Forest-Based Medicinal Plants for Cancer Cure

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1 Introduction

Since ancient times, plants are being used as a continuous source of medicinal products for animals and humans in rudimentary forms, such as syrups, powders, ointments, liniments, infusions, and decoctions (Ghorbani 2014). It is considered that about 70–95% of the human population in developing countries uses traditional medicines in their routine life in the form of herbal teas, plant extracts, powders, or plant parts. A plethora of evidence has reported the use of plant-derived active compounds in the treatment of cancer. Current data suggest that about 25–28% of all modern medicines have the presence of plant derivatives that explains the nutraceutical and medicinal potential of plants known for thousands of years in traditional medicine.

Cancer is one of the leading causes of mortalities worldwide and is the second major cause of death after cardiovascular diseases (Uscanga-Perales et al. 2019). The disease commences with the deformation of a normal cell caused by genetic defects and affects a large number of individuals worldwide. It is a common disease around the world and is a severe health concern. Breast cancer, lung cancer, colon or rectal cancer, blood cancer, bladder cancer, ovarian cancer, etc. are the most common cancers all over the world. The predisposing risk factors include smoking, consuming alcohol, obesity, lack of a healthy diet and physical activities, and excessive exposure to sun rays. According to the International Agency for Research on Cancer, the global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. As per the estimated data, 23.4% of the global cancer cases have been reported in Europe with 20.3% of the cancer deaths. America accounts for 21.0% of cancer incidence and 14.4% of mortality worldwide. In contrast, Asia and Africa contribute a higher proportion of cancer incidences (48.4% and 5.8%, respectively), and deaths (57.3% and 7.3%, respectively) (GLOBOCAN 2018). An estimated 2.25 million people are living with cancer in India and more than 1,157,294 new cancer patients have registered annually, while 7,84,821 people have died of cancer (4,13,519 men and 3,71,302 women) according to the National Cancer Prevention and Research Institute (NICPR 2018) (Ramu 2020)

Herbal therapy is an essential alternative approach concerning the treatment of cancer. According to the World Health Organization reports, around 80% of the world's population depends on conventional medicine as a means of primary health

care (WHO 2019). Any realistic approach is of utmost importance in the fight against cancer. Herbal medicines preserve individuals' health and fertility, cure illnesses, and even avoid, suppress, or reverse cancer development without inducing toxicity. Herbal products are more than 50% of all modern medications in clinical use, and a lot of them can control cancer. More than 60% of cancer patients use herbal therapy, while recently much focus has been emphasized in the study on complementary and alternative medicine for cancer treatment (Nayeri et al. 2020).

In remote and rural areas around the world, people still rely on traditional medicines to treat various diseases. African traditional medicine has been regarded as holistic and is interwoven with divination, spiritualism, and herbalism. In Africa, traditional medical practitioners or traditional healers include the most trusted and experienced high priests, priestesses, witch doctors, midwives, spiritualists, and herbalists who use herbs, minerals, parts of animals, incantations, and other traditional methods for many ailments like heart disease, diabetes mellitus, HIV, gynecological illness, asthma, and mental disorders. In Japan and China, traditional medicines account for 70% and 40%, respectively, of the health care system and are actively prescribed by allopathic doctors for their patients. Similarly, 48% of the population in Australia, 70% in Canada, 42% in the United States, 38% in Belgium, and 75% in France have used traditional medicines in their life with the popularity of traditional medicines, the market value of herbal medicines has also increased tremendously. As per the WHO report, the world market for herbal medicines based on traditional knowledge is estimated for 2015 at the US $90 billion, while the annual market sales of herbal medicines in 2007, 2008, and 2009 were US$ 200 000, US$ 600,000 and US$ 1,300,000, respectively (WHO 2019).

Reducing the toxic side effects caused by chemotherapy and radiotherapy agents may make herbs useful for cancer control. One of the mechanisms of action of herbal biological modifiers is the inhibition of cancer by regulation of complex hormonal and enzymatic activities. The studies are now mainly focusing on the separation of active components from natural sources that may be having an application as an active anticarcinogen. Rasayana is an important component of the complementary and alternative medicinal system in which herbs help in alleviating the body's imbalances. These traditional means of therapy have a profound effect on shielding the body from the counter-effects of deleterious chemotherapy and radiation therapy specific to the tumor (Chakraborty et al. 2012).

The purpose of this chapter is to summarize some of the most effective medicinal plants reportedly to have a considerable anticancer effect. Also, the experimental evidence based on published research articles has been examined to overview active phyto-compounds responsible for the anticancer potential of these medicinal plants.

2 Cancer Therapies

Based on the clinical factors, such as type of cancer, its stage, metastasis and patient's age, there are patients at high or low risk, whereas individual risk groups go around with a different system for therapy. Therapists face a daunting series of obstacles as cancer is diagnosed. The available anticancer treatment options are apoptin, chemotherapy, cryotherapy, cytokine therapy, hormone therapy, immunoadjuvant therapy, radiation therapy, surgery, etc. (Natesan et al. 2007a, b). In modern times, the application of gold-conjugated and carbon nanoparticles has enhanced the anticancer potential of drugs such as doxorubicin and paclitaxel (Bromma and Chithrani 2020). However, cancer therapies have several reported side effects like anemia, lymphedema, memory loss, peripheral neuropathy, etc. which might varies with the mode of the treatment, including traditional therapy or advanced targeted therapy. Chemotherapy drugs have a profound detrimental effect on cancer cells along with healthy leukocytes which makes the patient more vulnerable to other diseases and further deteriorate the health (CDC 2020).

Patients' survival under the umbrella of traditional treatment is extremely marginal (2.4%). However, confusion about the efficacy of such a cancer treatment strategy generates the urge for alternative therapies that cause fewer side effects and improve survival rates (Paul and Dredze 2011).

3 Herbal Medicinal Plants with Anticancer Potential

Around the world, ongoing research is underway to explore successful cancer treatments using herbal plants as therapeutics in cancer patients. Naturally occurring compounds in plants known for their ability to inhibit the growth of carcinogenic cells are used in the procedure of cancer treatment. Organically based therapies do not have the significant side effects of radiotherapy and chemotherapy, which is the most common method of treating cancer by physicians and specialists (Newhauser et al. 2016).

