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Effective Medicinal Plant in Cancer Treatment, Part 2: Review Study

Wesam Kooti, MSC[1], Karo Servatyari, MD[1], Masoud Behzadifar, PhD[2], Majid Asadi-Samani, PhD[3], Fatemeh Sadeghi, MSc[1], Bijan Nouri, PhD[4], and Hadi Zare Marzouni, MSc[5]

Abstract

Cancer is the second cause of death after cardiovascular diseases. With due attention to rapid progress in the phytochemical study of plants, they are becoming popular because of their anticancer effects. The aim of this study was to investigate the effective medicinal plants in the treatment of cancer and study their mechanism of action. In order to gather information the keywords "traditional medicine," "plant compounds," "medicinal plant," "medicinal herb," "toxicity," "anticancer effect," "cell line," and "treatment" were searched in international databases such as ScienceDirect, PubMed, and Scopus and national databases such as Magiran, Sid, and Iranmedex, and a total of 228 articles were collected. In this phase, 49 nonrelevant articles were excluded. Enhancement P53 protein expression, reducing the expression of proteins P27, P21, NFκB expression and induction of apoptosis, inhibition of the PI3K/Akt pathway, and reduction of the level of acid phosphatase and lipid peroxidation are the most effective mechanisms of herbal plants that can inhibit cell cycle and proliferation. Common treatments such as radiotherapy and chemotherapy can cause some complications. According to results of this study, herbal extracts have antioxidant compounds that can induce apoptosis and inhibit cell proliferation by the investigated mechanisms.

Keywords

toxicity, medicinal herbs, plant compounds, cell line

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Cancer is one of the major causes of death in the world, and it is the second leading cause of mortality after cardiovascular diseases.[1] Cancer starts with the deformation of a natural cell caused by genetic mutations in DNA. This abnormal cell reproduces in an abnormal way by asexual reproduction, that is, it ignores signals related to regulation of cell's growth around it and obtains invasion characteristics and causes changes in surrounded tissues.[2]

Cancer is an important health problem in developing and developed countries. Every year, an average 182 per 100 000 persons suffer from cancer worldwide, and 102 die by cancer. According to the World Health Organization, 14 million people suffer from cancer and 8 million die by cancer worldwide. The prevalence rate of cancer in Iran is 7/134 per 100 000 people. Based on this statistics, 85 000 people suffer from cancer in Iran each year, and 55 000 people die from cancer.[3] Mortality caused by cancers is increasing throughout the world, and it is predicted that more than 13.1 million deaths will occur due to cancer worldwide by 2030.[4]

Nowadays, various methods are used for cancer treatment such as chemotherapy, but in this method, because of nonselectivity of medicines, a high percentage of healthy cells will be lost with cancer cells. The most important problem in cancer treatment is destroying tumor cells in the presence of natural cells, without damaging natural cells. In order to prepare anticancer medicines

[1] Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran
[2] Student of Health Policy, Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran
[3] Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4] Social Determinants of Health Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
[5] Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding Author:
Hadi Zare Marzouni, Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: zaremh931@gmail.com

from natural resources like plants, testing cytotoxic compounds and screening raw extracts of plants is necessary.[5]

Therefore, availability of natural products with higher effectiveness and lower side effects is desired.[6] Medicinal herbs are important for cancer treatment due to their multiple chemical compound for discovering new active materials against cancer.[7]

Plants produce a wide range of chemical compounds that apparently have no direct role in the plants' growth. These compounds are called secondary metabolite. Alkaloids, terpenoids, flavonoids, pigments, and tannins are important constituents of these compounds. Secondary metabolites have biologic effects such as anti-inflammatory, anticancer, contraceptive, and different effects on hematopoietic cells,[8] lipids,[9] and cardiovascular systems.[10]

Different improvements are reported in common treatments of cancer by finding secondary compounds of natural products and medicinal herbs. It is believed that anticancer effects of plants develop by suppressing cancer's stimulating enzymes, repairing DNA, stimulating production of antitumor enzymes in cell, increasing body immunity, and inducing antioxidant effects.[11]

Cancer is a painful disease and fighting against this disease is very important for public health. Regarding the fast progress in the phytochemical study of herbal products, plants are transforming to popular anticancer sources. In cancer, initial tumors will be treated by chemical supplement therapies or surgery. But cancers in the metastasis stage will resist against care.[12]

But in chemotherapy, due to nonselectivity of used medicines, a high percentage of healthy cells will be destroyed with cancer cells. Nowadays, more than 60% of anticancer compounds that are useful for cancer patients are obtained from herbal, marine, and microorganism sources.

The positive effect of plants in cancer treatment have been studied extensively and has shown positive results.[13] Also, different researches and studies have proved the positive effect of plants in curing diabetes,[14] fertility[15] and sterility,[16,17] thyroid disorders,[18] anemia,[19] and psychological disorder.[20] Finding plants that replace chemotherapy and cumbersome cures of cancer with cytotoxic effects is necessary.[21]

In previous article,[13] we tried to systematically study some effective Iranian plants in cancer treatment. In this article, we want to study plants, their important compounds, and effective mechanisms in detail.

