits anti-proliferative effects against colonic tumorigenesis due to its rich diversity for the presence of several polyphenol compounds which might be correlated to its potent radical scavenging and anti-oxidative efficacy

(Yang and Wang 1993). Luo et al. (2014) also reported that *C. sinensis* extract induced 4T1 apoptosis in a dose-dependent manner as assessed by annexin-V and propidium iodide staining and caspase-3 activity. *C. sinensis* also inhibited 4T1 cell migration and invasion at 0.06–0.125 mg/ml (Luo et al. 2014). In addition, *C. sinensis* extract (0.6 g/kg, orally fed daily for 4 weeks) was effective in decreasing the tumor weight by 34.8 % in female BALB/c mice against control (Luo et al. 2014). Apart from the anti-tumor effect, *C. sinensis* extract significantly decreased lung and liver metastasis in BALB/c mice bearing 4T1 tumors by 54.5 and 72.6 %, respectively (Luo et al. 2014). Furthermore, micro-computed tomography and osteoclast staining analysis confirmed that *C. sinensis* extract was effective in bone protection against breast cancer-induced bone destruction.

Catharanthus roseus, a medicinal plant has a long history of using as a diuretic, anti-dysenteric, hemorrhagic, and antiseptic agent as well as used in the treatment of diabetes in Jamaica and India (Mouli et al. 2009). Some alkaloids isolated from the leaves of *C. roseus* such as vinblastine and vincristine have been shown to work as anticancer drugs. Specifically, vinblastine in combination with other anticancer agents is used for the treatment of lymphocytic lymphoma, Hodgkin's disease cancer, lymph glands, spleen, liver, testicular carcinoma, and choriocarcinoma cells (Mouli et al. 2009). On the other hand, vincristine is used in acute leukemia, lymphosarcoma, and Wilm's tumor (Virmani et al. 1978). These alkaloids synergistically in combination with other cancer drugs are used in chemotherapy for the treatment of a variety of cancers including leukemia, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma (Cragg and Newman 2005). Recently, Widowati et al. (2013) observed that *C. roseus* was able to reduce T47D cell proliferation with a median inhibition concentration (IC_{50}) of 2.8 %. Also, the apoptotic analysis result showed that *C. roseus* was able to induce apoptosis by 37.67 %, meanwhile doxorubicin at 10 μg/ml induced apoptosis by 36.06 % (Widowati et al. 2013).

Datura metel is a well-known medicinal plant with a majority of phytochemicals called alkaloids which have not only been found to exert potent anticancer and anti-tumor activities but also they exert narcotic, anthelmintic, spasmolytic anesthetic, sedative, ophthalmic, antirheumatic, antiasthmatic, antidiarrhoeal, and anticatarrhal activities (Thakur et al. 1989). Concerning its potent biological efficacy, each part of this plant has shown diverse range of pharmacological activities. The leaf of *D. metal* has shown antitumour, antirheumatic, and vermicidal effects, whereas floral parts have been found to exert antiasthmatic and anesthetic properties and are used in the treatment of swellings and eruptions on face. Besides, fruits of *D. metal* have been used for earache and seed decoction in ophthalmia (Mouli et al. 2009). Hyoscyamine, hyoscine, and meteloidine are known to found the major alkaloid compounds in *D. metal* with potent pharmaceutical interest. In concern to clinical utility, *D. metel* has a wide range of traditional applications, including the treatment of epilepsy, hysteria, insanity, heart diseases, fever, diarrhea, and skin diseases. Crushed leaves are used to relieve pain (Kam and Liew 2002). In China, the plant is used in the treatment of asthma. About 3–5 g of the flower extract can be used as an anesthetic through oral consumption that produces general anesthesia within 5 min, which lasted for about 5–6 h. The flowers of the *D. metel* are used in the treatment of pain, chronic bronchitis, and asthma (Kam and Liew 2002).