Several herbs protect the body against potential or current cancer, thereby contributing to providing flexibility in cancer treatment and strengthening the patient's immune system. The mechanism of action of herbal anticancer drugs has been divided into two different groups, i.e. direct cytotoxicity and immune-modulation cytotoxicity. Abnormal cell proliferation and the inhibition of cell apoptosis which is governed by some genes are responsible for causing cancer. In this respect, some oncogenes or tumor suppressor genes may be modulated by medicinal herbs. As far as immune-modulation is concerned in the case of malignancy, herbal medicines can enhance the immune response that has different therapeutic applications (Zhu et al. 2008).

Various communities have used many distinct anticancer herbs for medicinal purposes throughout time. With such a diverse range of herbs available globally,

there are quite a few antiherbal plants with known anticancer potential. *Alfalfa* is one of the main anticancer herbs with the potential to combat the effects of chemotherapy and is considered one of the most nutritious foods accessible. With known antibacterial and antifungal properties, *Alfalfa* (*Medicago sativa*) is an effective infection fighter and body cleanser (Greenwell and Rahman 2015). It acts to increase white blood cell output and replace those that are damaged during treatment. *Andrographis* is another anticancer plant cultivated in Asia's forests and wastelands and is well studied for its use against cancer, AIDS, bacterial and viral infections. This herb has been shown to stop the abnormal growth of cancer cells in the stomach.

Similar to these medicinal plants, there are several other herbs with multiple health benefits. *Cnicus benedictus*, commonly called "Blessed thistle," exhibits an ability to decrease tumor size. The active ingredient of this plant is cnicin which is credited for eliciting antitumor and antibacterial effect. Another anticancer herb is *Arctium lappa* commonly called Burdock) having potent anti-inflammatory properties, which helps to rejuvenate the body and enhances the healing process. Herbal preparations can work in a mechanism similar to pharmaceuticals without having a chance of any side effects. Herbal plants possess natural anti-inflammatory compounds that widely contribute to their renowned health benefits. Thus, the need to investigate natural nonsteroidal anti-inflammatory substances for cancer prevention has therefore increased. Anticancer herbs also include rosemary (*Rosmarinus officinalis*) which is an effective antispasmodic and antiseptic antioxidant. Rosemary interferes with the early stage of cancer development mainly by aiding in averting the attachment of carcinogenic chemicals to cells and escaping cancer-causing mutations (Allegra et al. 2020). Some of the important herbs, shrubs and trees and their active phyto-compounds used in cancer cure are presented in Table 1.

3.1 Acacia nilotica

A. nilotica belongs to the family fabaceae, also known as babul or Indian gum arabic tree, has several known medicinal properties, and is used in the treatment of cancers and tumors of the ear and eye. The plant is also beneficial in the therapy against dysentery, diarrhea, ulcer, leprosy, diabetes, and various cancers (Roozbeh and Darvish 2016). It has been reported that the use of its various preparations decreases the tumor burden, tumor occurrence, and a cumulative number of papilloma during the periods of peri- and post-initiation of 7,12-Dimethylbenz[a]anthracene and croton oil use. Besides, in treatment groups, a substantial decrease in the occurrence of micronuclei was apparent, both of which were correlated with a decrease in total chromosomal aberrations (Sakthivel et al. 2012). In a recent study, *A. nilotica* extract showed reduced growth of Dalton's ascitic lymphoma (DAL) MDA-MB-231 (breast cancer), and HEp-2 (cervical cancer). The study also depicted a significant increase in hemoglobin and W.B.C count, while a decrease in the level of liver enzymes was reported in the treated mice model (Revathi et al. 2017).

Table 1 List of some plants and their active phyto-compounds used for the treatment of cancer

Plant name	Common name	Plant parts used for active phyto-compound isolation	Active phyto-compound(s)	Key References
Aegle marmelos	Bael fruit	Leaves and fruit	Lupeol and skimmianine	Akhouri et al. (2020)
Ammi majus	Amme, Bullwort	Fruit	Coumarin	Aydogmus-Ozturk et al. (2019)
Artemisia absinthium	Sage brush, wormwood	Leaves and flower	Artemisinin	Akrout et al. (2011)
Boswellia serrata	Olibanum or Indian Frankincense	Resin	Boswellic acid	Wang et al. (2018a, b)
Camellia sinensis	Tea plant	Leaves	Epigallocatechin gallate (EGCG)	Imran et al. (2019)
Catharanthus roseus	Madagascan periwinkle	Leaves and flower	Vincristine, vinblastine and vindesine	Harshini et al. (2020)
Cephalotaxus harringtonia	English Yew, Japanese Plum Yew	Bark and fruit	Homoharringtonine	Isah (2016); Yakhni et al. (2019)
Citrullus colocynthis	Bitter apple, desert gourd	Leaves, stem, root, and fruit	Quercetin and β-sitosterol	Perveen et al. (2021)
Clematis manhsrica	*Clematis*	Bark	Hederagenin saponin and embelin	Zhao et al. (2005); Cheng et al. (2018)
Combretum caffrum	Cape bushwillow tree, African willow tree	Bark	Combretastatin A-4 phosphate	Kwak et al. (2019)
Crocus sativus	Saffron	Stigma	Crocin, crocetin, picrocrocin, and safranal	Nassar et al. (2020); Veisi et al. (2020)
Curcuma longa	Turmeric	Rhizome	Curcumin	Liu and Ying (2020)
Ferula asafoetida	Asafoetida—Devil's Dung	Dried latex	β-sitosterol and oleic acid	Abroudi et al. (2020)
Glycyrrhiza glabra	Licorice	Root	Glycyrrhizin, glycyrrhetinic acid, glabridin, gycyrrhetinic acid, and glycyrrhizic acid	Wang et al. (2018a, b); Goel et al. (2020)
Lawsonia inermis	Henna tree, the mignonette tree	Leaves	Lawsone (2-hydroxy-1, 4-naphthoquinone)	Mungle et al. (2019)
Medicago sativa	Alfalfa	Leaves and flower	Coumarin, flavonoid, alkaloid, and terpenes	Brodribb (2018); Dziok et al. (2020)
Ocimum sanctum	Holi Basil	Leaves	Apigenin, β-D-glucuronic acid, ocimarin and luteolin	Harsha et al. (2020)
Olea europae	European olive	Leaves, fruit, and roots	Oleic acid, maslinic, and oleanolic acids	Ziberna et al. (2017)

