

Medicinal Plants in the Management of Cancer: A Review

Abstract

Globally cancer is one of the commonly life-threatening diseases which severely affect the human being. It is recognized by the uncontrollable division of cells. There is a demand for new methods to prevent this disease. Conventional therapies have several adverse effects on the on healthy cells, therefore, an alternative and effective medication are required to combat this disease. Benefits of using plant derive product over synthetic medicine have increased the importance of medicinal plants in the field of healthcare. Many plants derive product shows potent in cancer treatment by inhibiting cancer activating enzymes, stimulate DNA repair mechanism, induce antioxidant action, and promote protective enzymes production. In the present review, an effort has been done to provide information about the various compounds present in the medicinal plants that have shown potent activity against various forms of cancer.

Keywords: Anticancer activity; Cytotoxic effect; Medicinal plants; Phytocompounds

Review Article

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Introduction

Plants have always been a basis for the traditional medicine systems and they have provided continuous remedies to the mankind for thousands of years. Knowledge of the medicinal plants for the preparation of various drugs has been of great significance [1]. Medicinal plants are considered as a rich source of wide variety of ingredients which can be used for the development of drug. Cancer is a one of the deadly diseases which is characterized by irregular cell proliferation. It is the major health issue in developing and developed countries. The most common reason behind the cancer is changing lifestyle and due to this it become a global problem across the world. Thus there is an urgent need to find better treatment possible for this disease. As chemotherapy and radiation therapy causes various side effects, so there is a necessity to discover novel agents for the treatment of this disease; it could be possible with the use of naturally occurring compounds [2].

According to World Health Organization (WHO), more than 14 million people diagnosed with cancer and 8 million dies in 2012 (www.who.int). High mortality and incidence make it an important public health and economic issue which requires an effective prevention. Radiotherapy, immunotherapy and chemotherapy are the most common method used for the cancer treatment, but these techniques adversely affect the healthy cells. Thus, inhibition of damaging behavior to the healthy tissues with the use of commonly used therapies motivates to explore the new safe methods to treat cancer. Interestingly, natural drugs show an alternative to limit the emergence and spread of cancer [3]. The endless diversity of the plant kingdom, presents an extraordinary opportunity to develop novel anticancer drugs. Isolation and identification of compounds that are derived from plant source continues to expand, particularly in the cancer chemotherapy drugs discovery. In this sense, novel anticancer drugs developed from natural resources may increase the efficacy of conventional

chemotherapeutic drugs. Numerous phytochemicals derived from plant resources interfere with the specific stage of carcinogenesis [4]. Compounds isolated from plants are natural and have an advantage over synthetic chemical compounds as they are readily available in nature, since they are natural products so the problem of acquiring resistance against these compounds is minimized to a very great extent. Several studies have been done on naturally occurring compounds which are known to possess cytotoxicity effects and have the potential to destroy cancer cells. Therefore in this review an effort has been made to give an insight about some of the medicinal plants that posses anticancer activity.

Anticancer Activity of Medicinal Plants

Medicinal plants have various advantages over chemical products, because plant derived compounds are more tolerated and non-toxic to the normal human cells. Already available conventional therapies for the treatment of cancer are radiotherapy and chemotherapy and they have possesses various side effects like neurological, cardiac, renal and pulmonary toxicity, which seriously affects the health of the person. Therefore, an alternative method is required to develop that include less toxic and more potent anticancer drug as compare to the drugs available in the market.

Andrographis paniculata

It is commonly known as kalmegha in Hindi and king of bitters in English and belongs to *Acanthaceae* family. It is found in the India and Sri Lanka. Generally roots and leaves are used for the medicinal purpose; extract of this plant contains flavonoids, stigmasterols and diterpenes [5]. The main compound of this plant is the andrographolide which is a diterpene, it is colorless crystalline in nature and bitter in taste. Leaves contains highest amount of andrographolide (approximately 2.25%) while the seeds contains very low amount of this compound. Studies in mice have shown that *Andrographis paniculata* stimulates

immune system and activates both the antigen specific and non specific immune response [6]. Due to this ability, plant is effective against various oncogenic and infectious agents [6]. Andrographolide shows cytotoxic effects against various cancer cells [7]. It shows cytotoxic effect against breast cancer cells (MCF-7), P388 lymphocytic cells and colon cancer cells (HCT-116) [8]. Andrographolide shows inhibition of growth in colon cancer cell line HT 29 and enhance growth and division of human peripheral blood lymphocytes on mouse myeloid leukemia M1 cell lines [8].