Methodology

In order to collect data about different compounds, keywords "traditional medicine," "plant compounds," "medicinal plant," "medicinal herb," "toxicity," "anticancer effect," " cell line," and "treatment" were searched in domestic databases such as Magiran, Sid, and Iranmedex and international databases like ScienceDirect, PubMed, and Scopus. Searches were limited to articles in English and Persian languages, and the search interval was from 1975 to 2016. A total of 228 articles were collected. Among these, 49 articles were excluded because they were irrelevant. Finally, information was obtained from 179 articles and entered in this survey.

Findings

Achillea wilhelmsii

Achillea plant with scientific name *Achillea wilhelmsii* is from Asteraceae order and Compositaea genus. *Achillea* has different species but *Achillea wilhelmsii* is more frequent in Iran and grows in different areas. *Achillea wilhelmsii* is a gramineous, perennial, and short plant of 15 to 40 cm.

Methanol extracts and essence of leaves of this plant have cytotoxic effects on colon cancer cells (HT-29) and cytotoxic effects of essence are higher.[22] In other studies, effects of methanol extracts of plant's leaves against cell lineage of colon cancer and cancer of stomach and breast are shown.[23] Methanol extract of plant contains phenol compounds, especially flavonoids, which suppress reproduction of cancer cells through inducing apoptosis.[24,25] One of the most important monoterpene compounds of this plant that causes apoptosis in human melanoma cells is 1,8-cineole and α-piene in plants' leaf essence.[26]

Allium sativum *L*

Allium sativum is a plant from Aparagales order, Amaryllidaceae family, Allianceae subfamily and *Allium* genus. *Allium sativum* is a garmineous and permanent plant, with a stem size of 40 cm. Its underground part is inflated and composed of 5 to 12 parts enclosed in fine and slender membranes in gray-white. Its leaf is thin and filet in dark green, and its flowers are small and pink like an umbrella at end of the stem.

Various research have shown that *Allium sativum* and organosulfuric compounds reduce the risk of cancer in breast, larynx, colon, skin, womb, gullet, bladder, and lung.[27,28] In other research, we refer to the role of the most important *Allium sativum* compound, that is, Allicin, and the antitumor characteristics of this compound on breast and prostate cancer are proved. This compound induces planned death of cells and has a anticancer role.[29,30] When *Allium sativum* is crushed and cracked up, Allicin 1, under the effect of an enzyme, changes to Allicin 2. Allicin is a proliferation inhibitor of malignant human cells. Ajoene is another compound that suppresses proliferation of leukemia and will cause planned death of cell.[31,32]

Ammi majus

A white flower with scientific name *Ammi majus* belongs to Apiaceae family, and it is an annual and dicotyledonous plant with autumn germination. It is a long and thin plant that grows to 100 cm in general conditions, in wet and soft lands, saline grassland, and coastal areas. This plant is cultivated in Europe and Mediterranean area, western Asia, and even in India.[33]

The effect of ethanol's extract of this plant on HeLa and MCF7 was studied and results showed that this plant's extract has toxic effect on these cells.[34] Comorian compounds (as part of phenol compounds) are major compounds of this plant, and main biological activities of this plant are attributed to them. Research has referred to cell toxicity of coumarin compounds

on cell lineages, and apoptosis induction by these compounds is studied and confirmed. Psoralens are the most important coumarin compounds of this plant that can play an anticancer role, inhibiting cytochrome p450 activity.[35]

Ammi visnaga

Ammi visnaga L is a garmineous and perennial plant that grows in Mediterranean areas. This species is divided into 3 components: alegrian, furanochromones, and flavonoids.[36] It is seen in the north of Iran in Geilan, Roudbar, Manjil and in south of Iran in Bushehr and Shahbazan at a height of 800 meters. Its leaves have more cuttings and its flowers are white and umbellate. This odorant plant is of Apiaceae family, and its antibacterial, antifungal, and therapeutic effects in vitiligo have been published.[36,37]

The killing activity of different extracts of the above-ground part of this plant on T47D cancer cells has been studied.[38] Also, the inhibitory and dose-dependent effect of this plant on 2 human cell lineages, pelvic rhabdomyosarcoma and L20B of mice, have been proven.[39] Khellol, visnadine, cimitugin, and β-sitosterol are the most important compounds of this plant. Flavonoids like quercetin and kaempferol are isolated from the aqueous extract of this plant, and these compounds can justify the anticancer effects of this plant.[40]

Artemisia absinthium *L*

Artemisia is a plant in the Asteraceae family. *Artemisia* has 200 to 400 species that have clustered and bitter flowers. One species, *Artemisia absinthium* L, is native of Asian moderate areas, north of Africa, and vast areas of America. The size of this plant is 80 to 120 cm. Flowers of this plant are yellow and clustered.[41]

A research on breast cancer cells MCF-7 has been reported.[42] Similar results related to the anticancer characteristics of this plant on 3 cancer cells HeLa, HT-29, and MCF7 have been reported. In a study about the Artemisinin effect of this plant on breast cancer cells, it was determined that plethoric reaction in cancer cells involves inhibiting cell's growth, apoptosis, preventing angiogenesis, preventing cell migration, and decreasing responses of core receptors.[43] Quercetin, isorhamnetin, kamfrolinalol, alphapinin, limonene, and myrecene are the other compounds of this plant.