3.2 *Achillea wilhelmsii*

A. wilhelmsii belongs to the family Asteraceae. A distinct race of *Achillea* exists; however, *A. wilhelmsii* is prevalent in Iran. The plant is a 15–40 cm grassy, perennial and short herb. The essential oil of the plant leaf contains a-Pinene and 1,8 Cineole, which have been studied to induce cytotoxic effects on colon cancer cells (HT-29), breast cancer cell lines and cervix cancer HeLa cells (Acar et al. 2020). It is reported that the plant methanolic extract contains phenolic compounds, in particular flavonoids, which inhibit the replication of cancer cells by inducing apoptosis (Sharma et al. 2011). In another study, the expression of telomerase reverse transcriptase (hTERT) in prostate cancer (PC3 cell lines) was reported to be reduced by the treatment of cells with hydroalcoholic extract of *A. wilhelmsii* at the concentration of 150 μg/mL concentration (IC50) (Ashtiani et al. 2017).

3.3 *Aegle marmelos*

A. marmelos belongs to the family Rutaceae and is commonly called the Bael tree in India. The plant has a rich presence of bioactive compounds, such as flavonoids, phenolics, alcohols, fatty acids, methyl esters, aldehydes, aromatic compounds and steroids by GC-MS analysis. Lupeol, a tri-terpenoid, is the main bioactive component of the plant and has significant anticancer activity against malignant ascites, multiple brains, primitive neuroectodermal tumors (PNET), thyroid cancer, and spinal cord malignant tumors (Lampronti et al. 2003). This plant has been explored for its antineoplastic and antimutagenic activity in animal studies. Skimmianine has been identified as a bioactive agent in leaf extract which may induce apoptosis in cancer cells. The fruit extract of *A. marmelos* has shown cytotoxicity against 7,12-dimethylbenz(a)anthracene (DMBA)-induced breast cancer in mice, where the extract showed significantly reduced growth of a mammary tumor and decrease in the level of TNF-α, serum malondialdehyde, and glucose (Akhouri et al. 2020).

3.4 *Aloe vera*

A. vera is a succulent plant from the family Asphodeloideae. It is one of the herbal plants that are used as a source of anticancer therapy as studied in vitro and in vivo for its anticancer potential. It is a rich source of carotenoids, steroids, terpenes, phytosterols, and enzymes, such as bradykinase, carboxypeptidase, cyclooxygenase, and carboxypeptidase. Oral administration of aloe leaf in Swiss albino mice at various levels of tumors, including second-stage skin carcinogenesis, was found to reduce papillomas in size and number. In contrast, to control groups, it reduced cancer growth and improved the latency time for papillomas. Also, the study reported a substantial decrease in the levels of lipid peroxidation, glutathione, DNA,

protein, and catalase in the mice's skin (Chaudhary et al. 2008). Recent studies on hepatocellular carcinoma (HepG2) cells have indicated that the extract of *A. vera* could exert an anti-hepatocarcinogenic effect through modulation of apoptosis (Karpagam et al. 2019).

3.5 Ammi majus

It is a member of the family Apiaceae and is an annual, dicotyledonous, autumn-growing herb plant. *A. majus* is a native of Europe, the Mediterranean region, western Asia, and India. The plant is long and thin which grows to the length of about 100 cm in different habitats like saline grasslands, wet and soft soils, and coastal areas. The coumarin compounds (as part of the phenol compounds) are attributed to the plant's anticancer potential. Research has been conducted on the cell toxicity of coumarin on cancer cell lineages, and studies have confirmed the triggering of apoptosis as the mechanism of action of these compounds. Psoralens are the most essential coumarin compounds found in this plant which reportedly contributes to anticancer activity by suppressing the action of cytochrome p450 (Shokoohinia et al. 2014). Recent studies have identified the anticancer potential of visnagin, a furanochromone derivative, from *A. visnaga*, against malignant melanoma (HT 144) cell lines (Aydogmus-Ozturk et al. 2019).

3.6 Andrographis paniculata

A. paniculata (Kalmegh, a member of the Acanthaceae family has andrographolide, a bicyclic diterpenoid lactone, as a major element in the leaves. It exerts direct anticancer action via cell cycle arrest at G0/G1 level and induces reduced expression of cyclin-dependent kinase 4 (CDK4). Andrographolide also possesses immunostimulatory activity and is known to increase lymphocyte proliferation and interleukin-2 synthesis. It exerts indirect anticancer activity by enhancing the level of TNF-α and expression of CD marker leading to a substantial increase in the potency of lymphocytes against tumors (Paul et al. 2019). In a study conducted by Singh et al, hydroalcoholic extract of *A. apniculata* showed 51.12% inhibition of ovarian cancer cell lines (ovcar-5), while the combination of *A. paniculata* and *Silybum marianum* showed synergistic inhibition activity against liver cancer cells (HepG2) (Singh et al. 2013).

3.7 Artemisia absinthium

Artemisia has 200 and 400 species that belong to the Asteraceae family. The species, *A. absinthium* L, originates from moderate regions of Asia, northern Africa,

and large areas of America. The plant could reach a height up to 80–120 cm and bears clustered, bitter, and yellow-colored flowers. Research has been reported for relevant anticancer properties of this plant on HeLa, HT-29, and MCF7 cancer cells (Koyuncu 2018). The active compound, artemisinin, has been reported to inhibit the growth of breast cancer cells via apoptosis and prevents angiogenesis, and cell migration. Besides artemisinin, the plant is recognized to possess phytocompounds like quercetin, kamfrolinalol, alphapinin, isorhamnetin, limonene, and myrecene. The anticancer potential of quercetin and isorhamnetin has been studied and reported to inhibit cancerous cell growth in cancer cells like MB-435, SKMEL-5, Du-145, and MCF-7. Artesunate is one of the most effective artemisinin that inhibits the production of the angiogenic factor VEGF, prevents angiogenesis, and exerts anticancer effects. A recent study has identified the anticancer potential α-pinene, β-pinene, limonene, and myercin found in *A. absinthium* against human breast cancer, hepatic cancer, colon cancer, and melanoma growth (Akrout et al. 2011).