Azadirachta indica

It belongs to the Meliaceae family and commonly known as neem or the Indian liliac. It is a tree native to the Indian subcontinent and belongs to the family Meliaceae. The lead anticancer component in neem is limonoids including azadirachtin and nimbolide that induce apoptosis of tumor cells by targeting different cell signaling pathways. There are various theories of cell apoptosis by neem such as activation of proapoptotic proteins like Bax and Bak to permeabilize mitochondria and inhibiting the activity of Bcl-2 and mutant p53 in the 7, 12-dimethylbenz (a) anthracene (DMBA)-induced cancer cells. However there is no evidence on the culminating reasons of neem induced apoptosis. A study on limonoids shows that neem exhibits caspase dependent cell apoptosis and release reactive oxygen species to inhibit metastasis [9]. The neem leaf glycoprotein regulates the activity of M2 macrophages, by converting it to M1 phenotypes in tumor core. This restricts the growth of melanoma and prevents the relapse of tumor by disseminating tumor mass. The vital properties of neem components on tumor cells include enhancing immune response, inhibiting cell proliferation, inducing cell apoptosis, suppression of cancer angiogenesis, and restoration of cellular reduction/oxidation (redox) balance. Neem extracts enhance the efficacy of certain chemotherapeutic drugs and sensitize malignant cells to immunotherapy and radiotherapy.

Boesenbergia pandurata

It belongs to the Zingiberaceae family and it's a perennial herb. It is native to the South east Asia and commonly called as finger root or Chinese ginger. The active compounds in *B. pandurata* are boesenbergin, cardamonin, pinostrobin, pinocembrin, panduratin A and 4-hydroxypanduratin A. These compounds act as antioxidant, antibacterial, antifungal, anti-inflammatory, antitumor and anti-tuberculosis agents. A cyclohexenylchalcone derivative, Panduratin A, present in *B. pandurata* is shown to inhibit the growth and induce apoptosis of HT-29 colon cancer cells. A study reported that Panduratin A arrested the cancer cell lines A549 non-small cell lung cancer; PC3 and DU145 prostate cancer cells and MCF-7 breast cancer cells and illustrated proapoptotic activities. Mohd Isa et al. [10] investigated the anticancer role of Boesenbergin A (BA) isolated from *Boesenbergia rotunda* in human non-small cell lung cancer (A549) cells. BA arrested the cell cycle by accumulating the cells in sub G1 phase. BA stimulated the expression of pro-apoptotic Bcl-2 family members, caspase 3/7, 9 and 8. The study thus concludes that BA could be a promising agent for the treatment of lung cancer [10].

Boswellia serrata

It belongs to Burseraceae family and found in India North Africa, and Middle East. It is commonly known as olibanum or

Indian olibanum. It contains various compounds like terpenoids, oils and sugars. The main constituent of this plant is Boswellic acid [11]. Gummy exudates of this plant are associated with the therapeutic effect which includes anti-arthritic, astringent, stimulant and anti-septic effects. Acetyl-11-keto- β -boswellic acid which is an active compound of this plant shows potential activity to inhibit tumor angiogenesis through the vascular endothelial growth factor signaling. Studies showed that treatment with acetyl-11-keto- β -boswellic acid (dose-10mg/kg) suppress tumor growth in xenograft mice with human prostate [12]. This shows the anti-tumor activity of this plant.

