Review Article

Evaluation of Effectiveness of Herbal Medication in Cancer Care: A Review Study

Javad Tavakoli[1], Solaleh Miar[1], Mohammad Majid Zadehzare[1], Hossein Akbari[1]

Abstract

Based on a common belief, herbal medicine with the least possible side effects should be the center of attention in cancer care; however, in many cases they have not been properly studied with reliable clinical trials in human subjects. In this review, it was attempted to identify the available evidence on the use and clinical effects of herbs in cancer care. The research consists of two major parts including immunomodulator and chemopreventive herbal compounds whose mechanism, biological response, anticancer element of extract and related benefits were completely studied. Also, the safety of herbal anticancer compounds was discussed. Although the use of herbal medicines in treating cancer shows less chemotherapy-induced, toxicity, more researches are required to reach their full therapeutic potentials.

Keywords: Neoplasms; Plants; Immunologic factors; Prevention; Safety

Please cite this article as: Tavakoli J, Miar S, Zadehzare MM, Akbari H. Evaluation of Effectiveness of Herbal Medication in Cancer Care: A Review Study. Iran J Cancer Prev. 2012;5(3):144-56.

1. Dept. of Biomedical Engineering, Biomedical Engineering Faculty, Science and Research Branch of Islamic Azad University, Tehran, Iran

Corresponding Author:
Javad Tavakoli, Ph.D;
Assistant Professor of Biomedical Engineering
Tel: (+98)21 44 47 43 23
E-mail: drjavadtavakoli@yahoo.com
Received: 5 Jan. 2012
Accepted: 2 Apr. 2012
Iran J Cancer Prev 2012; 3:144-156

Introduction

Cancer is a hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Cancers with alarming statistics, cause more than 7 million deaths per year worldwide, more than HIV/AIDS, malaria and tuberculosis combined [1]. It is estimated that the number of new cancer cases will reach 15 million every year by 2020; 70% of which will be in developing countries [2]. Patients confronting a diagnosis of advanced cancer face the statistical reality that conventional chemotherapy can affect a cure for only a tiny minority of all such cases. More often than not, the reasonable impulse of these patients to investigate alternative treatment options such as herbal medicine is met with physician's doubt.

For a long time, natural and herbal products have been considered as precise sources of treatment used in traditional medicine to treat a variety of diseases including infections and malignant diseases [3]. Several researches demonstrated the fact that extracts from a number of herbal plants exhibit anticancer activities both in vitro and in vivo [4-10]. A growing number of studies indicate that herbal medicine (looking at frequency, type and reasons for use) might have the anti-cancer effect by enhancing the immune system [11], inducing cell differentiation [12], inhibiting telomerase activities [13] and inducing apoptosis of cancer cells [14].

It is strongly believed that herbal medicines are natural and hence without significant side effects and less likely to cause dependency [15]. Nevertheless, many herbs can be toxic especially in higher quantities and with frequent use. Besides, herb-synthetic drug interactions are controversial [16].

The prevalence of herbs use ranges from 60 to 80% among cancer patients depending on the definition of herbal medicine used in each study, sample size, and the place where the study was conducted [17]. In UK, a population-based survey indicates that about 25% of cancer patients had consulted an herbal medicine practitioner in the past, although authors suggest that this number maybe underestimated [18]. A Canadian study shows that 20% of breast cancer patients used at least one herbal medicine treatment in the past[19], whereas American studies more consistently report rates well above 65% [20,21], such rates are considerably higher than those reported in general population [22] or among other cancer diagnostic groups [23].

Despite extensive use of herbal medicines in cancer care, most of the evidence is anecdotal and has not been properly studied with significant clinical trials, especially in human subjects [24]. Further, interaction of chemical drug-herbs should be considered as another important factor [25], because herbs cannot replace surgery or radiotherapy for

early stages of cancer, even though it is believed that they do have merits of their own [26].

The objective of this review is to identify the available evidence on the use of herbs and their clinical effects in cancer care. The present work intends to make a review about this subject using ISI Web of Knowledge (Thomson Reuters) database from 2000 up to 2011. In some few cases, references other than 2000 to 2011(publishing date) can be cited as introductory to more recent works. Therefore, some references are mentioned whose dates do not match the period of the study. Search keys used for the study were a combination of: Cancer; Medicinal Herbs; Immunomodulator; Preventive therapy; Safety; 2000 to 2011 (year published). About 100 works were found including proceedings and articles. Patents, abstracts, and other scientific documents whose availability was restricted were not used.

Roles of Herbal Medicines in Cancer

From 200 to 1800 AD, following the teachings of Aristotle and Galen, which was believed that cancer, was a consequence of the coagulation of "black bile" till now when prevalence of biology has contributed to a 25% reduction in mortality [27], herbs play an important role in cancer symptom management, patients' quality of life and survival.