3.8 Azadirachta indica

A. indica, also known as "the wonder tree" and "the drug store of nature," belongs to the family of Meliaceae and is recognized for its enormous therapeutic and ethnomedicinal significance. Numerous reports are available citing the medicinal importance of its bark, leaves, seed oil, and related purified products. Terpenoids and steroids found in the bark, leaves and seeds of the plant are frequently used to treat and heal different cancers such as cervical, ovarian, and breast neoplasia. The plant has immunomodulatory and apoptotic activities against several types of cancers and is recommended for the prevention and inhibition of tumors (WHO 2019). The role of the active principles in the genesis of the forestomach, cervical cancer, and skin papilloma has been studied and identified to induce substantial carcinogen detoxification in the liver of Swiss albino mice. The anticancer effect of methanolic extract of *A. indica* has been studied against MCF breast cancer cells and showed inhibition of MCF cell lines in a dose-dependent manner. The concentration of 200 μg/ml of the extract was found to induce 65.5% of inhibition in the MCF cells (Malar et al. 2020).

3.9 Boswellia serrate

B. serrate is a medicinal plant also called Olibanum or Indian Frankincense and belongs to the order of the Spindales, family Burseraceae. Hydroalcoholic extract of this plant has been reported to induce death of cervical cancer cells in a time and dose-dependent manner (Akbar 2020). The resin made from the plant extract is an intrinsic part of the Asian and African folk medicine system and is also known to cure chronic inflammatory disease and other health conditions. The major

phyto-compounds of frankincense resins that are shown to induce apoptosis in cancer cells include boswellic acid, monoterpene, diterpene, and triterpene. Frankincense extract induces apoptosis and causes significant cell damage by enhancing the production of reactive oxygen species (ROS) and caspases (Poornima and Deeba 2020). The anticancer potential of boswellic acids has been reportedly shown to induce apoptosis in myeloid leukemia cells, fibrosarcoma, metastatic melanoma, brain tumor cells, Hep G2 cell line, and HCT-116 human colon cancer cells (Wang et al. 2018a, b). Recently, a study conducted on 4T1 breast cancer mouse model showed inhibition of tumor growth (25.7%), and angiogenesis using *B. serrata* gum resin alcoholic extract (BSE) at the concentration of 150 mg/kg. The histopathological analysis of liver and lung tissues of cancer implanted mouse model also revealed inhibition of metastasis (Alipanah and Zareian 2018).

3.10 Camellia sinensis

C. sinensis is an evergreen shrub and belongs to the family Theaceae. The leaves are the source of tea that is one of the most consumed beverages in the world and is being used as a medicinal drink for centuries in the Chinese, Japanese, and Asian subcontinents. Based on the processing of leaves, there are mainly four tea varieties known as white, green, oolong, and black tea. The major components found in *C. sinensis* are catechins, epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate, and epicatechin, which exert an antioxidant, anticancer, and anti-inflammatory effect. Other than EGCG, other active compounds like rutin and quercetin have been studied to contribute to the inhibition of oxidative activation in carcinogenesis. There is a plethora of evidence indicating the anticancer potential of green tea and black tea. The anticarcinogenic effect is believed to be induced through controlling the proliferation of the cell and inducing apoptosis and angiogenesis in cancer cells (Anand et al. 2012). The in vivo studies have depicted anticancer efficacy of green tea on prostate cancer, where green tea was found to inhibit 5-alfardoctase enzymes that convert testosterone to dihydrotestosterone, a prostate carcinogenic agent to have an inhibitory effect on prostate cancer (Imran et al. 2019). In vitro and in vivo studies have reported that green tea catechins like epigallocatechin gallate (EGCG) inhibit the malignant growth of breast cancer cells bladder cancer, lung cancer, pancreatic cancer, liver cancer, and esophageal cancer (Filippini et al. 2020).

3.11 Camptotheca acuminata

C. acuminate belongs to the Nyssaceae family and possesses camptothecin which is a potential source of steroidal precursors for cortisone development. Its semisynthetic derivatives are topotecan and irinotecan known for their efficacy in the

treatment of ovarian, colorectal and lung cancers (Bertino 1997). However, due to some cases of bladder toxicity reported, its application has now been discontinued. To counteract the side effects, broad-spectrum mode of action of camptothecin from *C. acuminata* against cancer cell lines have been well reported in the literature. The camptothecin has been shown to exhibit its inhibitory effect against topoisomerase-I activity (Chaudhari et al. 2020).

3.12 Careya arborea

One of the common vegetables in northeast Thailand, *C. arborea*, is usually consumed fresh as a side dish or eaten as a soup. It belongs to the family of Barringtonieacea. In the ancient ethnomedical system, the bark of *C. arborea* had wide application in the treatment of tumors. Scientific studies have reported the anticancer activity of bark's methanolic extract against Dalton's lymphoma ascites (DLA)-induced ascitic and solid tumors in mice (Natesan et al. 2007a, b). The experiments using young leaves and flowers have demonstrated the inhibition of metastasis and cell death in MCF-7 cells, followed by increased generation of ROS, stimulation of caspase-3 activity, and reduced mitochondrial function. *C. arborea* extract therapy had also shown reduced protein-inhibited cell viability of cyclin D1, protein, and protein-induced cell apoptosis of caspase-3 and cytochrome C protein. As a mode of action, *C. arborea* is reported to block the migration of breast cancer cells, followed by repression of MMP2 and MMP9 expressions (Buranrat et al. 2020).

