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Review Article

Review on Iranian Medicinal Plants with anticancer Properties

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ABSTRACT

Introduction: Cancer is abnormal and uncontrolled cell proliferation. Carcinogens cause DNA damage and loss of function of tumor suppressor genes, resulting in tumor formation and metastasis. Some carcinogens are physical factors such as ultraviolet radiation, chemical factors such as cancer-inducing chemical compounds, cigarette smoke, unbalanced diet, occupational, hereditary, hormonal, metabolic, and biological factors, especially some bacteria and viruses.
Materials: Nowadays, an essential cancer treatment is chemotherapy that may cause drug resistance and various side effects. Some plants have long been considered reliable and excellent sources for developing anticancer drugs. Some plants play a protective and therapeutic role in cancer, while others reduce the side effects of chemotherapy and radiotherapy and are also economically viable. Some natural marine compounds and minerals are also known to inhibit tumors.
Results: The present paper reviews the most critical natural anticancer substances globally and introduces the most essential mechanisms of their effect. Traditional medicine of most countries includes various natural compounds used to treat different types of cancers. Some of the most essential traditional natural anticancer substances known worldwide include *Catharanthus roseus, Podophylum peltatum, Combretum caffrum; Campetotheca acuminate; Brucea antidysenterica*.
Conclusion: The mechanism of anticancer effect of most of these substances is related to their antioxidant properties and inhibition of the growth of their tumor cells. Many of these materials are traditionally used in different parts of the world.

Keywords: Antioxidant, anticancer agents, malignancy, phytochemicals.

1. Medicinal Plants Containing Anticancer Compounds

In many parts of the world, cancer is the second leading cause of death after cardiovascular disease. Current problems in the use of chemotherapy and radiation therapy and their use numerous side effects for the patient and the resistance of cancer cells to conventional therapies, researchers were encouraged to new

drugs with greater effectiveness and less toxicity for the following reasons [1].

Plants have a long history of treating cancer. However, many of these claims should be doubted, as cancer is vaguely defined as a disease in popular culture and traditional medicine. Even diseases such as warts and pimples are considered cancers in some traditional medicine systems [1]. However, natural products have been shown to play an undeniable role in treating cancers. A study of anti-neoplastic drugs in Western countries and Japan found that most of the 140 substances used (54%) were of natural origin. In the meantime, some of them were supplied only from biological sources. Others were derivatives of natural products. The synthetic production of natural products produced some. Exploring new anticancer agents from natural sources, especially plant secondary metabolites, is still ongoing, and such research has aroused much scientific and commercial interest [2, 3]. Nature is a fantastic source of suitable new drug compounds with great chemical diversity. The purpose of this study is the effect of medicinal plants on cancers in Iran. Potent plant-based anticancer drugs are used clinically with a wide range of effects and different mechanisms of action. Some of the most important plants with anticancer properties are as follows [1]. This article reviews Iran's medicinal plants that have been already examined for anticancer effects and alsoreviews Iran's medicinal plants that have been already examined for anticancer effects and seek to offer their main compounds and mechanisms anticancer activities. This review article could open a way to develop new anticancer drugs to prevent and treat cancers.

1.1. *Catharanthus Roseus* (Apocynaceae)

Catharanthus roseus has a long history of treating a wide range of diseases and has been used for centuries in Europe, the West Indies, and the islands in the Indian Ocean against diabetes. Drugs such as Vincolin in the UK and Quincka in South Africa, derived from this plant, are now used to treat diabetes [1]. This traditional use of *Catharanthus roseus* led to preliminary laboratory studies in the 1950s. The results showed that the treated experimental animals had low levels of white blood cells, which left them vulnerable to bacterial infections. This observation suggests that one or more alkaloids may be present in *Catharanthus roseus,* reducing or stopping white blood cells' production. This mechanism may have evolved in nature to protect this plant from herbivores. Subsequently, more than 150 alkaloids were isolated and identified, some identified as indole alkaloids, such as dimeric alkaloids and bisandole alkaloids. Separation of these compounds by bioassay led to identifying the complex alkaloid compounds of vincristine and vinblastine (Figure 1) [3, 4].