The main objectives of herbal therapies are:

- Primary prevention of cancer; this is important for those who have a strong family history of cancer
- Secondary presentation; prevention of a recurrence of cancer is therefore the objective for this group
- To enhance body's immune system
- To reduce the side effects resulting from conventional therapies such as chemotherapy or radiation therapy
- In advanced stages of cancer, when conventional therapies have failed, many patients have no choice but resort to alternative treatments

The way herbal medicine fight cancer is significantly different from conventional chemical drugs, where no DNA mutation in surviving cell occurs. Specifically, natural compounds fight cancer by strengthening the immune system preventing the spread of cancer cells through inhibition of angiogenesis or growth of new blood vessels feeding the cancer cells, detoxifying the body and preventing further toxic build-up in the body, quenching free radicals that cause mutational changes that lead to cancer formation and supporting all targeted organs, especially those affected directly by the cancer. Besides creating an unfavourable environment for cancer growth is another benefit of herbal medicines, where, the ideal environment creates a high level of oxygen and temperature including increased metabolism rate, low sugar level and a high alkalinity space in the body [28].

Some of the herbs commonly used in traditional knowledge are listed in Figure 1, 2 and 3 based on active component, chemical structure and source.

The approach to treat advanced cancer using natural medicines has consisted of two main different visions. Indeed many herbal medicines are widely used as immunomodulators, although another group was known as chemopreventive (adaptogenic) plant compounds [29].

Immunomodulation Versus Chemo Preventive Herbs

An important key role for plant medicines in cancer is immunomodulation. Such natural medicines have been reported to serve as biological response modifiers by activating, increasing and restoring the reactivity of immunological effector mechanisms that are involved in resistance to tumor growth and metastasis [30, 31].

In fact, cancer evades immune system surveillance because of low immunogenicity of most tumors. Nonetheless, many cancer patients with advanced malignancy do have lowered levels of innate (Th1) immunity, the branch of immune system whose cells, such as Natural Killer (NK) cells, directly kill the tumor. A variety of herbal medicines and plant compounds directly stimulate this innate immune response. These same agents can be used to help protect bone marrow against the myelosuppressive effects of conventional chemotherapy. As it is described in figure 4, the two most important classes of herbs here are immunomodulating and adaptogens.

As it is described in Figure 1, in neither of the cases the herbal medicines have equivalents among pharmaceutical drugs. The mushrooms contain polysaccharides, which are not only immunostimulating of anticancer effects; they also have non-specific effects of increasing longevity and reducing stress. The adaptogenic herbs such as Panax ginseng are even more unique. Adaptogens are nonspecific, nontoxic and normalizing. This means the effect they produce varies according to the physiopathologic state. For instance, ginseng is an angiogenic in wound healing, versus cancer, and it is also antiangiogenic [32]. This apparent paradox is