Momordica charantia, a medicinal plant, has been found to show antimicrobial, antiviral (anti-HIV), antitumor, and anti-mutagenic effects (Lee et al. 1995; Chiampanichayakul et al. 2001; Nagasawa et al. 2002). Specifically, methanolic extract of *M. charantia* exhibited cytotoxic effect against various cancer cell lines including four human cancer cell lines, hone-1 nasopharyngeal carcinoma, AGS gastric adenocarcinoma, HCT-116 colorectal carcinoma, and CL1-0 lung adenocarcinoma cells with IC_{50} value ranging from 0.25 to 0.35 mg/ml (Li et al. 2012). Cell death induced by the methanolic extract of *M. charantia* was found to be time-dependent in these cell lines. This plant has shown great efficacy in South America to control constipation and dysentery. The root of *M. charantia* is known to work as aphrodisiac. The leaf and aerial parts of *M. charantia* are used in the treatment of measles and variety of inflammatory disorders in Peruvian herbal medicine. In Nicaragua, the leaves of *M. charantia* are commonly used to treat stomach pain, fever, cold, cough, headache, skin complaints, menstrual disorders, aches, and hypertension. In addition, a cucurbitane-type triterpene isolated from wild bitter gourd induced apoptotic death in breast cancer cells through peroxisome proliferator-activated receptor (PPAR) γ activation (Weng et al. 2013). Also, the extract of *M. charantia* significantly reduced the cell proliferation and induced apoptotic cell death in human breast cancer cells, MCF-7 and MDA-MB-231 which was accompanied by increased poly(ADP-ribose) polymerase cleavage and caspase activation (Ray et al. 2010).

Gymnema sylvestre (Asclepiadaceae), popularly known as "gurmar" for its distinct property as a sugar destroyer, is a reputed herb in the Ayurvedic system of medicine. The phytoconstituents responsible for sweet suppression activity include triterpene saponins known as gymnemic acids, gymnemasaponins, and a polypeptide, gurmarin (Tiwari et al. 2014). The leaves of *G. sylvestre* contain triterpene saponins belonging to oleanane and dammarane classes.

The major constituents such as gymnemic acids and gymnemasaponins are members of oleanane-types of saponins, whereas gymnemasides represent to dammarane types of saponins (Foster 2002; Khramov et al. 2008). Other phytochemicals present in *G. sylvestre* include anthraquinones, flavones, hentriacontane, pentatriacontane, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin-related glycosides, stigmasterol, and calcium oxalate which have shown great potential of biological efficacy (Sinsheimer et al. 1970). The leaves of *G. sylvestre* have been found to possess alkaloids, glycosides, and anthraquinones and their derivatives (Dateo and Long 1973). Previously, anticancer potential of gymnemagenol was determined on HeLa cancer cell lines (Jain et al. 2007). In addition, cytotoxic effect of *G. sylvestre*-derived saponins was determined by MTT cell proliferation assay, and it was found that gymnemagenol at different concentration (5, 15, 25, and 50 μg/ml) remarkable cytotoxic effect (73 %) with an IC_{50} value of 37 μg/ml on HeLa cells. The isolated bioactive constituent, gymnemagenol, was found to show a high degree of inhibition to the proliferation of HeLa cancer cell line with a profound confirmation that these saponins did not reveal toxic effect on the growth of normal cells in vitro (Khanna and Kannabiran 2009). With the rising percentage of cancer in people, the herbal formulation of *G. sylvestre* could be a prospective medication in cancer therapy.

Scutellaria is a genus of traditional herbal species with remarkable anticancer potential. Common biologically active flavonoids found in *Scutellaria* species include apigenin, baicalein, baicalin, chrysin, scutellarein, and wogonin. These flavonoids have been found to exhibit antitumor activity and shown positive interactions with different mechanisms of actions. In addition, leaf extracts of some selective species such as *Scutellaria angulosa, Scutellaria integrifolia, Scutellaria ocmulgee,* and *Scutellaria scandens* have shown potent anticancer efficacy (Parajuli et al. 2009). Yin et al. (2004) revealed the anti-tumor effect of *Scutellaria barbata* with a defined mode of action on human lung cancer cell line A549. It was found that ethanol extract of *Scutellaria barbata* significantly reduced the growth of A549 cells with an IC_{50} value of 0.21 mg/ml. Based on these results, similar compound tanshinone IIA was isolated from *Scutellaria* herbs, and it was hypothesized that this compound may also have potential anticancer activity on breast cancers, apoptosis, signal transduction, cell proliferation, transcriptional regulation, angiogenesis, invasive potential, and metastatic potential of cancer cells (Wang et al. 2005). Further, Lee et al. (2008) confirmed that microarray and pathway analysis of tumor-related genes may identify the differential expression of the genes responding to tanshinone I, suggesting that tanshinone I may show potent anticancer activities. Recently, it has been proved that some of the species belonging to genus *Scutellaria* such as *S. baicalensis* and *S. litwinowii* have shown efficient potential of anticancer efficacy both in vitro and in vivo models (Zahra et al. 2010).

