



A Systematic Review of Iran's Medicinal Plants With Anticancer Effects

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Abstract

Increase in cases of various cancers has encouraged the researchers to discover novel, more effective drugs from plant sources. This study is a review of medicinal plants in Iran with already investigated anticancer effects on various cell lines. Thirty-six medicinal plants alongside their products with anticancer effects as well as the most important plant compounds responsible for the plants' anticancer effect were introduced. Phenolic and alkaloid compounds were demonstrated to have anticancer effects on various cancers in most studies. The plants and their active compounds exerted anticancer effects by removing free radicals and antioxidant effects, cell cycle arrest, induction of apoptosis, and inhibition of angiogenesis. The investigated plants in Iran contain the compounds that are able to contribute effectively to fighting cancer cells. Therefore, the extract and active compounds of the medicinal plants introduced in this review article could open a way to conduct clinical trials on cancer and greatly help researchers and pharmacists develop new anticancer drugs.

Keywords

cancer, cytotoxicity, medicinal plants, phytochemicals

Received June 21, 2015. Received revised July 21, 2015. Accepted for publication July 22, 2015.

Introduction

Cancer is a main reason for mortality involving more than one-third of the global population in some way. Cancer is the cause of more than 20% of the whole mortality worldwide.¹ According to the report of the International Agency for Research on Cancer² of the World Health Organization published in 2014, the global incidence of cancer has been approximately 14 million new cases and is projected to register 19.3 million in 2025. According to this report, lung cancer was the most prevalent cancer (13%) in 2012 followed by breast cancer (11.9%), colon cancer (9.7%), and prostate cancer (7.9%). In Iran, the mean rate of cancer incidence has been 7.134 per 100 000 population, 85 000 individuals are estimated to acquire cancer and nearly 55 000 individuals die due to cancer per year.^{2,3}

Meanwhile, there are a variety of therapeutic approaches to treat cancer, including surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy. Despite being highly efficient, surgery is not always practical under any circumstances. For radiotherapy, systemic radiotherapy is variously conducted, including external radiation therapy, brachiotherapy, and internal radiation therapy in view of the source and site of tumor and the type of cells with several side effects, alongside therapeutic effect, for the patient such as poisoning as the most significant one leading to variation in skin health as alopecia and destruction of epithelial cells (scaling) and epithelial moisture (dermis revealing and skin secretion of

serous fluid) and potentially mouth ulcers and complications, bone marrow suppression, and development of anemia, leukopenia, and thrombocytopenia.⁴ Chemotherapy drugs, including antimetabolites (such as methotrexate), passive material of DNA (such as cisplatin and doxorubicin), antitubulin agents (such as taxol), and hormones that are most frequently used cause unwanted effects, including hair loss, bone marrow suppression, drug resistance, gastric ulcer, neurological dysfunction, and cardiac toxicity.⁵⁻⁷

In view of the above complications of the therapies currently considered for cancer, high costs of conventional therapies, and growing incidence of cancer in both developed and developing countries, it seems necessary to develop more novel approaches with higher efficiency so that the disease intensity could be declined. In this regard, there is considerable scientific and

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commercial interest in developing new anticancer agents from natural sources and the research aimed to develop new anticancer drugs has been turned into a significant research area.⁸ In fact, naturally derived combinations have been under pharmacists' focus to synthesize new drugs and treat diseases due to availability, less frequent side effects and drug interactions, and cheapness.^{9,10}

Plants produce a wide spectrum of chemical compounds with apparently no direct contribution to their growth and development, namely secondary metabolites. Terpenes, nitrogen-containing, and phenolic compounds are 3 main classes of these compounds with various biological properties in plants that are used for a wide variety of diseases including cancers,^{11,12} neurological disorders,¹³ chronic inflammation and lesions, particularly due to diabetes,^{14,15} atherosclerosis,^{16,17} cardiovascular diseases,^{18,19} and wounds.²⁰ In addition, these natural products have been used alongside radiotherapy.

This article is a review of Iran's medicinal plants that have been already examined for anticancer effects, and also seeks to offer their main compounds and mechanisms of anticancer activities. This review article could open a way to develop new anticancer drugs for prevention and treatment of cancers.