Capparis spinosa

It belongs to the Capparaceae family and an important culinary ingredient in Mediterranean and Middle Eastern cuisines. It is known as *Himsra*, *Cabra* in Sanskrit. *Caper* constitutes various volatile and nonvolatile compounds like flavonol glycoside, rutin and 5-caffeoyl-quinic acid those are potent anti-cancer agents. A protein analogous to imidazoleglycerol phosphate synthase was purified from fresh *Caper* seeds, that inhibited proliferation of hepatoma HepG2 cells, colon cancer HT29 cells and breast cancer MCF-7 cells [13]. Essential oils and aqueous infusions extracted from *Caper* have shown significant inhibitory effect on HT-29 cell proliferation and on nuclear factor κ B (NF- κ B) activity in a dose dependent manner. *Caper* essential oil and aqueous infusion ceased the cells in G2/ M phase of cell cycle. A study has reported *C. spinosa* extract mediated apoptosis through permeabilization of mitochondria and activation of Caspase 9 in SGC-7901 cells [14].

Centella asiatica

It belongs to the Apiaceae family and commonly known as brahmananduki in Hindi, mandukaparni in Sanskrit and pennywort in English. It is commonly found in the India, Australia, Pacific Islands, New Guinea, Iran and Malaysia. It contains numerous compounds such as asiaticoside, pectic acid, hydrocotyline, sterol, flavonoid, vallerine, ascorbic acid and thiankunosides [15]. Partially purified fraction of *Centella asiatica* suppressed mouse lung fibroblast cell proliferation and oral administration slowed the solid development and ascites tumours [16]. Pre-treatment with this plant increase the survival time of irradiated animals and show protection against radiation induces damage in liver [17]. This plant shows inhibition in lipid peroxidation in various organs like lungs, liver, heart, brain, spleen and kidney and shows potential towards the cancer inhibition [18].

Curcuma longa

It belongs to the Zingiberaceae family and commonly known as haldi in Hindi, harida in Sanskrit and turmeric in English. Curcumin is the active ingredient of this plant, which is a polyphenol derived from plant rhizome and this plant is used for both cancer prevention and treatment. Numerous studies showed that curcumin induces apoptosis, interfere with progression of cell cycle and inhibits proliferation [19]. Curcumin also showed colon and gastric cancer prevention in rodents [20]. Curcumin shows protective effect by inhibiting the growth of several angiogenesis associates and tumor associated genes [21]. Curcumin shows anticancer activity by inhibiting the proliferation of tumor cells

[22]. Curcumin possess anti-proliferative property by down regulating the numerous gene expressions which includes activator protein 1, NF- kappa B, cyclooxygenase 2, epidermal growth receptor 1, nitric oxidase synthase and tumor necrosis factor [22].

Panax ginseng

It belongs to the Araliaceae family and found in the Korea, China, Japan, United States and Russia. Its active compound is ginsenosides which is a steroidal saponin [23]. It possesses anti-inflammatory and immune-modulatory activity and also helps in the appetite stimulation, physical stamina improvement, memory enhancement and behavior [24]. Anticancer activity of ginsenosides is due to the induction of cell death and its other properties as an anti-invasion, anti-angiogenesis and anti-proliferation activity [25].

Psidium cattleianum

It is commonly known as the strawberry guava or cattley guava is a native to temperate zones of Brazil. More than 200 volatile compounds have been identified in the fruit oil of *P. cattleianum*. In a study conducted by Moon et al. 2011, the anticancer properties of chloroform extract of *P. cattleianum* leaves were reported. The effect of chloroform fraction of guava leaf extract was evaluated against various cancer cell lines. Significant cytotoxicity was observed against SNU-16, a gastric cancer cell line. Strawberry guava acts as an inducer of apoptosis and inhibits the proliferation of cancer cells. It induces apoptosis by stimulating the activities of proapoptotic factors like caspase-8, caspase-3, Bcl-2, Bax and poly (ADP-ribose) polymerase (PARP). The chloroform extract of guava leaves ceases the SNU-16 cancer cell lines in G1 phase of the cell cycle thus acting as an anti-proliferative agent.