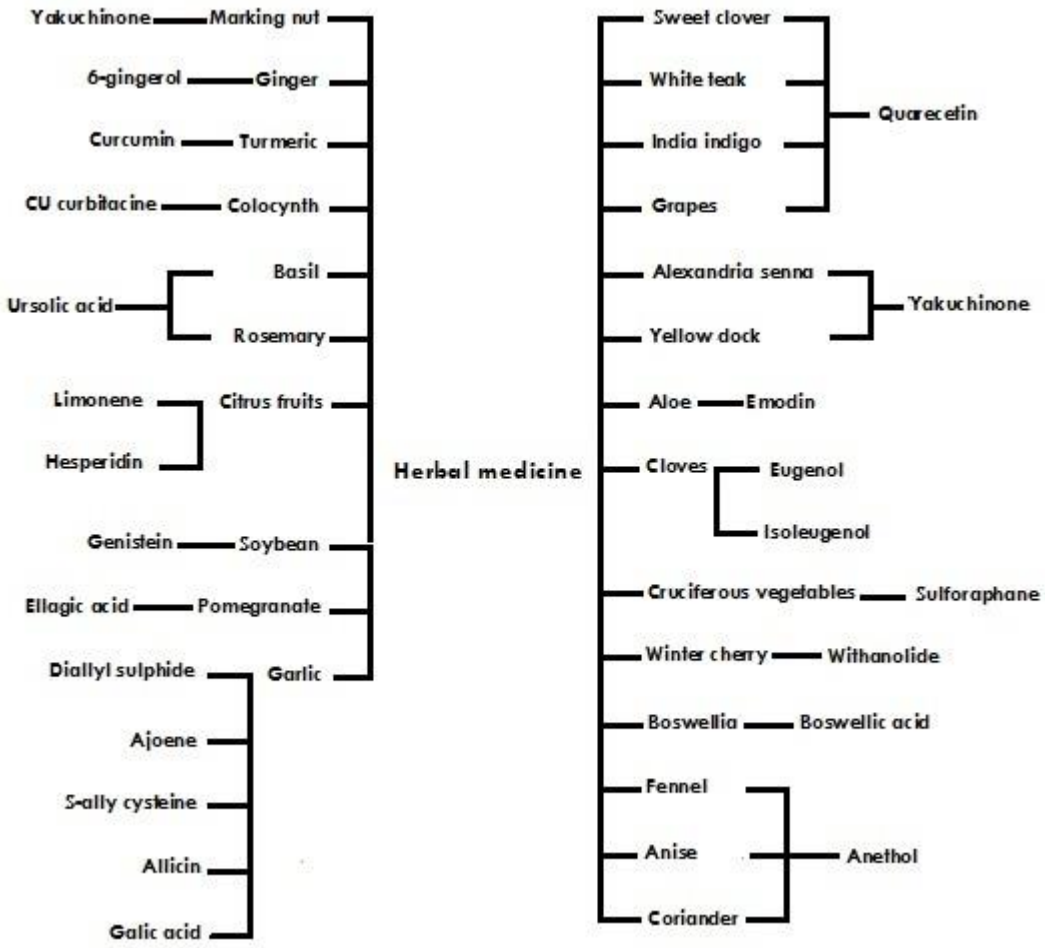

Figure 1. Active components from herbal medicine

typical of normalizing properties of adaptogens, which also have multiple anticancer effects as well as beneficial interactions with conventional chemotherapy and radiation. Some molecular targets of chemopreventive plants are illustrated in Figure 5. Most of these herbs operate on several of the mentioned targets simultaneously and often synergistically.

Immunomodulation Herbs

Ganoderma lucidum, a highly ranked medicinal mushroom has potent enhancing effect on immune system and anticancer activity. Preclinical studies demonstrated its anti-tumor activity, and further studies indicated that the Polysaccharide (PS) fractions were the major active components for the anti-tumor action [33, 34].

Ganoderma lucidum was found to activate macrophages, T lymphocytes and NK cells and to induce the production of cytokines such as tumor necrosis factor, interleukins and interferons in in-vitro with human immune cells and in vivo in mice [35,37].

Herba taraxucum mongolicum is also shown immune stimulating effects [38]. Studies indicate that its chemical constituents such as taraxasterol, taraxacin, choline, inulin and pectin remove toxic heat, swelling and nodulation.

Sophora flavescens also increases leukocytes and promotes peripheral immune response. Scutellaria baicalensis is another potent heat and toxin- clearing with anti- tumor and immune-stimulating properties in vivo and in vitro that inhibits platelet aggregation and induces apoptosis [39]. Isatis tinctoria contains the compound indirubin, inhibits DNA synthesis in neoplastic cells, while simultaneously stimulating immune response[40].

Also, herbs such as Panax ginseng, Poria cocos, Atractylodes macrocephala, Angelica sinensis, Ligustici wallichii, Paeonia lactiflora, Rehmannia glutinosa and Astragalus membranaceus show an