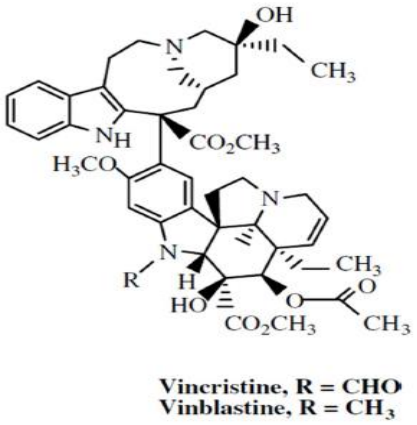


Figure 1. Vinblastine and Vincristine [2].

The concentration of vincristine in the plant is extremely low (0.0002%), and therefore, this drug is costly. Vincristine and vinblastine exert their anticancer properties by inhibiting mitosis by binding to tubulin, which prevents the

formation of spindles (which are necessary for the movement of chromosomes during division) [3].

Vinblastine is marketed under the brand name *Eli Lilly* and is used to treat Hodgkin's disease, lymphomas, advanced testicular cancer, advanced breast cancer, and Kaposi's sarcoma.

However, it has significant side effects: hair loss, nausea, decreased blood cells, etc. [2, 3].

Vinblastine is marketed as Oncovine by Eli Lilly to treat acute leukemia, Hodgkin's disease and other lymphomas. The semi-synthetic alkaloid windsin (sold as aldycin) is used to treat leukemia and lung cancer. In contrast, vinorelbine (sold as navelin) is sold by Glaxo Smith Kline to treat ovarian cancer.

Vinorelbine has a broader antitumor spectrum than other Vinca alkaloids and is combined with cisplatin to treat non-small cell lung cancer [3].

1.2. *Podophylum peltatum* (Berberidaceae)

The common name of this plant is the Satan's apple or American mandrake. This perennial plant is found in forested areas of North America. The plant's rhizome (the most crucial part) is poisonous. The most important compounds in it are podophyllotoxin (Figure 2) and alpha and beta-platinum, all toxic. Podophyllotoxin lignans are also found in other podophyllum species. This plant has a long history in the traditional medicine of Native Americans and Asian tribes. The natives collected the rhizomes in the fall and then ground them. They cured constipation or intestinal worms by eating this powder or drinking its decoction. Today, extracts of this plant are used to treat genital warts and some skin cancers, but it should be noted that these extracts and their compounds are toxic to the extent that should be avoided arbitrarily [3, 5].

Podophyllotoxin was first purified in 1880, and its structure was determined in 1932. By carefully examining the structures of active compounds belonging to this material, the presence of structural forms such as 5-lactone ring, a group of 3, 4, 5-trimethoxyphenyl and a group of methylene dioxyphenyl as factors responsible for the biological activity of these compounds is confirmed. This natural compound is used to produce its semi-synthetic derivatives, autoposide and teniposide. Autoposides are now used to treat small cell lung cancer, testicular cancer, and lymphomas, while carcasses treat brain tumors [5].

Podophyllotoxin binds to tubulin to prevent the formation of microtubules, thereby preventing cell division. Such compounds are called samaduk. Although autoposides and teniposides are podophyllotoxin derivatives, they act through different mechanisms. These compounds work by inhibiting the enzyme topoisomerase II and thus inhibiting DNA synthesis. Interestingly, the difference in the mechanism of action of these compounds occurs only due to minor differences in the stereochemistry of these molecules [2].

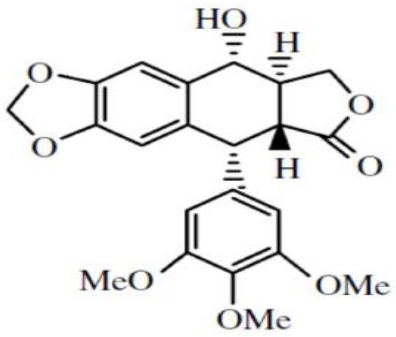


Figure 2. Podophyllotoxin [2].

1.3. *Combretum caffrum* (Combretaceae)

The roots of the African bush-willow tree, found in South Africa, are commonly used in traditional medicine to treat body

aches. Screening of plant extracts led to the separation of camberostatins. Among these substances, camberostatin was one of the most critical potential anti-mitotic agents (Figure 3). Camberostatins belong to the acetylene family and act as anticoagulants which cause blood vessels to block in tumors. The use of this compound against challenging tumors leads to tumor necrosis [3, 6].