Materials and Methods

In this systematic review, to collect data, different combinations of keywords *medicinal plants, anticancer, Iran, cytotoxicity, cell line, and phytochemical compounds* and their Persian equivalents were entered into databases consisting of Magiran, SID, and Iran Medex, as well as, international databases of Web of Knowledge, PubMed, and Scopus. The articles only in English and Persian languages published between 1976 and March, 2015 were only searched. Then, the articles on application of Iran's medicinal plants for prevention and treatment of cancers were selected, and those demonstrating anticancer effects of these plants and/or their compounds were reported.

Results

From the findings, 36 medicinal plants in Iran with studies conducted on their anticancer effects were reported (Table 1). Despite the fact that lung cancer has been the most prevalent cancer in 2014, little research has been conducted on the effects of medicinal plants on this cancer. Most studies have addressed breast cancer (Table 2). In most conducted studies, no clear mechanism of the plant effect has been offered. However, some compounds of the plants have been reported to be possibly responsible for anticancer effects. In addition, in some of the studies some compounds were extracted from the plants and the effect of these compounds on various cell lines were studied. Phenolic and alkaloid compounds were demonstrated to have anticancer effects on various cancers in most studies.

Discussion

The available therapeutic approaches to treat cancers are mostly accompanied with undesirable side effects (gastrointestinal disorders, kidney damage, etc). The present study indicated that the studied medicinal plants in Iran contain the

compounds engaging specifically in fighting cancer cells and inhibiting growth and destruction of tumor cells only by affecting cancer cells.

These compounds mainly include alkaloids and phenolic and monoterpene compounds. Vinblastine, vincristine, curcumin, myrtucommulone, taxol, boswellic acids, and umbelliprenin, quercetin, catechin, cucurbitacin, kaempferol, thymol, carvacrol, 1,8-cineole, α -pinene, myrcene, β -sitosterol were some compounds with reported anticancer effects in most works. Alkaloids are nitrogen-containing compounds with plant origin, which often have a complex structure, high molecular weight, and show physiological activity in humans. Alkaloids cause cell cycle arrest in metaphase stage by preventing the formation of microtubules and hence could prevent cancer.¹⁷²

Cancers and most difficult-to-cure diseases are associated with high level of oxidative stress.¹⁷³⁻¹⁷⁵ Oxidative stress is a phenomenon which may cause damage to various physiological and biochemical processes. Overproduction of such free radicals may also cause oxidative damage to biomolecules such as DNA, lipids, and proteins.¹⁷⁶⁻¹⁷⁸ This process eventually may lead to many chronic diseases, including cancer, atherosclerosis, diabetes, aging, and other degenerative diseases in humans.¹⁷⁹⁻¹⁸¹ Most of medicinal plants with anticancer property have antioxidant activity due to phenolic compounds. Therefore, these plants may, at least in part, exert their anticancer effects by counteracting free radicals. Antioxidant property of phenolic compounds (including flavonols and flavonoids) is due to the presence of hydroxyl groups.^{182,183} Actually, medicinal plants with antioxidant activity play a crucial role in scavenging free radicals. They also are able to reduce the toxicity of toxic agents which induce oxidative stress.¹⁸⁴⁻¹⁸⁸ If this is true, other plants with antioxidant property are likely to have anticancer activity, which should be further investigated.

On the other hand, the ability to induce apoptosis is an important marker for cytotoxic antitumor agents. Studies have shown that cytotoxic effect of alkaloids and phenols against different tumors is mediated through apoptosis.

Phenolic compounds exhibit anticancer effects through affecting cell proliferation processes (eg, through the G2/M cell cycle arrest and inhibition of topoisomerase II), apoptosis, angiogenesis, and the impact on the routes of phosphoinositide 3-kinase (PI3-K) and protein kinase B (Akt). Studies have demonstrated that inhibition of PI3-K activity inhibits phosphorylation of Akt and mammalian target of rapamycin (mTOR), which leads to reduced activity of nuclear factor- κ B (NF- κ B). Through this mechanism, transcription and synthesis of the cell cycle-driving proteins are inhibited and thus the growth of cancer cells is reduced and the cell death increases.¹⁸⁹⁻¹⁹² For example, quercetin, a phenolic compound in plants, prevents the activation of the transcription factor NF- κ B through inhibiting Akt and Ikka-a phosphorylation and hence the anticancer activity is exerted.¹⁹³ Curcumin, as a major pigment in turmeric, induces apoptosis in transformed rodent and human cells in inhibition of the culture of formation of cyclooxygenase metabolite.⁶⁹⁻⁷²

Table 1. Anticancer Effects of Various Iranian Medicinal Plants.