3.13 Catharanthus roseus

The *C. roseus belongs* to the Apocynaceae family has a rich source of vinca alkaloids which possesses antimitotic and anti-microtubule activity. This group of alkaloids includes bioactive compounds such as vincristine, vinblastine, and vindesine which have depicted anticancer potential against human acute leukemia, hepatocellular carcinoma, Hodgkin's syndrome, non-Hodgkin's lymphoma, Swing's sarcoma, Wilms' tumor, neuroblastoma, and transmissible venereal tumor (TVT) (Harshini et al. 2020). The anticancer potential of vinca alkaloids includes microtubule destruction, inhibition of mitosis, protein and nucleic acid synthesis, increased concentration of glutathione oxidation and cAMP, and altered lipid metabolism (Tucker et al. 1977). In the treatment of hematological malignancies and few solid tumors originating in the lung and colon, vinca alkaloid has been identified to induce apoptosis through a pathway independent of cell cycle arrest and is still crucial along with its analogs. The effects of alkaloids of this plant on breast, prostate, and cervix cancer cells (MCF-7, PC3-1C, and HeLa) have been studied indicating that these alkaloids' tubular protein links changed its structure by blocking the

division of cancerous cells, and thus these compounds having antioxidant properties preventing the cancer cells from progression (Sharma et al. 2016).

3.14 Cephalotaxus harringtonia

Homoharringtonine (cephalotaxine 4-methyl-2-hydroxy-4-methylpentyl butanedioate) is an active compound isolated from *C. harringtonia*var, a Chinese tree from the family Taxaceae. A racemic mixture of harringtonine and homo harringtonine has been successfully used in elderly cancer patients with acute myelogenous leukemia and chronic myelogenous leukemia. Due to its relatively mild cytotoxicity and high efficacy against different kinds of leukemia, Homoharringtonine is an FDA-approved anticancer drug considered to be a safer alternative therapeutic (Yakhni et al. 2019). Historically, its bark has been used as a traditional Chinese medicine to cure various cancers. The antileukemic effect of homoharringtonine esters, such as harringtonine, homoharringtonine, deoxyharringtonine, and isoharringtonine, has been well established on mouse P-388 and L-1210 cell lines. The mode of action in homoharringtonine involves protein synthesis inhibition in a dose and time-dependent manner blocking the cell cycle progression from G1 to S phase and G2 into M phase causing apoptosis (Isah 2016).

3.15 Citrullus colocynthis

The plant *C. colocynthis* is a member of the family Cucurbitaceae and a native to the Mediterranean Basin, Northern Africa, Turkey, Nubia, and Asia. It is also known as bitter apple, bitter cucumber, and desert gourd. The plant has been used as a traditional medicine for centuries. The active constituents of this plant such as quercetin and b-sitosterol have been studied to exert anticancer effect against liver (HepG2) and breast (MCF7) cancers. These compounds act by inhibiting the cell cycle and the induction of apoptosis (Perveen et al. 2021). In another related study, the anticancer potential of seed and pulp extracts of the fruit was reported to induce cell death through regulation of p53 pathways and mitochondrial regulated apoptosis. Using computational molecular docking tools, the study also identified isoorientin and isovitexin as the bioactive phytocompounds responsible for the inhibition of ROS production and proliferation of cancer cells (Joshi et al. 2019).

3.16 *Clematis mandshurica*

C. mandshurica plant belongs to the family Ranunculaceae. Due to the presence of saponins, *C. mandshurica* has apparent antitumor effects. The embelin derivatives of *C. mandshurica* include 1, 4-benzoquinone derivative 5-0 ethyl embelin (1) and 5-0 methyl embelin which are recognized to inhibit cancer progression. Experimentally, the saponins in plants have shown cytocidal effects on tumor cells like EAC cells, S180A cells, and HepA tumors. In another study, the *C. mandshurica* saponins have shown significant anticancer activities on Sarcoma-180, HepA and P388 transplanted mice (Zhao et al. 2005). Saponins like hederagenin saponin have shown to induce apoptosis in MCF-7 and MDA-MB-231 breast cancer cell lines through reduced activity of mitochondrial Apaf-1 and cytochrome *c* proteins (Cheng et al. 2018).

3.17 *Combretum caffrum*

C. caffrum is a South African tree that belongs to the Combretaceae family. Combretastatin A-4 phosphate is a natural antitumor compound isolated from *C. caffrum* and has shown significant cytotoxicity against colon, lung, and leukemia cancers (Ohsumi et al. 1998). It has antiangiogenic properties that cause tumors to shut down vascularly and contribute to tumor necrosis. Combretastatin A-2, a methylenedioxy derivative of combretastatin A-4, has been examined for its antiproliferative activities against human cancer cell lines (HeLa, SK-OV-3, A549, and HT-29) using molecular docking studies (Kwak et al. 2019).

3.18 *Crocus sativus*

The saffron plant *C. sativus* is a member of the Iridaceae family and is originally from Khorasan, Iran. The plant is a 10–30 cm long perennial herb with narrow leaves coming from the bulbs of this plant. There are between one and three purple flowers on this herb. The used part of this plant is stigma, known as saffron. The active constituents like crocin, crocetin, picrocrocin, and safranal extracted from saffron are reported to have induced cancer cell death via apoptosis (Nassar et al. 2020). The potential anticancer properties of saffron extract and its purified quercetin have been demonstrated against colorectal cancer cells, breast cancer cells (MCF-7), HeLa, and HepG2 cells. The study indicated the inhibition of DNA synthesis and angiogenesis in cancer cells as the mechanism of action of the saffron (Veisi et al. 2020).