Quercetin inhibits growth of many cancer cells such as MCF-7, and isorhamnetin inhibits growth of many cancer cells such as MB-435, SKMEL-5, Du-145, MCF-7, and DLD.[44] Also, artesunate is one of the most important artemisinin that has angiogenic effect, and in addition to anticancer effects on K569 (leukemia cancer), it inhibits the production of angiogenic factor VEGF.[45] In other research, alpha-pinene, beta-pinene, limonene, and myercin available in the plant are probable factors of inhibiting the growth of human breast cancer and hepatic and melanoma. Alpha-pinene, beta pinene, and limonene available in methanol and ethanol extracts of this plant are inhibitory factor of HT-29 cells (colon cancer).[46]

Astragalus cytosus

Astragalus cytosus is perennial plant from the Leguminoseae family and its height reaches to 75 cm. Its reproduction is done by seeds. Its stems are dark purple. Its leaves are composed of leaflets that are placed in 11 to 30 pairs in each leaf's axis. Its flowers are usually amethystine, blue, or white close to the end of flowering branches.

More than 200 species of *Astragalus cytosus* grow in Iran. In a research on HeLa cancer cells, the effect of toxicity of this plant's extract on cancer cell was shown.[47] Also in a clinical study on 24 patients suffering from lung cancer, 21 patients showed positive response to this plant's extract.[48] In vitro studies show that flavonoids in other species of this plant can direct carcinoma cells to apoptosis.[49]

Astrodaucus orientalis

This is biennial plant from the umbellate family. Extract of root and above-ground part of this plant show antiproliferation effects on breast cancer cells (T47D).[50] α-Pinene, α-thujene, α-copaene, fenchyl-acetate, anisole, myrecene, and sabinene are the most important compounds in this plant.[51,52] Inhibition of cell cycle and also induction of apoptosis is the main mechanism of anticancer effects of the plant.[50]

Avicennia marina

Avicennia marina is species of mangrove plants. Mangrove plants are halophyte plants resistant against sea salt. Mangrove is dominant species in the Mangro ecosystem. This plant is like a bush or shrub with a height of 1 to 10 meters. It has a white shell or gray or yellowish green, and its leaves are oval or sharp. Its flowers have 4 white or yellowish orange petals.

Flavonoid compounds of its leaf extract have anticancer effect on human breast cancer BT-20 cells. In another study, by separating naphthoquinone from leaf of the plant, anticancer effect of this compound on laryngeal cancer cells (kb) was shown.[53] A cytotoxic effect of the extract on breast cancer cells (row 231MDA-MB) is confirmed.[54]

Boswellia serrata

Boswellia serrata is a medical plant from Spindales order and Burseraceae family with names Olibanum or Frankincense. It is obtained from specie *B sacara*, *B frereana*, and *B serrate* in Bosoolia. Hydroalcoholic extract of this plant causes death of cervical cancer cells (HeLa cell) and this effect is dependent on dosage and time.[55,56]

In another study, alcoholic extract of frankincense resin caused disorder in the biosynthesis of DNA and RNA and proteins inhibit the tumor growth and induce apoptosis in cancerous cells in mice. In a research on leukemic cells HL60, it was shown that frankincense reduces viability of the cells.[57,58] Monoterpene, diterpene, and triterpene and boswellic acid are the main ingredients of frankincense resin, which can induce apoptosis in cancerous cells.[59] In fact, frankincense extract, by

increasing production of reactive oxygen species and by activating caspases, causes apoptosis and severe damage to cells.[60]

Camellia sinensis

This plant is a kind of tea that is obtained from the buds and petals of fresh herb. In the process of producing this tea, little oxidation occurs. Tea is a natural source of caffeine, theophylline, thianin, and antioxidants. In a study on rats, it was found that green tea could inhibit 5-alfardoctase enzymes. This enzyme converts testosterone to di-hydrotestosterone, which is a prostate carcinogenic agent. Accordingly, it has been found that green tea can have an inhibitory effect on prostate cancer.[61]

In this regard, the antitumor effect of green tea on prostate cancer has been shown.[62] Green tea contains polyphenols such as epicatechin, epigallocatechin, epigallocatechin, and epigallocatechin-3, which have anticancer effects.[63-65] Cytotoxic effects of green tea on breast cancer cells has been demonstrated.[66]