Nelumbo nucifera, also known as "lotus," has shown diverse range of biological and therapeutic potential. The ethanolic extracts of *N. nucifera* were found to inhibit the cell proliferation and cytokines in primary human peripheral blood mononuclear cell (Liu et al. 2004). Further, a bioactive compound 7-hydroxydehydronuciferine isolated from *N. nucifera* significantly inhibited the proliferation of melanoma, prostate and gastric cancer cells (Liu et al. 2014). In addition, Yoon et al. (2013) demonstrated potential efficacy of neferine isolated from *N. nucifera* which induced ER stress and apoptosis, acting through multiple signaling cascades by the activation of Bim, Bid, Bax, Bak, Puma, caspases-3, -6, -7, -8, and PARP. Also, neferine dramatically upregulated the protein expression levels of Bip, calnexin, PDI, calpain-2, and caspase-12 (Yoon et al. 2013). Yang et al. 2011 also investigated the anti-tumor effect of Yang et al. (2011) and reported the anti-tumor effects of leaf extract of *N. nucifera* on human MCF-7 cell line in vitro and in vivo. It was found that leaf extract of *N. nucifera* at the concentration of 0.5 and 1 % significantly reduced the volume and weight of tumor in experimental mice inoculated with MCF-7 cells as compared to the control. It was confirmed in this study that sufficient rate of cell cycle arrest was achieved by the treatment of *N. nucifera* leaf extract, leading to tumor regression, thus exerting anticancer effect (Yang et al. 2011). Recently, our research group also observed in vivo anti-angiogenic activity of N. nucifera Leaf methanol extract in a chick chorioallantoic membrane (CAM) model using fertilized chicken eggs, in HUVECs using cell viability, cell proliferation, and tube formation assays, and by determining intracellular ROS in vitro. It was found in our study that *N. nucifera* leaf extracts (10–100 μg/ml) exhibited significant and dose-dependent inhibition of vascular endothelial growth factor (VEGF)-induced angiogenesis, as well as VEGF-induced proliferation and tube formation in HUVECs. Moreover, *N. nucifera* leaf extracts significantly blocked VEGF-induced ROS production in HUVECs, confirming their possible anti-angiogenic mechanism (unpublished data).

Oroxylum indicum (Sonapatha) is a medicinal plant used in various polyherbal formulations in traditional Indian system of medicine. Studies have proved anticancer potential of *O. indicum* using various in vitro and in vivo models. As reported previously, ethanolic extract of *O. indicum* at a concentration of 0.05 % exhibited potent cytotoxic activity against Hep2 cell lines (Narisa et al. 2006). A flavonoid baicalein (25–30 mM) isolated from *O. indicum* was found to exhibit anti-tumor effect on human

Table 1 List of some important medicinal plants with a profile of major anticancer phytochemicals

Botanical name	Family	Phytochemical	Specific cancer	Reference
Allium sativum	Liliaceae	Allin	Carcinoma of human (mammary) gland	Sabnis (2006)
Aloe vera	Liliaceae	Polysaccharides, emodin	Anti-angiogenic activity	Sabnis (2006)
Curcuma longa	Zinziberaceae	Curcumine	Stomach cancer	Agarwal et al. (2003)
Linum usitatissimum	Linaceae	Cynogenetic glycosides	Breast cancer	Sakarkar and Deshmukh (2011)
Emblica officinalis	Euphorbiaceae	Polyphenols, tannins	Lymphoma, melanoma	Merina et al. (2012)
Momordica charantia	Cucurbitaceae	Charantin, cucurbitane-type triterpene	Colon cancer, breast cancer	Sabnis (2006); Weng et al. (2013)
Boerrhavia diffusa	Boraginaceae	Punarnavine	Malignant melanoma cancer	Merina et al. (2012)
Stevia rebaudiana	Asteraceae	Labdane sclareol properties	Anti-tumorous and cytotoxic	Kaushik et al. (2010)
Nelumbo nucifera		Neferine	Anti-tumorous	Yoon et al. (2013)
Gymnema sylvestre	Asclepiadaceae	Gymnemagenol	Anticancer	Jain et al. (2007)