Scientific Name	Part(s) Used	Important Compounds	Mechanisms	References
<i>Ferula assa-foetida</i>	Shoot, resin	Coumarin compounds (especially sesquicoumarins), sulfur-containing compounds, and β -sitosterol and oleic acid	Inhibition of mutagenesis, DNA destruction and cancer cells proliferation; increase of proteolytic enzymes activity	21–24
<i>Thymus vulgaris</i>	Shoot	Thymol and carvacrol	Cell cycle arrest	25–27
<i>Thymbra spicata</i>	Shoot	Thymol and carvacrol	Inhibition of DNA destruction	28–30
<i>Taverniera sparteae</i>	Shoot	Isoflavonoid compounds and saponins	Induction of necrosis and apoptosis	31, 32
<i>Peganum harmala</i>	Seed	Alkaloids	Induction of apoptosis (by caspase activation and increase of proteolytic enzymes activity)	33–35
<i>Viola tricolor</i>	Shoot	Flavonoids (especially rutin and quercetin)	Cell cycle arrest	36–38
<i>Achillea wilhelmsii</i>	Shoot	Phenolic compounds (especially flavonoids and monoterpenes such as 1,8-cineole and α -pinene)	Induction of apoptosis	39–43
<i>Mentha pulegium</i>	Shoot	Pulegone, menthone, piperitone, limonene, isomenthone, octen-3-ol	Induction of apoptosis	44–46
<i>Ammi visnaga</i>	Shoot	Visnadine, cimifugin, khellol, β -sitosterol, kaempferol, quercetin	Cell cycle arrest	47–50
<i>Camellia sinensis</i>	Leaf	Epicatechin, epigallocatechin, epigallocatechin gallate, epigallocatechin-3-gallate	Inhibition of cancer cells proliferation (by inhibit of 5- α reductase enzyme activity)	20, 51–55
<i>Avicennia marina</i>	Leaf	Flavonoids (especially naphthoquinone compounds such as 3-chlorodeoxylapachol)	Antioxidant effects; induction of apoptosis	56–58
<i>Silybum marianum</i>	Seed	Flavonoids (especially silymarin)	Antioxidant effects; cell cycle arrest	59, 60
<i>Artemisia absinthium</i> L	Root, shoot	Artemisinin, quercetin, isorhamnetin, limonene, myrcene, linalool, α -pinene, β -pinene, artesunate	Inhibition of cancer cells proliferation (decrease in response to nuclear receptors); inhibition of angiogenesis and cell migration; induction of apoptosis	61–64
<i>Curcuma longa</i>	Rhizome	Curcumin	Inhibition of cancer cells proliferation (by adjusting gene expression); inhibition of angiogenesis; induction of apoptosis	65–72
<i>Crocus sativus</i> L	Stigma	Phenolic compounds (especially quercetin)	Inhibition of cancer cells proliferation (inhibits DNA synthesis)	73–76
<i>Zingiber officinale</i>	Rhizome	Flavonoids (especially kaempferol, catechin, fisetin, and quercetin)	Induction of apoptosis	66, 77, 78
<i>Olea europae</i>	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	52, 79–81
<i>Taxus baccata</i> L	Leaf	Taxol	Cell cycle arrest	82–84
<i>Nigella sativa</i>	Seed	Thymoquinone, dinitroquinone	Cell cycle arrest; induction of apoptosis	85–90
<i>Allium sativum</i> L	Fruit	Allicin, ajoene	Cell cycle arrest; induction of apoptosis	91–101
<i>Lepidium sativum</i>	Shoot	Vitamins (A, B, C and E), isothiocyanate, α -linolenic acid, glucosinolates	Antioxidant effects; cell cycle arrest	102–104
<i>Trigonella foenum-graceum</i> L	Shoot	Flavonoids and alkaloids (such as gingerol, cedrene, zingerone, vanillin, and eugenol)	Antioxidant effects; induction of apoptosis	105–108
<i>Glycyrrhiza glabra</i>	Root	Glycyrrhizin	Inhibition of cancer cells proliferation (bcl-2 phosphorylation); morphological changes in cancer cells and induction of apoptosis	109–112
<i>Physalis alkekengi</i>	Fruit	Physalins	Induction of apoptosis	113–116
<i>Lagenaria siceraria</i> Standl	Shoot, fruit	Vitamins (B group and C), saponins, cucurbitacin	Cell cycle arrest	117–121
<i>Ferula gummosa</i>	Shoot	Sesquiterpenes and coumarins	Cell cycle arrest; induction of apoptosis	122–130
<i>Boswellia serrata</i>	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)	131–133