In a research conducted by Wang and colleagues in China, they concluded that green tea drinking habits, including regular drinking, greater amount of intake, and lower temperature were associated with reduced risk of gastric cancer.[67]

Citrullus colocynthis

Citrullus colocynthis belongs to Cucurbitales order and *Citrullus* genus. Used part of the plant is yellow and a very bitter fruit with the size of an apple.[68] A study showed that the extract of this plant may (Hep2) have toxic effects on larynx cancer cells.[69] According to studies, chemical constituents of this plant such as cucurbitales are used as anticancer medicine in cancers such as liver (HepG2) and breast (MCF7) cancers; quercetin and β-sitosterol as antitumor agents have been studied in in many researchs. These compounds act by inhibiting cell cycle (cycle stops at G2/M), and the induction of apoptosis can impose anticancer effects.[70-73]

*Saffron (*Crocus sativus *L)*

Saffron *Crocus sativus* L belongs to the Iridaceae family. This plant in Iran is native of Khorasan. Saffron is a perennial plant, with height 10 to 30 cm, from the bulbs of this plant, with narrow leaves exits. This plant has 1 to 3 purple flowers. The used part of this plant is stigma, known as saffron.[74]

Various studies showed anticancer effect of the saffron extract on cancer cells in vitro; for example, Escribano et al, in a study on the effect of saffron extract on human cancer cells, found that the materials separated from saffron such as crocin, crocetin, picrocrocin, and safranal induced apoptosis in cancer cells.[75,76]

In another study, the effect of saffron extract and other major plant substance called quercetin on colorectal cancer cells was studied and the results showed the toxic effects of this plant on these cells.[77] Another study also showed the anti-angiogenic effects of this plant on breast cancer cells (MCF-7), and extract of this plant inhibits angiogenesis in these cells.[78]

In fact, the saffron extract, by inhibiting DNA synthesis, can exert its anticancer effects.[79] However, in the consumption of high doses of this herb, the necessary precautions should be taken because according to Rahimifard et al's study on the human cervical cancer cells, larynges cancer cells, and natural human monkey kidney, it was observed that toxicity on natural cell is higher than 2 cancer lines, which indicated precaution in consumption of high dose of saffron.[80]

Another research has studied effect of cellular toxicity and apoptogenic properties of saffron extract on the cancer cells and concluded that saffron can play an important role in cell death of HeLa and HepG2 cells and apoptosis. Saffron can be used as a chemotherapeutic agent to treat cancer in the human in future.[81]

Curcuma longa

Turmeric is a plant with scientific name *Curcuma longa* from the Zingiberaceae family. This perennial plant usually requires humid and rainy environment. The main habitat of turmeric is hot areas of Asia such as India, Pakistan, Indonesia, and southern China, and it is native of Africa and South America. Turmeric has underground stem called rhizome. Several aerial shoots as high as 1 to 1.5 meters exit from these rhizomes. Edible part of turmeric is dried rhizomes.[82]

The study of cytotoxic properties of turmeric on liver cancer cells (Hep-2) showed that the cytotoxicity mediated by curcumin in a dose-dependent manner leads to apoptosis of cancer cells through mitochondrial pathway.[83]

The results of studying the effects of its extract on telomerase activity in breast cancer showed anti-proliferative and inhibitory effects of telomerase.[84]

In another study, it was found that turmeric imposes its cytotoxic effects on lung cancer cells through inhibition of telomerase activity in a dose-dependent manner.[85]

Curcumin, as an important ingredient of turmeric, plays a significant role in the prevention and treatment of primary ovarian cancer, and multiple clinical studies have proven its effectiveness.[86]

The anticancer potential of curcumin against cancers, including leukemia, lymphoma, digestive, urinary, reproductive, breast, uterus, ovary, lung, melanoma, colon cancers, and brain tumors have been shown.[87] Free radicals and toxic products of oxidative stress play a significant role in the development of many diseases, including cancer, and curcumin has antioxidant effects that reduce or inhibit damage caused by free radicals.[88]

One study showed that treatment of human blood lymphocytes with curcumin significantly reduces genetic damage caused by radioactive iodine-131.[89] Another study showed that curcumin induces apoptosis and inhibits proliferation of cancer cells. Apoptosis occurs due to release of cytochrome and its effect on P53 protein as well as the effect on intracellular signals is responsible for stopping cell growth.[90] In fact, the mechanisms by which curcumin inhibits tumor formation are combination of properties including antioxidant,

anti-inflammatory, anti-angiogenic, anti-metastatic, inhibition of cell cycle, and proapoptotic, which induce inhibitory effects on the cancer through regulating genes and molecules involved in these paths.[91]

Ferula assa-foetida

Ferula assa-foetida plant grows in Iran in different regions of Khorasan, Sistan, and Baluchestan and southern parts of Iran such as Kerman, Dasht-e Murghab, Abade, and Nain. Asafoetida is a perennial plant with strong, thick, and fiber stems. Used part of this plant is a resin, which is used as a gum.