cancer cell lines and inhibited the 50 % proliferation of HL-60 cell lines (Roy et al. 2007). In addition, methanolic extract of *O. indicum* strongly inhibited the mutagenicity of Trp-P-1 in Ames test (Nakahara et al. 2001). Administration of crude fractions of *O. indicum* at the concentration range of 0.25–2 g/kg body weight has been found to be genotoxic and showed cell proliferative activity in the pyloric mucosa of rat stomach (Tepsuwan et al. 1992). Also, ethanolic extract derived from *O. indicum* has been found to exert potent toxicity effect on tumor cell lines such as CEM, HL-60, B-16, and HCT-8 with an IC_{50} value of 19.6, 14.2, 17.2, and 32.5 μg/ml, respectively (Lotufo et al. 2005). Moreover, recent study confirmed that methanolic and aqueous extracts of *O. indicum* have been found to demonstrate extensive cytotoxicity in selected cell lines and found to moderate levels of DNA protection from oxidative stress (Kumar et al. 2010).

Ocimum sanctum, commonly known as Tulsi, is a medicinal herb, and found in semitropical and tropical parts India. It has been found to exert number of human health beneficial effects. A number of biologically active compounds have been isolated and characterized from *O. sanctum* with potent biologically efficacy. The major bioactive compound in the leaf essential oil of *O. sanctum* has been reported to be eugenol along with other bio-significant components including caryophyllene, terpineol, decyladehyde, selinene, α-pinene, camphor, and carvacrol (Prakash and Gupta 2005). Different parts of *O. sanctum* have been found to display number of medicinal properties along with their diverse therapeutic potential to serve as expectorant, analgesic, anticancer, antiasthmatic, antiemetic, diaphoretic, antidiabetic, antifertility, hepatoprotective, hypotensive, hypolipidmic, and anti-stress agents (Dixit and Ali 2010). Administration of *O. sanctum*-derived formulations to experimental mice mediated a significant reduction in sarcoma-180 solid tumor volume and increased the life span, confirming its medicinal potential as potent anticancer agent (Dixit and Ali 2010). A brief description of some important medicinal plants with a profile of major anticancer phytochemicals has been summarized in Table 1.

Plant-derived anticancer agents in clinical use

The vinca alkaloids such as vinblastine and vincristine isolated from periwinkle plant, *Catharanthus roseus,* opened a new era on the use of plant materials as anticancer drugs. The first clinical trial was performed to advance these alkaloids to serve as anticancer agents (Cragg and Newman 2005). Primarily, vinblastine and vincristine were used in combination with other chemotherapeutic drugs for the treatment of a variety of cancers including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma (Cragg and Newman 2005).

Further, a new anticancer drug paclitaxel was isolated from yew tree (*Taxus brevifolia*) leading to its structural determination which was first successfully used in clinical trials in the US in 1990s (Wani et al. 1971; Rowinsky et al. 1992). Paclitaxel has shown great potential of medicinal importance and has been found significantly active against ovarian cancer, advanced breast cancer, and small and non-small cell lung cancer (Rowinsky et al. 1992).