3.19 *Curcuma longa*

The turmeric plant is scientifically known as *C. longa* is a member of the family Zingiberaceae. Cultivation of this perennial plant requires a wet and rainy climate. It is native to Africa and South America and hot areas of Asia, such as India, southern China, Pakistan, and Indonesia. The active compound has been used for the prevention of oral ulcerative cancer, breast cancer, skin squamous cell carcinoma, and malignant leukoplakia transformation. Dried rhizomes are the edible component of turmeric. The cytotoxic analysis of turmeric in Hep-2-liver tumor cells showed that curcumin-induced dose-dependent cytotoxicity contributes to cancer cell apoptosis through the mitochondrial pathway (San and Lee Yue 2020). Curcumin, the active component of turmeric, plays a major role in the prevention and treatment of primary ovarian cancer. Curcumin's anticancer potential has been demonstrated against leukemia, lymphoma, melanoma, intestinal cancer, urinary cancer, breast cancer, lung cancer, colon cancer, and brain tumors. In several cellular systems, an antioxidant, antitumor, and anti-inflammatory activity of *C. longa* were reported to induce apoptosis (Liu and Ying 2020). It prevents cancer growth by inhibiting the formation of deleterious eicosanoids such as PGE-2. The condensates of curcumin like 7, 12-dimethylbenz(a) anthracene (DMBA) and benzopyrene suppress the mutagenic influence of various mutagens. The experimental studies have also shown the potential of *C. longa* to inhibit nitrosamine production and an increase in glutathione levels, which improves the body's natural antioxidant functions (Rawal et al. 2015).

3.20 *Ferula asafoetida*

F. asafoetida is a herbaceous plant of the Umbelliferae family. It is mainly cultivated in different parts of Iran, Khorasan, Sistan, and Baluchestan. It is an evergreen perennial herb growing 1–1.5 m with strong, thick fibrous stems. The resin from this plant is exuded from the rhizome or taproot. Consumption of gum substantially shown to decrease the risk of colon cancer and breast cancer (Panwar et al. 2015). Sulfur-containing compounds such as β-sitosterol and oleic acid are the most important ingredients with anticancer potential. The anticancer effects of the ethanolic extract are being demonstrated by various mechanisms including inhibition of gene mutation, inhibition of DNA degradation, the effect on cell proliferation, and changes in enzyme activity. The significant mechanism of anticancer activity includes the induction of apoptosis. Furthermore, the epidemiological studies on the cytotoxic potential of phytochemical compounds of *F. asafoetida* have reported the inhibitory effect against ovarian carcinoma, colon cancer, breast cancer, Hepatocellular carcinoma, lung cancer, and melanoma (Verma et al. 2020). Recently, an investigation has demonstrated a significant increase in apoptotic activity and anticancer potential of ethanolic extract of *F. asafoetida* against adrenal tumor cells

(PC12) and MCF7 breast cancer cells at different concentrations of 7, 5, 10, and 2.5 μM in a time and dose-dependent manner (Abroudi et al. 2020).

3.21 Glycyrrhiza glabra

G. glabra, a member of the family Fabaceae, is also called Licorice. *G. glabra* is a wild vegetable plant native to the temperate regions of Asia, Southern Europe, and North Africa. It is cultivated in most parts of Iran, especially in Khatam Marvast, Azerbaijan, and Eghlid. The leaves are composed of four to seven leaflet pairs with one sticky leaflet due to the secretion of juice. The flowers are blue in color, and five to six brown seeds are found in the fruit. Its active phytocompounds include glycyrrhizin, glycyrrhetinic acid, glabridin, gycyrrhetinic acid, and glycyrrhizic acid. The key component glycyrrhizin has anticarcinogenic and anti-inflammatory properties and has demonstrated prevention from unwanted cell proliferation and inhibition of breast, liver, and skin tumor growth. Glycyrrhizin is a triterpene glycoside which is the key compound found in the root extract and acts as an antiproliferative agent against tumor cells, particularly breast cancer cell lines (MCF-7) and HEP-2 (Baltina 2003). In an experimental study, it has been reported that root extracts of *G. glabra* exert an anticancer effect on HT-29 cells and breast cancer cell lines through stimulation of apoptosis (Nazmi et al. 2018). The root extract of the plant has been shown to induce morphological changes in the mammary cell line 4T1 and reduction in cell viability. The root extract induces phosphorylation of BCL2 and stops the cycle of G2/M cells in the tumor cell line (Wang et al. 2018a, b). Licochalcone (LA) isolated from roots of *G. glabra* is a novel estrogenic flavonoid and has significant antitumor activity in different lines of human malignant cells. LA has shown to induce mild apoptosis and a noticeable effect on cell cycle progression, resulting in a reduced level of Cyclin B1 and cdc2 by arresting cells in the G2 or M process. The studies also depicted inhibition of Rb or S780 phosphorylation and decreased expression of transcription factor E2F, Cyclin D1, and CDK 4 and 6 (Lim 2015). Other active phytocompounds, namely glycyrrhetic acid, glabrol, and glabridin, isolated from the root extract *of G. glabra* also display the presence of anticancer activity and have been identified to exhibit significant cytotoxicity against C6 glial cells. These compound also shows inhibitory potential against topoisomerase *in silico* (Goel et al. 2020).

3.22 Indigofera aspalathoides

I. aspalathoides is a member of the family Papilionaceae. As a whole plant, it induces a cooling effect, is used as a demulcent agent and reduces oedematous tumors. In Swiss albino mice, the ethanolic extract of *I. aspalathoides* showed reduced growth of Dalton's ascitic lymphoma. The study also indicated its

chemoprotective effect against N-nitrosodiethylamine-induced hepatocellular carcinogenesis in vivo in which the activity of tumor inducer N-nitrosodiethylamine was reduced with a further reduction in necrosis in the liver tumor of mice treated with ethanol root extract of *I. aspalathoides* (Claimer et al. 2012). In another study, the antioxidant potential of methanolic extract of *I. cassioides* was reported, and the extract induced enzymatic antioxidant defense system in mice implanted with EAC and DLA tumor-bearing mice (Kumar et al. 2011).

3.23 Lawsonia inermis

L. inermis, commonly referred to as Mehndi in India, is also a well-established medicinal plant and has been extensively studied for its anticancer activity. The study using solvent extracts of leaves and oil was conducted on a human liver cancer cell line (HepG2) that showed the induction of the apoptotic, DNA fragmentation, and chromatin condensation (Rahmat et al. 2006). Lawsone, 2-hydroxy-1, 4-naphthoquinone, is an active component of *L. inermis* (Henna). *L. alba* and other species of the family Lythraceae is claimed to possesses various medicinal properties including the anticancer effect (Mungle et al. 2019). The anticancer effect of *L. inermis* was demonstrated in mice and showed an increased level of antioxidant enzymes and reduced forestomach and liver papillomatosis. In animal studies, chemopreventive reactions were found to decrease the percentage of tumor-bearing animals and the multiplicity of tumors (Kapadia et al. 2013).