Phyllanthus Amarus

It belongs to the Euphorbiaceae Family and known as jaramla in Hindi, bhumyamalaki in Sanskrit and stone breaker in English. It is found in the Asia (warmer parts of India). Whole plant, shoots, roots and leaves are utilized for the medicinal purpose. *P. amarus* contains flavanoids, tannins and lignans and used in the liver, stomach, kidney, spleen and genitourinary system problems. Oral administration of *P. amarus* extract reduce tumor size and increase life span in mice bearing Erlich ascites carcinoma and Dalton's lymphoma ascites [26]. Anticancer activities of this plant are due to the ability to induce cell cycle arrest, interfere with DNA repair and inhibition of metabolic activation of carcinogenic compounds [26]. Extract of *P. amarus* also showed anti-angiogenic effects in mice (bearing Lewis lung carcinoma) by interfering with the vascular endothelial cells migration [27].

Plumbago zeylanica

It belongs to the Plumbaginaceae family and commonly known as white leadwort, chitrak and Ceylon leadwort. It is found in the warmer part of India and Sri Lanka. Several studies reveal the presence of various phytochemicals in this plant which includes plumbagin, plumbagin acid, coumarins, saponaretin, isoaffinetin, isoorientin, steroids, glucosides and psoralen [15]. This plant shows therapeutic activity against skin diseases, rheumatic pain,

wounds and scabies [28]. Plumbagin is a naphthoquinone which is isolated from the roots of this plant and it possess anti-tumor activity by controlling the hormone refractory invasive prostate cancer. Inhibitory effect of plumbagin against various molecular targets (STAT-3, AKT and PI-3K) results in the growth inhibition and invasion of prostate cancer. Plumbagin shows apoptosis induction in cancer cells and also inhibits growth of these cells.

Rhinacanthus nasutus

It belongs to the Acanthaceae family and found in the sub-continental parts of India, China and Southeast Asia. It is commonly known as 'snake jasmine'. It contains rhinacanthins (A-D,G-Q), naphthoquinone, lignin groups and rhinacanthone [29]. This plant shows potential in the treatment of pulmonary tuberculosis, eczema, diabetes and herpes. Studies showed that rhinacanthins M, N and Q inhibits human cancer cell (HeLa, HepG2 and KB) growth and normal Vero cells. Rhinacanthins N partially arrest the M phase cells and prevents from further damage and repair cell defects [30].

Scutellaria baicalensis

It belongs to the Lamiaceae family and found in eastern Asia. It is commonly known as Baikal, scute and scutellaria. It contains chalcones, anthocyanidins, flavanones, flavonols, flavanonols and flavones. Its anti-tumor property is due to the presence of wogonosid, wogonin, baicalein and skullcapflavone II. All these compounds (at micro molar concentration) show inhibitory effects against human tumor cell line 529L and LXFL proliferation. Baicalein inhibits the activity of 12-lipoxygenase and contributes to the anti-cancer activity against various other cancers [31]. It also possesses anti-inflammatory, anti-diabetic, anti-tumor, hepatoprotective, anti-anxiety and anti-hypertensive effects [32].

Tinospora cordifolia

It belongs to Menispermaceae family and commonly found in Sri Lanka, India, Myanmar and China. Stem and roots contain important alkaloids. It is known as 'giloya' in Hindi, 'guduchi' in Sanskrit and heartleaf moonseed plant in English. Root of this plant contains various alkaloids which includes tinosporin, choline, isocolumbin, columbin, tetrahydroplamatin, magnoflorimine and palmatin [33]. *Tinospora cordifolia* stem is generally used for the treatment of fever, dyspepsia, jaundice, skin and urinary disease [34]. *In-vitro* study shows *Tinospora cordifolia* able to kill HeLa cells this shows the potential of this plant as an anticancer agent. *Tinospora cordifolia* extract shows dose dependent cell death as compared to the controls [35]. Dichloromethane extract of *T. cordifolia* showed anticancer activity in mice transplanted with Ehrlich ascites carcinoma [36].

Vitis vinifera

It belongs to the Vitaceae family and commonly known as grape vine. Grape extracts exhibit cytotoxic effect against PC-3, A-549 and MCF-7 cancer cells. Extracts isolated from the grape seeds and stems demonstrated antitumor activity in human breast cancer cell lines MCF-7 and MDA-MB-23), colon (HT29), renal (786-0 and Caki-1), thyroid (K1), hepatocellular carcinoma cell lines, oral squamous cell carcinoma and normal human

fibroblasts [37]. Grape skin possesses a chemopreventive agent, Resveratrol that induces autophagy and acts as an anticancer agent. In a clinical trial methanolic extracts from Greek raisins have been reported to demonstrate a decrease in gastric cancer cell proliferation and mRNA levels of ICAM-1 in TNF-alpha stimulated cells with an induction in cell apoptosis and inhibition of inflammation [38].