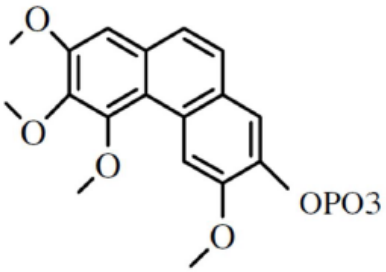


Figure 3. Camberostatin A_4 phosphate [3].

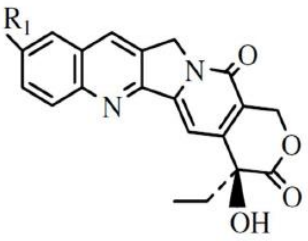
It has high cytotoxicity against many cancer cells, such as multidrug-resistant cancer cell lines. It has also been shown to have particular effects on proliferating endothelial cells. Disodium phosphate is a water-soluble prodrug that has been shown to have antiperspirant and antitumor properties in a wide range of preclinical tumor models. Cemberstatin phosphate has successfully passed the Phase I clinical trials and is currently undergoing the Phase 2 clinical trials.

$CA-4$ has high cytotoxicity against many cancer cells, such as multidrug-resistant cancer cell lines. It has also been shown to have highly specific effects on proliferating endothelial cells. $CA-4$ disodium phosphate (CA4DP) is a water-soluble prodrug that has been shown to have antiperspirant and antitumor properties in a wide range of preclinical tumor models. Cemberstatin A4 phosphate has completed phase 1 clinical trials and is currently undergoing phase 2 clinical trials.

This drug has also shown to have no cumulative toxicity (accumulation of toxins at any stage of use). These results have led to the synthesis of many compounds based on the skeletal structure of camberostatin to provide more effective therapeutic agents [3].

1.4. *Campetotheca acuminata* (Nyssaceae)

To find anticancer agents, the National Cancer Institute screened extracts of the bark of a Chinese ornamental plant called *Campetotheca acuminate*, locally known as the happy tree (Xi Shu in Chinese). Initial screenings showed that the extracts were effective against mouse leukemia. Separation of its active compounds based on biometrics led to identifying its active ingredient, comptotsin, which is a quinoline alkaloid. This compound is very effective against leukemia cells and hard tumors in its sodium salt form. Analogs of this drug have been prepared, such as Topotcan, 9-Computotsin, and CPT-11. Computotsin and its analogues have been studied to treat many cancers, yet these compounds are highly toxic. 10-hydroxy-competocin (Figure 4) has better biological activity than compotocin, among other Campetotheca metabolites [3, 6].



R_1 = H, Camptothecin
R_1 = OH, 10-Hydroxycamptothecin

Figure 4. Computotsin and 10-Hydroxy Computocin [3].

Interest in research on camptotsin is due to its ability to inhibit topoisomerase I activity (this enzyme is involved in many cellular processes due to its interaction with DNA). Using the

structure of computotsin as a model, products such as topotcan (hicamptamine) and irinotecan have been developed. While computotsin (as sodium salt) underwent clinical trials by the NCI in the 1970s, it was discontinued in clinical trials due to severe bladder toxicity. However, irinotecan, which is much less toxic than comptotsin, has been approved in the United States for the treatment of metastatic colorectal cancer as well as a variety of leukemias. Irinotecan has a much higher solubility in water. It is a prodrug that is metabolized by hydrolysis in this vivo to produce the topoisomerase I inhibitor, 1000 times more active than its parent compound. Topotcan has also been approved in the United States for the treatment of ovarian cancer and is also being tested in pediatrics on people with resistant and recurrent challenging tumors [3].

There have been concerns about the ongoing operation to extract active metabolites from the bark and seeds of this plant, with the growing demand for Computation secondary metabolite (about $ 1 billion for 2003). Nowadays, a new horizon has been provided that provides an alternative and very stable system for producing this critical alkaloid with the development of capillary root cultures, cloning, and identification of genes encoding key enzymes in the pathway leading to the production of computotsin in plants [3].

1.5. *Brucea antidysenterica* (Simaroubaceae)

B. antidysenterica is a plant that grows in Northeast Africa, especially in Ethiopia. This plant is used by local communities against infectious diseases such as dysentery and has gained its botanical name for this reason. Further research on this plant led to the separation of the covasinoid bruceanthin (Figure 5). It was found that the pure compound, along with other dependent covasinoids, is toxic in vitro on the histolytic agent Entamoeba histolytic [8].