3.24 Lepidium sativum

L. sativum also referred to as watercress or garden cress is an annual herb with an approximate length of 50 mm and a width of 4 mm. It is also referred to as Jrjizbastany or Rashad in ancient Iranian medicine. It has light green leaves and small, softly fragrant, red or white flowers that appear together at the end of the branch. It is well documented that the plant and its seeds have a rich presence of active phytocompounds, like phenolic compounds, tocopherol, and terpenoids, conferring high antioxidant and anticancer activity. The methanolic extract of its seeds has shown cytotoxic effects on the bladder cell line (ECV-304). Experimental evidence on anticancer activity of the aqueous extracts of *L. sativum* leaves revealed inhibition of human tongue squamous carcinoma (CAL-27 cells), Leukemia (K562 cell line), and breast cancer cells (MCF-7) in a dose-dependent manner (Mahassni and Al-Reemi 2013; Aslani et al. 2014). In a recent study, the methanolic extract of *L. sativum* has demonstrated induced apoptosis and genotoxicity against colon and endometrium cancer cells at a concentration of 200 µg/ml (Selek et al. 2018).

3.25 *Medicago sativa*

M. sativa also called Alfalfa (father of all foods) is a perennial flowering plant from the Fabaceae family. The roots of the plant could reach a depth of 4–9 m in well-drained soil. It is commonly used as an herbal medicine for the treatment of hepatic disorders. Phytoestrogens in the plant have an estrogenic activity which is useful in the treatment of hormone-dependent cancers. Alfalfa contains considerable quantities of vitamins, digestive enzymes, coumarin, flavonoids, alkaloid, terpenes, and amino acids and is well known to have antioxidant, anti-inflammatory, and anticancer activities. The cytotoxicity and apoptosis in cell lines have been reported in doxorubicin-resistant counterparts suggesting inhibition of cancer cells mediated by DNA fragmentation (Dziok et al. 2020). Beneficial for breast cancer as well as for breast milk enhancement, alfalfa generates triconlin, alkaloids that play a hormonal role in the plant and are considered to have anticancer properties (Brodribb 2018).

3.26 *Morinda citrifolia*

M. citrifolia belongs to the family Rubiaceae is commonly familiar in India as large morinda, Indian mulberry. Its properties include immune stimulation, dietary supplementation, and the inclusion of bio-anticarcinogenic ingredients, which helps to resolve maximal side effects and improve the effectiveness of chemotherapeutic agents against cases of cancer. In rats with chemically induced tumors, the extracts have shown inhibition of tumorigenesis in the rat esophagus, peripheral T-cell non-Hodgkin's lymphoma, breast cancer, and gastric cancer (Taskin et al. 2009). Besides, the fruit juice of *M. citrifolia* has demonstrated antitumor activity and cytotoxic activity against Lewis Lung peritoneal Carcinomatosis (LLC) and various cancer cell lines such as neuroblastoma (LAN5) cell lines, breast cancer cell lines (MCF7), human laryngeal carcinoma cells (Hep2) and colorectal cancer cells (HCT-116, SW480, and LoVo) (Almeida et al. 2019).

3.27 *Ocimum sanctum*

The *O. sanctum* is a herbal plant with religious values in India. It is known as Tulsi and belongs to the Lamiaceae family. The plant also referred to as "the elixir of life" or "the queen of herbs" has traditional importance since almost all its parts are believed to be a healer of multiple health problems like cough, cold, diabetes, ulcers, inflammation, liver disorders, etc. (Jamshidi and Cohen 2017). The leaves possess several bioactive compounds such as eugenol, apigenin, apigenin-7-O-β-D--glucuronic acid, ocimarin, luteolin, ocimumosides A and B, ursolic acid, luteolin-5-O-β-D-glucopyranoside, and cerebrosides which have been recognized to possess

anticancer, antimicrobial, and antioxidant activities. The topical application of extract has shown a significant reduction in glutathione content, increased activity of glutathione S-transferase, and reduced growth of papillomas in 7,12-Dimethylbenz(a)anthracene (DMBA)-induced skin papillomas in rats (Karthikeyan et al. 2008). Several in vivo studies have indicated anticancer potential of aqueous and ethanolic extracts of *O. sanctum* and shown to reduce tumor growth in Sarcoma-180 solid tumors implanted mice model (Harsha et al. 2020).

3.28 Olea europae

The olive plant, *O. europae*, contains approximately 35–40 species and belongs to the family Oleaceae. It is widely distributed in the Mediterranean, North Africa, South East Asia, North and South China, Scotland, and East Australia. The oleic acid, Oleuropein in leaves, is known to possess anticancer effects. The role of the phenolic compound oleuropein in olive oil has been greatly explored and is reportedly downregulates the her-2 gene expression in the breast cancer cell (Farooqi et al. 2017). The triterpenes compounds like maslinic acid and oleanolic acid have shown a suitable antitumor effect in the model of colon cancer in rats, and these compounds are important factors that inhibit tumor growth and angiogenesis (Zhu et al. 2015). In another study, restoration of apoptosis in colon cancer cells was shown by maslinic and oleanolic acids present in olive fruit extracts (Ziberna et al. 2017).

3.29 Podophyllum spp.

Epipodophyllotoxin (podophyllotoxin isomer) is a bioactive compound isolated from the roots of *P. peltatum* and *P. emodi*, family Berberidaceae. Its semisynthetic derivatives like etoposide and teniposide have anticancer effects and interfere with cell division, resulting in cell growth arrest in lymphoma, bronchial, skin, vertebral cancers, and testicular cancers. The plant rhizome contains a resin known as Indian Podophyllum resin that is derived from podophyllotoxin or podophyllin. Podophyllotoxin functions as a microtubule assembly inhibitor and is used to treat testicular cancer, prostate cancer, hepatoma, and neuroblastoma (Abad et al. 2012). A plethora of evidence has identified an antineoplastic potential of semisynthetic podophyllotoxins like etoposide, teniposide, and etopophos and suggested inhibition of DNA topoisomerase II as their mechanism of action (Ardalani et al. 2017).