Another research led to the identification of camptothecin, firstly isolated from the Chinese ornamental tree *Camptotheca acuminate* which advanced to clinical trials by NCI in the 1970s effectively; however, due to several

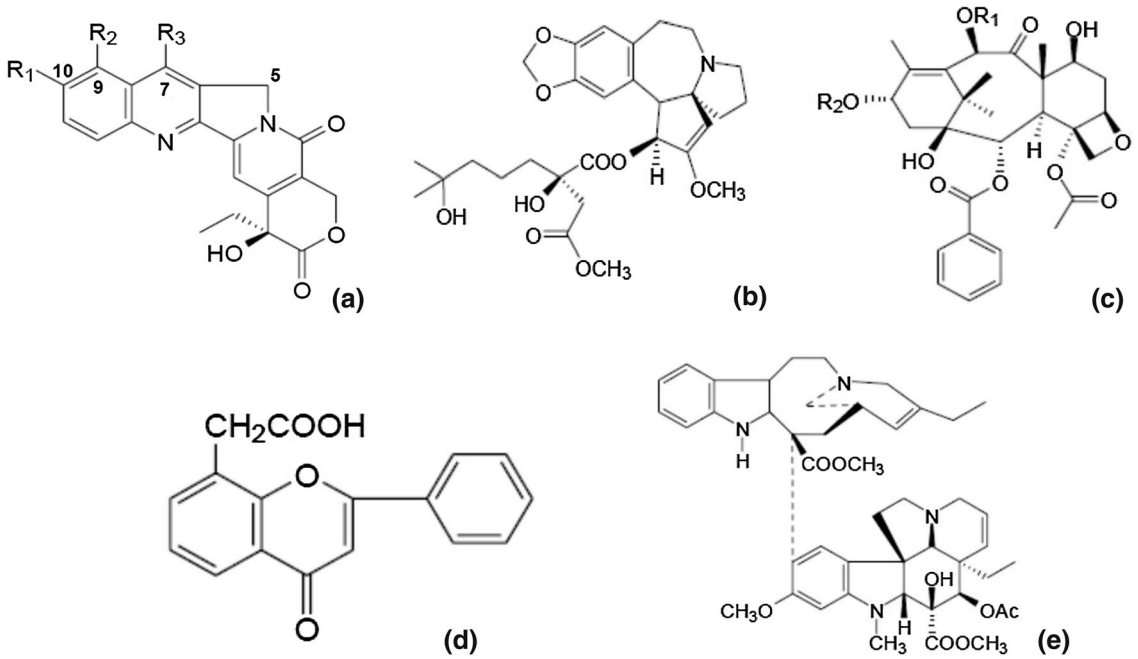

Fig. 1 Chemical structures of few selected natural anticancer compounds **a** camptothecin, **b** homoharringtonin, **c** taxol, **d** flavone-8-acetic acid; and **e** vinorelbine

disputes on its sever bladder toxicity, it became a major issue of ongoing research in cancer therapy (Potmeisel and Pinedo 1995). Some of the semi-synthetic derivatives of camptothecin such as topotecan and irinotecan have been used successfully in the treatment of ovarian and small cell lung cancers, as well as colorectal cancers (Creemers et al. 1996; Bertino 1997).

Continued research on anticancer drug development resulted in the discovery of homoharringtonine, a cytotoxic alkaloid isolated from the evergreen Chinese tree *Cephalotaxus harringtonia* var. *drupacea* with clinical application (Itokawa et al. 2005; Powell et al. 1970). It works on 80S ribosome in eukaryotic cells and inhibits protein synthesis by interfering with chain elongation. Homoharringtonine also blocks progression of leukemic cells. A racemic mixture of harringtonine and homoharringtonine has been used successfully in China for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia (Kantarjian et al. 1996; Cragg and Newman 2005). Elliptinium, a derivative of ellipticine, isolated from a Fijian medicinal plant *Bleekeria vitiensis*, has been effectively used clinically in France for the treatment of breast cancer (Cragg and Newman 2005).

Chemistry of natural products resulted in the isolation of two novel alkaloids, schischkinnin and montamine from the seeds of *Centaurea schischkinii* and *Centaurea montana* (Shoeb et al. 2006). Later, schischkinnin and montamine showed significant anticancer potential in human colon cancer cell lines. The unique structural features of schischkinnin and montamine can be exploited as a template to certain extent level of drug discovery for developing compounds of interest with enhanced anticancer activity.