Cytotoxic effect of ethanol extract of asafoetida on liver cancer cells has been proved (category HepG2).[92] Also, consuming gum of this plant has significantly reduced the risk of colon cancer.[93] The most important ingredients in coumarin compounds are sulfur-containing compounds, and compounds such as β-sitosterol and oleic acid. In order to justify anticancer effects of ethanol extract of this plant and orgnosulfuric compounds, different mechanisms are suggested, including inhibition of gene mutation, effect on the activity of enzymes, inhibition of DNA destruction, effect on cell proliferation, and changing the activity of enzyme.[94,95] However, induction of planned cellular death is an important mechanism for anticancer effects of this plant.[96] Cytotoxic activity of phytochemical compounds in some species of *Ferula* against cell lines including ovarian carcinoma (CH1), lung cancer (A549), and melanoma (SK-MEL-28) has been studied, and it has been shown that these compounds can have mild killing effect on cells.[97]

Glycyrrhiza glabra

Glycyrrhiza glabra is wild plant from vegetables family, native to southern Europe, North Africa, and temperate regions of Asia. It grows in most parts of Iran, especially in the eastern and northeastern Khatam Marvast city and territories as well as Azerbaijan and Eghlid city. Its leaves are compound and consists of 4 to 7 leaf pairs plus an end leaflet that is sticky due to secretion of juice. Flowers are blue and its fruit contains 5 to 6 brown seeds. Its roots and stems have medical use.[98] Extract contents of the root lead to morphological changes in the mammary cell line 4T1 and reduce their viability.[99] Its root extract induces BCL2 phosphorylation and, like Taxol, inhibits the cell cycle at the G2/M phases in tumor cell lines.[100]

Glycyrrhizin, is a triterpene glycoside that is the main compound in root extract and acts as an anti-proliferative agent against tumor cells, especially breast cancer cell line (MCF-7) and HEP-2 and plays its role by inducing apoptosis.[101,102]

Glycyrrhiza glabra root extract induces apoptosis in HT-29 cells; therefore, it is useful in the treatment of colon cancer.[103]

Lagenaria siceraria *Standl*

Bottle gourd is a species of Cucurbits that has yellow skin and is less edible. This plant has a very large head and a small head and a narrow waist. The naming of the pumpkin is because of its shape. The effect of the plant extract on human lung cancer cell line A549 has reviews, and it has been shown that the extract could significantly inhibit the cell line.[104]

Antitumor effect of methanol extract of aerial parts of this plant has been demonstrated.[105] In another study, water-soluble polysaccharide isolated from this plant and its effect on carcinoma of human breast cell lines (MCF7) has been proven.[106] In addition, its fruit is a source of vitamin C, beta-carotene, vitamin group B, saponins, and cucurbitacin. Cucurbitacin belongs to 4-ring terpenoids that has cytotoxic activity.[107,108]

Lepidium sativum

Watercress is an annual plant that is known as Jrjizbastany and Rashad in Iranian ancient medicine. It has light green leaves, small red or white flowers with gentle fragrance that jointly appear at the end of branch. The fruit is oval with an approximate length of 50 mm and a width of 4 mm. Cytotoxic effects of methanol extract of cress seeds on the bladder cell line (ECV-304) has been reported.[109] Also, Aslani et al have shown, in a study of aerial parts of the plant, the cytotoxic effect on K562 leukemia blood lines.[110] In another study, the effects of aqueous extract of seed on breast cancer cells (MCF-7) through induction of apoptosis have been demonstrated.[111]

This plant is rich in antioxidants such as vitamins E, C, B, A, isotiosinat, and omega-3 fatty acids such as alpha-linolenic acid as well as glucosinolates, and these compounds can impose their anticancer effects through antioxidant properties and inhibit the proliferation of plant cell.[110,112]

Medicago sativa *L*

Alfalfa is plant with scientific name *Medicago sativa* L that is usually found in most parts of the world and has been used in traditional medicine for the treatment of various diseases such as hepatic disorders.[113] Phytoestrogens in the plant and strong estrogenic activity of this plant is useful in treating hormone-dependent cancers.

Alfalfa contains large amounts of almost all vitamins, flavonoids, digestive enzymes, coumarin, the alkaloid amino acid, and trepans, and it is also useful for breast cancer and also increases the breast milk. Alfalfa contains triconlin, which is a plant alkaloid compound and has a hormone role in the plant. It is believed that this plant alkaloid has important medicinal properties such as anticancer effects.[114,115]

Mentha pulegium

This plant with the scientific name *Mentha pulegium* and the English name European pennyroyal belongs to the Labiaceae family. Pennyroyal is a gramineous plant, and its shrubs grow to a height of 60 cm, and grows wild in many fields. This plant has oval leaves and small, regular sharp teeth. Flowers of this plant with leaves and stalks are mostly in the upper shaft and the colors are purple.