3.30 *Taverniera spartea*

T. spartea grows on the Southern coast of Iran including Bandar Abbas, Minab, and Baluchistan. This woody plant from Leguminosae family grows to a height of between 50 and 110 cm and is covered with short shoots. The plant's flowers are purple and pink. The active compounds found in the plant include alkaloids and flavonoids eugenol, zingerone, ginger, cadence, and vanillin and are known to exert anticancer effect (Alsemari et al. 2014). The bioactive compound of *T. spartea* includes saponins and isoprenoids that are known to induce necrosis and apoptosis in cancer cells. Anticancer effects of the plant have been reported against breast cancer cell lines (MCF-7 and BT474) and human prostate cell lines (PC-3 and DU-145) (Khalighi-Sigaroodi et al. 2014).

3.31 *Taxus brevifolia*

T. brevifolia, also known as Pacific yew or Western yew, is an evergreen conifer that belongs to the family Taxaceae and is native to the Pacific Northwest of North America. The plant is well known for its chemopreventive activities imparted by the rich presence of diterpenoid derivatives termed taxanes (Sarli et al. 2020). The chemotherapeutic drug taxol (Paclitaxel) is an antineoplastic agent derived from the yew preparations from its needle and bark. The mode of action of taxol includes chromosome missegregation via inhibition of microtubules dissociation into tubulin and preventing mitosis and cell proliferation of cancer cells. Multiple experimental proofs have showcased the anticancer activity of taxol and other semisynthetic derivatives like Docetaxel and Cabazitaxel against lung cancer, liver cancer, pancreatic cancer, prostate cancer, breast cancer, and renal cancer. More recently, the anticancer activity of colloidal silver nanoparticles of *T. brevifolia* has been demonstrated against MCF-7 human breast cancer cell line (Sarli et al. 2020). However, there is accumulating evidence reporting acquired resistance to taxol mainly due to efflux of the drug, drug inactivation, mutation of the target protein that has become a major concern about its application as an anticancer drug (Ben-Hamo et al. 2019).

3.32 *Tinospora cordifolia*

T. cordifolia is also known as Guduci (one that safeguards the body), amrita, or nectar belongs to the Menispermaceae family. It is rich in glycoside, giloin, nonglycosides, tinosporin, tinosporic acid, gilenin, tinosporidin, sitosterol, tinosporide, gilosterol, berberine, and alkaloids. The studies have shown a decrease in metastasis and tumor mass reduction in B16F-10 melanoma cells and human colon adenocarcinoma (HCA-7) cell line treated with *T. cordifolia* extracts (Palmieri et al. 2019). It

has a stimulatory effect on leukocytes, suggesting its use in cancer treatment as an adjuvant. The studies have also reported the stimulatory effect of *T. cordofolia* on macrophages and an increase in leukocytosis and neutrophil function improvement (Alsuhaibani and Khan 2017).

3.33 Urtica dioica

U. dioica is a grassy, herbaceous perennial with branched legs. The plant can be seen in the Iranian wilderness near Tehran, Karaj, on the Alborz and Shemiranat slopes and in the northern regions of Mazandaran and Gilan. Studies have shown its inhibitory effect on cell proliferation on prostate cancer cells (LNCaP and as hPCPs). A recent report has also shown anticancer effect of methanolic extract of *U. dioica* leaves against human non-small cell lung cancer cell lines (H1299 and A549 NSCLC). The study depicted the inhibitory potential of the extract with an IC50 of 52.3 and 47.5 μg/mL, respectively, against both cells (D'Abrosca et al. 2019).

3.34 Withania somnifera

W. somnifera, which belongs to the Solanaceae family, is known as Ashwagandha or Indian ginseng. The active compounds found in *W. somnifera* are Withanine, Withanolide A-Y (Steroidal lactones), tropanol, somniferinine, somniferiene, scopoletin, cysteine, chlorogenic acid, beta-sitosterol, anahygrine, and anaferine alkaloid. Withanolides have immunomodulatory activity, while Withaferin A and Withanolide D are known to inhibit cancer growth. In an experiment conducted on Benzo(a)pyrene-induced forestomach papilloma in mice, the extract has been shown to inhibit the papilloma genesis up to 60–92%. The studies have also demonstrated the anticancer potential of *W. somnifera* extract on skin papilloma genesis, colon cancer, lung cancer, brain tumor, and breast cancer (Dutta et al. 2019).

3.35 Zingiber officinale

Z. officinale (Ginger or ginger or Shengir) belongs to Zingiberaceae family. It is a medicinal and edible plant. It is grown in hot and humid areas. Ginger powder is an aromatic spice and used for savory dishes traditionally. The rhizome and leaves of ginger have been investigated to possess anticancer activity It has been explored that *Z. officinale* is effective on human colorectal cancer, breast cancer cells (MCF-7 line and MDA-MB-231), and have potential in the treatment and prevention of cancer (Mao et al. 2019).

4 Conclusion and Future Prospects

Cancer is the leading cause of mortalities around the world. Usually, chemotherapy with drugs, antibiotics, analog steroids, and alkylating agents used in the treatment of cancer is associated with adverse effects. The herbal plants are an excellent source of bioactive ingredients such as etoposide, taxols, vinblastine, and vincristine which show lower toxicity and better efficacy in numbers of oncological conditions such as testicular cancer, leukemia, breast cancer, brain tumor, etc. As the population increases enormously day by day, the demand for alternative therapy is becoming increasingly significant. Sophisticated therapeutic methods in the treatment and managing human cancer do not reach all human population in all parts of the world. Due to the high cost of modern medicines and treatment facilities, a significant number of people still rely on conventional alternative medicine systems based on plants to treat crippling diseases and cancers. Herbs and herbal supplements are plentiful, with effective anticancer activity therefore, these plants can be used and explore as a natural resource of potentially bioactive compounds to fight a battle against cancer diseases. To verify the effectiveness of many conventional herbal medicines, comprehensive safety, and quality assessment, comparative clinical trials using modern methods are required.

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