Moreover, a selectively cytotoxic compound Pervilleine A has been found to active against a multidrug resistant (MDR) oral epidermoid cancer cell line (KB-V1) in combination with other chemotherapeutic agent vinblastine (Mi et al. 2003). Increased demand of effective anticancer molecules has opened a new platform for testing pervilleine A in pre-clinical trials (Mi et al. 2003). In addition, silvestrol, a translation inhibitor, was first isolated from *Aglaila sylvestre* fruit (Hwang et al. 2004). Although silvestrol has been found to exhibit cytotoxicity against lung and breast cancer cell lines (Cragg and Newman 2005), a precise anticancer mode of action is still with unknown status. Chemical structures of few selected anticancer compounds have been provided in Fig. 1.

Anticancer mode of action of phytochemicals

A plethora of scientific reports have claimed the pharmacological potential of plant-based biologically active compounds or phytochemicals, especially with increasing search of new and highly effective candidates in anticancer therapy. Phytochemicals as biological targets of interest have been found to be involved with inflammatory process and oncogenic transformation in mammalian cells

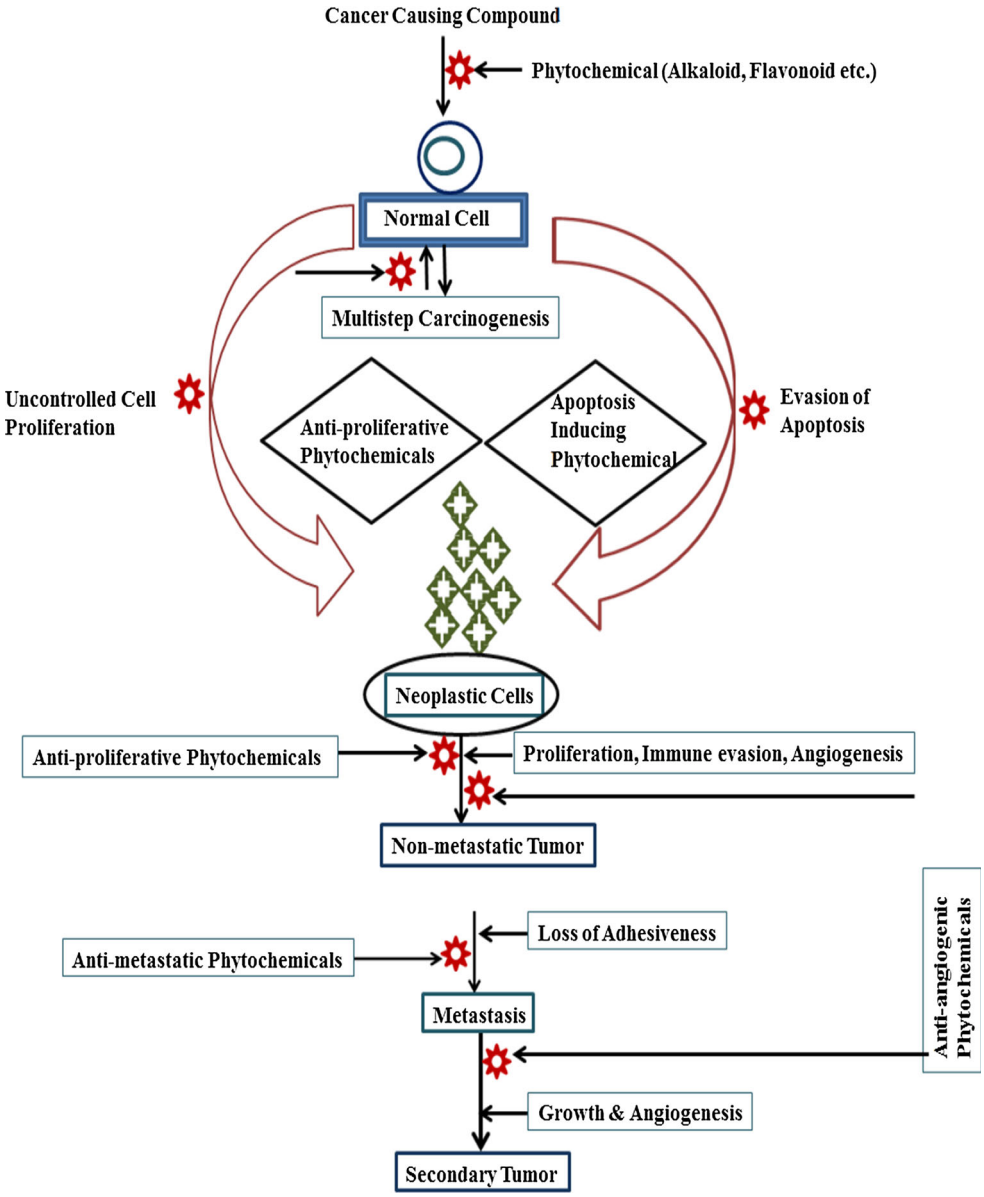

Fig. 2 Schematic representation of possible anticancer modes of action of phytochemicals (Modified and adopted from Aggarwal and Shishodia 2006; Russo et al. 2010; Rahman and Khan 2013)

which include alteration of cell cycle control, evasion of apoptosis, angiogenesis, and metastases (Surh 2003). In addition, epidemiological studies have suggested that the daily intake of certain phytochemicals can reduce the incidence of several types of cancers (Russo et al. 2010). Hence, uptake of dietary phytochemicals in chemo-prevention may immerge as one of the most promising approaches with reduced risk of cancer development. On the other hand, phytochemicals act synergistically with other chemo-preventive agents to overcome the resistance development in cancer cells, leading to utilization of the lowest amount of cancer drugs with increased anticancer efficacy (Liu 2004). Interestingly, as reported previously, approximately 80 % of the world's inhabitants rely on traditional plant-derived medicines for their primary health care (Farnsworth et al. 1985). Investigation of the underlying pharmacokinetic mechanisms through which phytochemicals evoke their anticancer effect introduces a panel of molecular targets. This panel includes apoptotic proteins (caspases and bax), protein kinases (PKA, PKC, MAPK, and TYK2), anti-apoptotic proteins (bcl2, TRAF1, and survivin), growth factors (TNF, EGF, FGF, and PDGF), transcription factors (Ap1, NF-κB, Nrf2, and p53), cell adhesion molecules (ICAM-1 and VCAM), and cell cycle proteins (Cyclin D, CDK1, CDK2, p27, and p21). Along with this, interference of phytochemicals has also been shown with multiple cell signaling pathways (Aggarwal and Shishodia 2006). A schematic diagram of the generalized anticancer mechanisms of phytochemicals has been illustrated in Fig. 2.