Withania somnifera

It is commonly known as ashwagandha in Hindi and Sanskrit, winter cherry in English. It belongs to the Solanaceae family and a subtropical shrub found in Mediterranean, Africa and India. It contains withanolides, withaferins, anferine, isopellertierine and sitoindosise. Due to its medicinal properties, leaves and roots have been used in the Indian traditional system of medicine and marketed globally. Extract of *Withania somnifera* modulates various biological responses [39]. It has been used in various preparations for its anti-stress, anti-ageing, anti-peroxidative, anti-inflammatory, anti-oxidant, anti-tumor, cardiotoxic, and immunomodulatory properties [40]. Withanolide A and withaferin A is the main constitute of this plant. Withaferin A which is mostly present in the leaves produces rapid apoptosis in the cancer cells [40]. Cell signaling pathways by this plant formulation largely depends up on the high content of withferin A present in it [40]. Formulation of *Withania somnifera* showed induction in cell cytotoxicity in various human cancer cell lines [18]. *Withania somnifera* formulation also up regulates population of T cell population in mice (bearing tumor) with increased expression of IL-2 and IFN-gamma levels [41].

Xanthium strumarium

It belongs to the Asteraceae family and commonly known as burweed or cocklebur. It is found in the North America and possesses anti-bacterial, anti-fungal, anti-tumor, anti-tussive, anti-inflammatory, anti-mitotic, anti-malarial, anti-oxidant, analgesic and insecticidal activities. It contains xanthinin, xanthumin, xanthostrumarin, xanthatin, phytosterols, xanthanolides, isoxanthanol, xanthanol and xanthinosin. 8-epi-xanthatin and its epoxide shows anti-tumor activity by inhibiting the tumor cell lines proliferation. 8-epi-xanthatin acts as a farnesyl transferase inhibitor and also inhibits microtubules interfering agents, this shows the potential of 8-epi-xanthatin in the anti-cancer activity [42].

Ziziphus nummularia

It belongs to the Rhamnaceae family and found in Iran, India, Iraq, Israel, Pakistan and Afghanistan. Stem, bark, roots seeds and flowers of this plant used for the medicinal purpose. It is known as harbor in Hindi, bhukamtaka sukhsharanphala in Sanskrit and wild jujube in English. Betulinic acid and betulin (present in stem and bark) is the active constitute of this plant which shows anti-tumor activity [43]. Betulinic acid shows cytotoxicity against various tumor cell lines and induces apoptosis by topoisomerase I inhibition, reactive oxygen species generation, angiogenesis inhibition and pro-growth transcriptional activator modulation [44] Betulinic acid also induces apoptosis by CD 95 and p53 independent mechanism, these mechanisms shows the potential of this compound against the cancer cells [43-54].

Conclusion

Cancer is one of big problems in both developing and developed countries. Various synthetic drugs have been used to treat cancer but they have limitations due to their toxic effects on the normal health cells. Therefore, there is demand for an alternative medicine for the treatment of cancer. Medicinal plant largely contributed to human being health and it contains various secondary metabolites which show their potential towards numerous disease treatments. Anti-cancer agents derived from the plant source have largely contributed to the development of new drugs. Extracts of various medicinal plants and their secondary metabolites are responsible for the anti-cancer activity. Discovery and development of plant derive drugs shows a great promise for future. This review contains medicinal plants with their secondary metabolites that show anti-cancer activity. *In-vitro* studies have showed the potential of secondary metabolites in the anti-cancer activity and plant metabolites mentioned in this review possesses variety of mechanisms that contributes to their anti-cancer nature. Therefore in this review effort has been made to summarized the various medicinal plants and their important phytocompounds used for the treatment of cancer.

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Conflict of Interest

All the authors have no conflict of interest.

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