(continued)

Table 1. (continued)

Scientific Name	Part(s) Used	Important Compounds	Mechanisms	References
<i>Urtica dioica</i> L	Leaf	Phenolic compounds	Antioxidant effects; cell cycle arrest	134–138
<i>Ammi majus</i>	Shoot, seed	Coumarin compounds (especially psoralens)	Cell cycle arrest; induction of apoptosis	139, 140
<i>Rosa damascena</i>	Petal	Phenolic compounds (such as gallic acid, catechin, and epicatechin)	Antioxidant effects; DNA protection	141–144
<i>Astragalus cystosus</i>	Shoot	Lectins, flavonoids and terpenoids	Cell cycle arrest; induction of apoptosis	145–148
<i>Myrtus communis</i>	Leaf	Polyphenols, myrtucommulone, semi-myrtucommulone, 1,8-cineole, α -pinene, myrtenyl acetate, limonene, linalool, α -terpinolene	Antioxidant effects, induction of apoptosis (DNA fragmentation and activation caspases)	149–155
<i>Vinca rosea</i>	Shoot	Vincristine, vindoline, vinflunine, vinblastin, catharantin	Antioxidant effects; inhibition of cancer cells proliferation (effect on microtubules)	156–159
<i>Citrullus colocynthis</i>	Fruit	Cucurbitacin, quercetin, β -sitosterol	Cell cycle arrest; induction of apoptosis	160–164
<i>Polygonum aviculare</i>	Shoot	Tannins, saponins, flavonoids and alkaloids	Antioxidant effects; cell cycle arrest; induction of apoptosis	165–168
<i>Astroudaucus orientalis</i>	Root, shoot	α -pinene, α -thujene, α -copaene, fenchyl-acetate, myrecene, sabinene	Cell cycle arrest; induction of apoptosis	169–171

Table 2. Effect of Iranian Medicinal Plants on Different Cancers.

Target Organ	Study Design	Scientific Name	Reference(s)
Lung	Clinical trial	<i>Astragalus cystosus</i>	146
	Cell line: A549	<i>Lagenaria siceraria</i> Standl <i>Ferula gummosa</i> (Umbelliprenin) <i>Rosa damascena</i> <i>Curcuma longa</i>	117 122 141 68
Breast	Cell line: SK-Mes-1	<i>Thymbra spicata</i>	28
	Cell line: QU-DB	<i>Curcuma longa</i>	67
	Mouse	<i>Silybum marianum</i> <i>Trigonella foenum-graceum</i> L	60 106
	Cell line: BT-20	<i>Avicennia marina</i> (3-chlorodeoxylapachol)	58
	Cell line: MDA-MB231	<i>Avicennia marina</i> <i>Zingiber officinale</i>	57 78
	Cell line: BT474	<i>Olea europae</i> <i>Taverniera spartea</i>	52 32
	Cell line: T47D	<i>Astrodaucus orientalis</i> <i>Camellia sinensis</i> <i>Curcuma longa</i> <i>Ammi visnaga</i>	169 54 67 48
	Cell line: MDA-MB468	<i>Taxus baccata</i> L	83, 84
	Cell line: MCF-7	<i>Polygonum aviculare</i> <i>Lagenaria siceraria</i> Standl <i>Crocus sativus</i> L <i>Zingiber officinale</i> <i>Allium sativum</i> L (diallyl disulfide) <i>Vinca rosea</i> (Alkaloids) <i>Glycyrrhiza glabra</i> (glycyrrhizin) <i>Rosa damascena</i> <i>Lepidium sativum</i> <i>Ammi majus</i>	167 119 75 77 95, 98 156 112 141 104 139
		<i>Citrullus colocynthis</i> (Cucurbitacin) <i>Taverniera spartea</i> <i>Myrtus communis</i>	164 32 149–151
		<i>Ferula gummosa</i> <i>Glycyrrhiza glabra</i> <i>Silybum marianum</i>	123 110 60