Aslani and colleagues reported research before flowering the plant's cytotoxicity effect on leukemia cells. There are natural substances that are included in Pennyroyal polygon, mentone, piperitone, limonene, isomenthone, and Octaan-3-ol;[116] in some studies the inhibitory effect of flavonoids on proliferation of cancer cells via apoptosis induction refers to Pennyroyal.[117]

Myrtus communis

The scientific name *Myrtus* or Mort is a genus of *Murdian*. Genus of evergreen shrubs or trees with 1 or 2 species native to southern Europe and North Africa are *Murdian*. This plant is an evergreen shrub or bush that sometimes reaches a height of 5 meters. Its leaves are about 3 to 5 inches long and have a nice smell. It has petals of white color and blue ball-shaped fruits.[118] In some studies, the plant has been referred for its anticancer effects. The plant also shows cytotoxic activity on cancer cell lines MCF7.[119-121] Polyphenols, myrtucommulone, semi-myrtucommulone, 1,8-cineole, α-pinene, myrtenyl acetate, limonene, linalool, and α-terpinolene are some of the most important compounds found in this plant.[118] In most studies anticancer properties of this plant are attributed to plant phenolic compounds (especially mitocomolon). Cell cytotoxic effects are on their cell layer.[122]

Induction of apoptosis in cancer cells due to external and internal ways is a mechanism to deal with cancer cells.[123]

Nigella sativa

Black seed is of the Ranunculales Ranunculaceae family. This annual flowering plant is native to southwest Asia. This plant grows in abundance in Arak and Isfahan in Iran. A study presented an overview of the antioxidant protective effects on the liver of the anticancer effects of the plant *Nigella*.[10] In this context, evaluation of alcohol on the effects of *Nigella sativa* on kidney cancer cells (ACHN) showed an apoptotic effect on these cells.[124] Its Kvyynvny compounds and dinitro-quinone are like thimoquinone.[125] In a study of colorectal cancer cells, the effects of thimoquinone on inhibiting cancer cell growth, apoptosis, and increased cell morphological changes was shown. It also has been shown to induce programmed cell death, with the anticancer activity being observed in an alcoholic extract of *Nigella sativa*.[126-129]

In a study the effect and mechanism of black beans has been shown in the treatment of breast cancer.[130]

In a research conducted by Elkady and colleagues, the effect of *Nigella* and the mechanism in the treatment of colon cancer in humans was demonstrated.[131]

Olea europae

Olive plant with the scientific name *Olea europae* L contains approximately 35 to 40 species and belongs to the family Oleaceae. Since ancient time hot or lukewarm areas such as the Mediterranean, North Africa, Southeast Asia, north to southern China, Scotland and East Australia have a wide distribution. Olive tree leaves are narrow, dark green, and permanent evergreen. Olive flower clusters have leaves that appear from the side and have 4 petals and 2 flags and flower cluster.[132]

In a study of the anticancer effects of olive oil, the most important leaf and its compounds (especially oleic acid) are mentioned.[24] In other anticancer effects, pinoresinol found in olive oil has an effect on colon cancer.[133] The role of phenolic compound oleuropein in olive oil is also important, suggesting that this compound acts directly on the her-2 gene in breast cancer cells and controls.[134] The study also showed that acidic triterpenes found in olive oil can inhibit tumor cell proliferation and induction of apoptosis in some categories. Two of these compounds, maslinic acid and oleanolic acid, showed acceptable antitumor effect on colon cancer model in rats, and these compounds inhibiting tumor growth and angiogenesis are important factors.[135]

Pegaum harmala *L*

This herbaceous perennial plant is from the perennial family Zyqophyllaceae Nitrariaceae. This plant grows in Mediterranean regions such as North Africa, Turkey, Syria, and usually grows in arid lands. It grows to about 30 to 50 cm length, and has a plant-like appearance, with green leaves and regular water-filled narrow divisions. It has large flowers with greenish-white sepal and large petals. Its extract also reduced the viability of epithelial cervical carcinoma cells and carcinoma of the colon.[136] This plant is made up of mainly alkaloids and these alkaloids have anticancer effects. In another study that was conducted using chemical analysis, the antioxidant activities of these alkaloids against human breast cancer cells were noted.[137]

Physalis alkekengi

It is a perennial herbaceous plant with creeping rhizome stems of potato corners. The effect of aqueous extract of this plant on U937 cell cytotoxicity was positive.[138] The basic compounds of physalin plants belong to the group of triterpenoids. Anticancer cytotoxic activity of physalins B and M extracted from the plant on cancer cells (especially human cell line HeLa and Hepatum cell lines SMMC-7721 and HL-60) is verified.[139]