Significance and future perspective of herbs in cancer therapy

In recent years, plant-derived phytochemicals possessing anticancer activities have received huge amount of common and scientific attention due to the adverse effects of chemo-prevention and radiation therapies. Biologically, active secondary metabolites as phytoconstituents derived from traditional medicinal plants have been found to possess various anticancer and chemo-protective effects, and they are considered safer for long-term therapies in cancer patients. These phytochemicals provide adequate nutrition and reduce the side effects of conventional cancer therapy due to their being potent antioxidants in nature. Although variety of new natural products with efficient biological efficacy are yet to come out from the folk medicines, they might be endangered due to the fast disappearance of tropical rainforests leading to new and uninvestigated plant species being extinct. However, traditional folk medicine system of India, called Ayurveda, has ever shown successful history of using medicinal natural herbal drugs from very early times in preventing or suppressing various tumors using various lines of treatment (Premalatha and Rajgopal 2005). Ayurvedic therapies have been found to be able to cure these chronic diseases in better ways, which were previously not amenable to treatment by western medical practices. The traditional Indian Ayurvedic medicine system with its evolution through centuries has always fascinated practitioners and researchers for its applications in cancer treatment on a scientifically proven research background. This may give good drug leads for cancer treatment since it is a well-proven therapy for centuries; hence, its systematic study and understanding is worth considering by pharmaceutical industries in order to develop their active ingredients as allopathic drugs for cancer treatment (Premalatha and Rajgopal 2005).

Concluding remarks

A number of important medicinal plants have been widely used world-wide for the treatment of various cancers in a traditional way for several generations. The variation in geography and environment of this region provides a rich plant biodiversity, many of which can be used as the sources of potent anticancer agents. Since the use of phytochemicals in cancer treatment is promising and increasing rapidly, the proper scientific study with diverse and biologically significant chemical structures of target phytochemicals along with their detailed anticancer role with clinical studies might be interesting subject of future cancer research.

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