(continued)

Table 2. (continued)

Target Organ	Study Design	Scientific Name	Reference(s)		
Prostate	Clinical trial; Mouse; Cell line: LNCaP, hPCPs Mouse	<i>Urtica dioica</i>	134–136		
		<i>Thymus vulgaris</i>	25		
	Cell line: DU-145	<i>Taverniera spartea</i>	32		
		<i>Camellia sinensis</i>	54		
	Cell line: PC-3	<i>Ferula szowitsiana</i> (Umbelliprenin)	126		
		<i>Allium sativum</i> L (diallyl disulfide)	96		
		<i>Taverniera spartea</i>	32		
	Cell line: PC-3M	<i>Curcuma longa</i>	66		
		<i>Zingiber officinale</i>	66		
		<i>Ammi majus</i>	139		
Cervix	Cell line: HeLa	<i>Rosa damascena</i>	142		
		<i>Polygonum aviculare</i>	165, 166		
		<i>Physalis alkekengi</i>	113, 116		
		<i>Astragalus cystosus</i>	145		
		<i>Taxus baccata</i> L	84		
		<i>Peganum harmala</i>	32, 33		
		<i>Viola tricolor</i>	36		
		<i>Boswellia serrata</i>	129		
		<i>Curcuma longa</i> (Curcumin)	70		
		<i>Ferula szowitsiana</i> (Umbelliprenin)	126		
		<i>Thymus vulgaris</i>	26		
		Head Colon	Cell line: PA1	<i>Olea europae</i> (pinosresinol)	79
			Clinical trial	<i>Crocus sativus</i> L	74
			Cell line: RKO, SW480, HCT116	<i>Nigella sativa</i> (Thymoquinone)	88
			Cell line: HT-29, SW480, HCT116	<i>Artemisia absinthium</i> L	62
Cell line: HCT-116	<i>Achillea wilhelmsii</i>		39		
Larynx	Cell line: HT-29	<i>Allium sativum</i> L	93		
		<i>Ferula szowitsiana</i> (Umbelliprenin)	126		
		<i>Avicennia marina</i> (3-chlorodeoxylapachol)	58		
		<i>Citrullus colocynthis</i>	160		
		<i>Curcuma longa</i>	65		
Liver	Cell line: HepG2	<i>Allium sativum</i> L	94		
		<i>Astragalus cystosus</i> (saponines and flavonoids)	147, 148		
		<i>Ferula assa-foetida</i>	21		
		<i>Crocus sativus</i> L	73, 76		
Skin	Cell line: Hep-2	<i>Citrullus colocynthis</i> (Cucurbitacin)	163		
		<i>Vinca rosea</i>	156		
		<i>Ferula gummosa</i>	122		
Blood cells	Cell line: A431	<i>Mentha pulegium</i>	44		
		<i>Artemisia absinthium</i> L (Artesunate)	64		
		<i>Lepidium sativum</i>	103		
		<i>Taxus baccata</i> L	84		
		<i>Ferula szowitsiana</i> (Umbelliprenin)	125		
Kidney	Cell line: SK-MEL-28	<i>Nigella sativa</i>	86		
		<i>Lepidium sativum</i>	102		
Bladder	Cell line: ECV-304	<i>Ferula gummosa</i>	124		
Stomach	Cell line: K562				
	Cell line: Jurkat T-CLL, Raji B-CLL				

Conclusion

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

Author Contributions

All the authors wrote the first draft of the manuscript equally. MAS and HS revised and edited the last version.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work has been extracted from the PhD thesis of Majid Asadi-Samani and it has been funded by Deputy of Research and Technology of Shahrekord University of Medical Sciences.

Ethical Approval

As this review did not involve any human or animal subjects, ethical approval was not required.

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