Polygonum aviculare

Caryophyllales Polygonaceae plant belongs to the genus *Polygonum*. *Aviculare* plants grow throughout the year and the chronometer stem reaches a length of 50 centimeters. Its leaves are small and sharp, with tiny pink flowers in it. This plant grows in most areas of Asia, Europe, Africa, and America and in most parts of Iran. In some studies, the effect of the extract on the inhibition of proliferation of cancer cells HeLa has been reasonable.[140,141] The effects on cell proliferation and expression of apoptotic genes in breast cancer cells (MCF7) showed that extracts of the plant through the induction of apoptosis can

cause cytotoxicity in cancer cells of breast.[142] Tannins, flavonoids, and alkaloids are the most important components of this plant.[143] However, studies of anticancer effects showed that despite phenol compounds the effects of the plant is considered the main cause.[140,142]

Rosa damascenes *Mill*

Rose or rose (scientific name: *Rosa damascenes* Mill) has long been cultivated in different climatic conditions. It is from the family Rosaceace and the flowers and leaves of the plant are its active ingredient is tannin. It is a perennial shrub, close to 5.1 meters in height, and has a cylindrical shaper without grooves.

The toxic effects of this essential oil on lung cancer cell lines (A549) and breast (MCF7) have been reported. The ethanol extract of the plant cell has killing effect on cervical cancer cells (HeLa).[144] Rosa Damascena essential oil affects gastric cancer cells in 2 specific ways: the soluble phase increases cell viability, while the vapor phase decreases cell survival. Also, flow cytometry showed that apoptosis is the important mechanism accompanied with cell death.[145]

Silybum marianum

It belongs to the family Astir Asteraceae. Milk thistle is a plant native to the Mediterranean and spread throughout Europe. It grows in vegetative arid land, roadsides, arable land, and similar places such as beaches and mountains. The vehicle and shrubs are for the duration of 1 or 2 years. It appears from 30 to 200 cm and its cone-shaped flower colors are red to purple.[146]

Also a study has shown that silymarin causes cell cycle arrest and apoptosis on the 4T1 cell line.[147]

Taverniera spartea *D*

Silver spartea plant with the scientific name *Taverniera spartea* D usually grows on the southern coast of Iran including Bandar Abbas, Minab, and Baluchistan. This woody plant, shrubs growing to a height of 50 to 110 cm, is covered with fluff on a bed, with short shoot. The flowers of this plant are purple and pink. This plant is flowering to March.[21] Methanol extract of the plant, especially chloroform fractions, showed toxic effects on breast cancer cell lines (MCF-7 and BT474) and human prostate cell lines (PC-3 and DU-145).[21] The anti-cancer effects of the plant have been reported.

Taxus baccata *L*

Yew tree with the scientific name *Taxus baccata* L is gymnosperms from the family Taxaceae. There are 3 species of yew trees, and *Taxus baccata* L is the only species native to Iran. Yew is an evergreen tree with a very long life and slow growth. This tree has a smooth trunk has a height of up to 30 meters and diameter up to 5 meters. This species is native to Europe, the Caucasus, North Africa, and Iran. Yew in the woods of northern Iran is often Azadshahr from Astara. Yew tree grows at high altitudes in mountain areas, deep dark valleys, steep slope ranging from rocky and semihumid to wet and cold conditions.

This plant is one of the first plants on which extensive research has been done on the effects of cancer prevention. Taxol is one of the natural ingredients of the plant that has anticancer effects.[148,149] A study has shown that the acetone-dichloromethane extracts of the plants have a cytotoxic effect on cancer cells k562, HeLa, and MDA-MB-468.[150]

Thymbra spicata

Zufaee thyme plant is from the family Labiaceae, and the plant grows preferably in dry and sunny areas and on the slopes of dunes. There are various plants that grow to 15 to 40 cm in height and has flowers that are purple. It is because of thymol and carvacrol that there is biological activity. Various parts of the plant essential oil is a good source of antibacterial and antioxidant properties. Hydro-alcoholic plant inhibitory effect on lung cancer cells (SK-Mes-1) has been shown.[151] Thyme, thymol, and carvacrol are the most important plant phenol compounds with antioxidant properties, prevents oxidative damage to DNA, and thus can prevent cancer.[152]

Thymus vulgaris

Thymus vulgaris L has the the English name garden thyme. It belongs to the family Lamiaceae and has a straight stem and is herbaceous or woody and grows to a height of 20 to 30 cm. This plant has branched stems that are covered with white fluff. This plant has aromatic leaves that are usually evergreen and flowers are pale purple to white in color.