In addition, further experiments were performed to investigate the antitumor properties of these compounds, which resulted in the separation of the covasinoid glucosides of bruceanthinoside A and B of the bruceanic acid. Early cytotoxic tests showed that these compounds were effective against tumor cell lines of malignant melanoma ($PRMI-7951$), lung carcinoma ($A-549$), ileuscular adenocarcinoma ($HCT-8$), nasopharyngeal epidermal carcinoma (KB), medulloblastoma (TE-671) and lymphatic leukemia (p-388) [8].

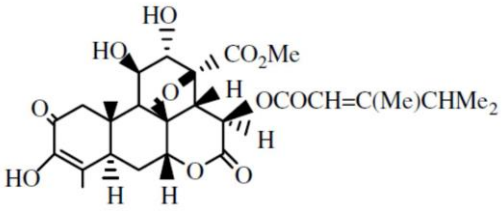


Figure 5. Bruceanthin [2].

Studies of this Vivo using xenografts $RPMI\ 8226\ human-SCI$ have shown that bruceanthin induces regression in primary and advanced tumors, which are associated with relatively few adverse events with favorable antitumor responses. Apoptosis was significantly increased in tumors derived from Bruceanthin-treated animals. It was inferred that Bruceanthin interfered with the growth of leukemia, lymphoma, and myeloma cells in culture and xenograft models. The clinical usefulness of this compound against blood diseases is also being studied [8].

Table 1. Anticancer Effects of Various Medicinal Plants

Scientific Name	Important	Important Compounds	Mechanisms	References
Ferula assa-foetida	Shoot, resin	Coumarin compounds (especially sesquicoumarins), sulfur-containing compounds, and b-sitosterol and oleic acid	Inhibition of mutagenesis, DNA destruction and cancer cells proliferation; increase of proteolytic enzymes activity	9
Thymus vulgaris	Shoot	Thymol and carvacro	Cell cycle arrest	10
Thymbra spicata	Shoot	Thymol and carvacro	Inhibition of DNA destruction	11
Taverniera spartea	Shoot	Isoflavonoid compounds and saponins	Induction of necrosis and apoptosis	12
Peganum harmala	Seed	Alkaloids	Induction of apoptosis (by caspase activation and increase of proteolytic enzymes activity)	13
Viola tricolor	Shoot	Flavonoids (especially rutin and quercetin)	Cell cycle arrest	14
Achillea wilhelmsii	Shoot	Phenolic compounds (especially flavonoids and monoterpens such as 1,8-cineole and a-pinene)	Induction of apoptosis	15
Mentha pulegium	Shoot	Pulegone, menthone, piperitone, limonene, isomenthone, octen-3-ol	Induction of apoptosis	16
Ammi visnaga	Shoot	Visnadine, cimifugin, khellol, b-sitosterol, kaempferol, quercetin	Cell cycle arrest	17
Camellia sinensis	Leaf	Epicatechin, epigallocatechin, epigallocatechin gallate, epigallocatechin3-gallate	Inhibition of cancer cells proliferation (by inhibit of 5-a reductase enzyme activity)	18
Avicennia marina	Leaf	Flavonoids (especially naphthoquinone compounds such as 3-chlorodeoxylapachol)	Antioxidant effects; induction of apoptosis	19
Silybum	Seed	Flavonoids (especially	Antioxidant effects;	20

marianum		silymarin)	cell cycle arrest	
Artemisia absinthium L	Root, shoot	Artemisinin, quercetin, isorhamnetin, limonene, myrecene, linalool, a-pinene, b-pinene, artesunate	Inhibition of cancer cells proliferation (decrease in response to nuclear receptors); inhibition of angiogenesis and cell migration; induction of apoptosis	21
Curcuma longa	Rhizome	Curcumin	Inhibition of cancer cells proliferation (by adjusting gene expression); inhibition of angiogenesis; induction of apoptosis	22
Crocus sativus L	Stigma	Phenolic compounds (especially quercetin)	Inhibition of cancer cells proliferation (inhibits DNA synthesis)	23
Zingiber officinale	Rhizome	Flavonoids (especially kaempferol, catechin, fisetin, and quercetin)	Induction of apoptosis	24
Olea europae	Leaf, fruit	Oleic acid, pinoresinol, oleuropein, acidic triterpenes, oleanolic acid, maslinic acid	Inhibition of cancer cells proliferation (inhibition of HER2 gene expression); inhibition of angiogenesis; induction of apoptosis	25
Taxus baccata L	Leaf	Taxol	Cell cycle arrest	26
Nigella sativa	Seed	Thymoquinone, dinitroquinone	Cell cycle arrest; induction of apoptosis	27
Allium sativum L	Fruit	Allicin, ajoene	Cell cycle arrest; induction of apoptosis	28
Lepidium sativum	Shoot	Vitamins (A, B, C and E), isothiocyanate, alinolenic acid, glucosinolates	Antioxidant effects; cell cycle arrest	29