In the prostate study on rats it was found that thyme extract inhibits the growth of abnormal and precancerous lesions and treats[153] and also inhibits the growth (in laboratory conditions) of squamous cell carcinoma of the head and neck.[154,155] This plant has a variety of compounds, including flavonoids. Thymol and carvacrol are the most important plant phenol compounds that are useful in the treatment of breast cancer and colorectal cancer.[156]

A study proved that thyme inhibits proliferation of human colorectal cancer cell migration and invasion.[156]

In another study, the effect of inhibiting growth was proved in human breast and colorectal cancer.[157]

Trigonella foenum-graecum *L*

Fenugreek or Shanblid (scientific name: *Trigonella foenum-graecum*) is a plant of the Fabaceae family with height of 10 to 50 cm with single flowers that are bright yellow to brown. This plant is native to Iran and in most parts of Iran, including Azerbaijan, Isfahan, Fars, Khorasan, Semnan, and Damghan and are edible vegetables.[158] In a study of the effects of crude extract of fenugreek, there was selective cytotoxicity against some cell lines such as MCF7, TCP (T-cell lymphoma), FRO (thyroid papillary carcinoma), and brain tumors.[159] It is also

protective effect against breast cancer induced by DMBA (7,12-dimethylbenz(a) anthracene) in mice.[160]

In another study, the inhibitory effects of the plant extract on the growth of cancer cells EAC was shown. Flavonoids and alkaloids in the plant, such as ginger, cadence, zinger one, vanillin, and eugenol, have been shown to be involved in anticancer effects.[159-162] The main mechanism of anticancer activity is apoptosis induction.[159,160]

Urtica dioica *L*

Nettle (scientific name: *Urtica dioica*) is a grassy, herbaceous perennial with branched legs. Shoot is straight and square, and leaves of bitter Azkrk are covered. It can be seen in the wile in Iran near Tehran, in Karaj in Alborz slopes, and the hive Shemiranat, and in the northern regions in Mazandaran and Gilan and Drazrbayjan, on the slopes of Sahand, Zanghab, and Lorestan (in the river).[163] Studies have shown cell proliferation inhibitory effect on prostate cancer cells (LNCaP and as hPCPs) by aqueous and ethanol extracts of the plant.[164-166] Also, a report has referred to the anticancer effects of this plant against esophageal cancer.[167] Plant compounds with antioxidant phenol compounds are those that may have an important role to prevent cancer. In a study, the antiproliferative effect on human prostate cancer cells by nettle root extract has been proven.[168]

Vinca rosea

Belonging to the genus *Vinca* and oleander it has for a very long time been an important medicinal plant of great concern. In a study on human skin cancer cell line A431, the methanol extract of the plant had a positive effect on reducing the proliferation in this category.[169] Alkaloids such as vincristine, vindoline, vinblastin, vinflunine, and catharantin in the aerial parts are different from vincristine and vinblastine, and among them 2 combinations of plant secondary metabolism are used today as anticancer drug.[170,171] The effects of this plant's alkaloids on cancer cells of breast, prostate, cervix (MCF-7, PC3-1C, HeLa) were studied, indicating that these alkaloids' tubular protein links changed its structure by blocking the division of cancerous cells; these compounds with antioxidant properties will prevent cancer cells from progression.[169,172]

Viola tricolor

Violet plant with the scientific name *Viola tricolor*. Violets are herbaceous plants, resistant to cold throughout the year and grows to a height of up to 25 cm. Small flowers of this plant with different colors including bright and family purple, white, and yellow flowers that appear in spring and summer and become the fruit capsule. Aqueous extract of this plant has a strong inhibitory effect on proliferation of cervical cancer, and the active ingredient of the plant responsible for this effect is ethyl acetate.[173] This plant contains a number of compounds that have cytotoxic effects of potent cells.[174] Studies have shown that flavonoids can have anticancer effects.[175,176]

Zingiber officinale

Zingiber officinale is a member of the Zingiberaceae family. Ginger or ginger or Shengir is an edible and medicinal plant. It is grown all over India, especially in hot and humid areas. Ordinary ginger rhizomes of ginger powder is spicy and aromatic spices are used for savory dishes traditionally.[177] This plant has bright green slender stalks that grow from glandular stem. Ginger flowers are yellowish green with purple edges and pale spots.

The aqueous extract of *Zingiber officinale* is effective on breast cancer cells (MCF-7 line and MDA-MB-231), and morphological changes observed in cancer cells that were extracted under array indicate that cell death induction program has been destroyed.[178,179]

Conclusion

Several therapeutic procedures are available for the treatment of cancer, and in most cases, undesirable side effects (gastrointestinal disorders, kidney damage, and other complications) are associated with them. These compounds include alkaloids, phenol compounds, and monoterpenes. In addition to these, indicators such as vinblastine, vincristine, curcumin, Taxol, boswellic acid, and umbelliprenin and compounds such as quercetin, catechin, cucurbitacin, kaempferol, thymol, carvacrol, 1 and 1,8-cineole, α-pinene, myrecene, and β-sitosterol have anticancer effects. These compounds have antioxidant properties, and inhibition of damage to DNA, cell cycle arrest (especially at the G2/M), induction of apoptosis, inhibition of angiogenesis in tumor cells, and its anticancer effects are new and more effective.

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Author Contributions

Study concept, design, and critical revision of the manuscript for important intellectual content: Wesam Kooti, Karo Servatyari. Drafting of the manuscript and advisor: Majid Asadi-Samani, Masoud Behzadifar, Fatemeh Sadeghi, Bijan Nouri, Hadi Zare Marzouni.

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