Trigonella foenumgraceum L	Shoot	Flavonoids and alkaloids (such as gingerol, cedrene, zingerone, vanillin, and eugenol)	Antioxidant effects; induction of apoptosis	30
Glycyrrhiza glabra	Root	Glycyrrhizin	Inhibition of cancer cells proliferation (bcl-2 phosphorylation); morphological changes in cancer cells and induction of apoptosis	31
Physalis alkekengi	Fruit	Physalins	Induction of apoptosis	32
Lagenaria siceraria Standl	Shoot, fruit	Vitamins (B group and C), saponins, cucurbitacin	Cell cycle arrest	33
Ferula gummosa	Shoot	Sesquiterpenes and coumarins	Cell cycle arrest; induction of apoptosis	34
Boswellia serrata	Resin	Boswellic acid	Inhibition of cancer cells proliferation (distribution in the biosynthesis of nucleic acids and proteins); decrease of cells viability (increase of reactive oxygen species production); induction of apoptosis (by activation of caspases)	35
Urtica dioica L	Leaf	Phenolic compounds	Antioxidant effects; cell cycle arrest	36
Ammi majus	Shoot, seed	Coumarin compounds (especially psoralens)	Cell cycle arrest; induction of apoptosis	37
Rosa damascena	Petal	Phenolic compounds (such as gallic acid, catechin, and epicatechin)	Antioxidant effects; DNA protection	38
Astragalus cystosus	Shoot	Lectins, flavonoids and terpenoids	Cell cycle arrest; induction of apoptosi	39

Myrtus communis	Leaf	Polyphenols, myrtucommulone, semimyrtucommulone, 1,8-cineole, a-pinene, myrtenyl acetate, limonene, linalool, aterpinolene	Antioxidant effects, induction of apoptosis (DNA fragmentation and activation caspases)	39-40
Vinca rosea	Shoot	Vincristine, vindoline, vinflunine, vinblastin, catharantin	Antioxidant effects; inhibition of cancer cells proliferation (effect on microtubules	41
Citrullus colocynthis	Fruit	Cucurbitacin, quercetin, b-sitosterol	Cell cycle arrest; induction of apoptosis	42
Polygonum aviculare	Shoot	Tannins, saponins, flavonoids and alkaloids	Antioxidant effects; cell cycle arrest; induction of apoptosis	42-43
Astroudaucus orientalis	Root, shoo	a-pinene, a-thujene, a-copaene, fenchylacetate, myrecene, sabinene	Cell cycle arrest; induction of apoptosis	43-44

2. Conclusion

Many natural ingredients for various types of cancer have been known in the traditional medicine of most countries. The World Health Organization has recommended the search for new natural anticancer substances. Herbal medicines with anticancer properties can be used as a substitute or supplement to chemical drugs effective in treating cancers. Many unique plant species need to be further studied to find anticancer compounds. The mechanism of the anticancer effect of most of these substances is related to their antioxidant properties and inhibition of the growth of their tumor cells.

The investigated medicinal plants in this article could be a key to identifying the compounds with anticancer effects; therefore, if their compounds are examined, they might help develop new, more efficient drugs and contribute to identifying the main mechanisms involved in cancer.

Many of these substances are traditionally used in different parts of the world. These substances can be provided to patients with drugs with appropriate doses and scientific studies. These studies are often done in laboratory settings using animals, and it is expected that they will be used in human clinical trials soon.

Conflict of interest

The author declares no conflict of interest.

Consent for publications

The author declares, reads, and approves the final manuscript for publication.

Availability of data and material

The author declares that he embedded all data in the manuscript.

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