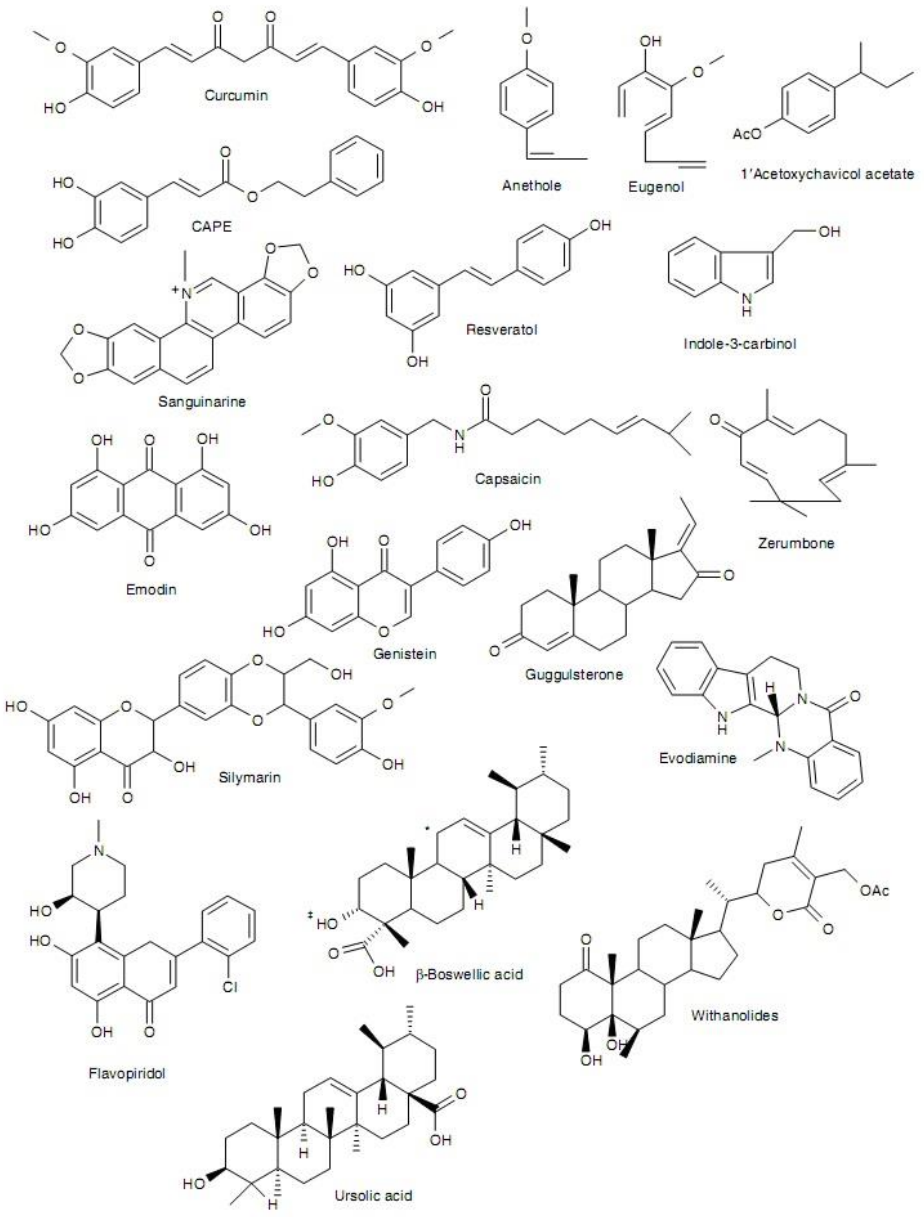

Figure 2. Chemical structures of selected active components in plants. (*can have a ketone group: 11-keto-ß boswellic acid. ‡can be acetylated: acetyl-ß boswellic acid. Both modifications together, result in acetyl- 11-keto-ß-boswellic acid.)

increase of white blood cell counts to normal levels in cancer patients [41].

Decades of pharmacological research have revealed that the polysaccharides and other compounds in Astragalus membranaceus promote cellular and humoral immune function and have vitro anti-tumor effects on cancer cell lines [42-44].

Multiple studies on patients with stomach cancer were conducted using formula Pishen Fang, which has immunostimulating properties. The formula contains: Codonopsis pilolusa, Atractylodes macrocephala, Lycium barbarum, Ligustrum lucidum, Cuscuta chinensis and Psoralea corylifolia [45].

Chemopreventive Herbs

The inhibitory effect of a herbal formula comprising Ginseng and Carthamus tinctorius on breast cancer was studied by Wings et al. [46]. This

Figure 3. Sources of traditional drugs

formula could be a useful anticancer compound against breast cancer by inhibiting proliferation in solid tumor. The compounds isolated from the pacific yew "Taxus brevifolia" has developed as the anticancer drug "Taxol". The extract from plant Scutellaria barbata has been shown to be cytotoxic to A549 human lung cancer cell lines [47, 48]. The synergetic effect on antiproliferative activity of chemotherapeutic agents (Doxorubicin) in combination with Thai herbal remedies (stem of Albizia procera, Diospyros mollis, Ficus hispida, smilax glabra, Gelonium multiflorum and Millingtonia hortensis) against lung cancer cells may induce DNA damage in lung cancer [49]. Amooranin extract (stem) which is a triterpene acid showed a strong inhibitory effect on survival of human breast

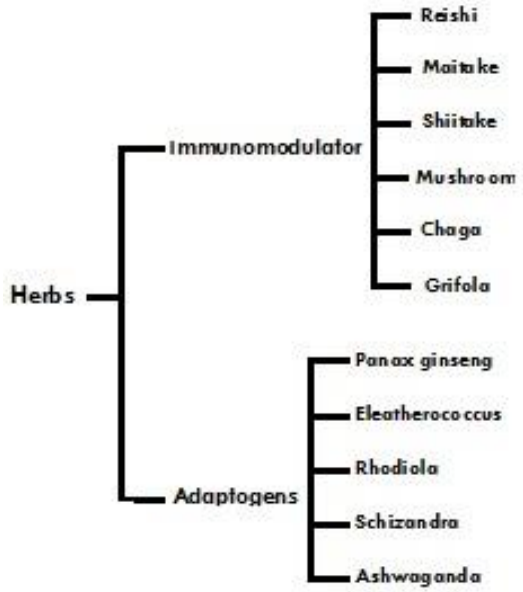

Figure 4. Adaptogenic and immunomdalaling herbs

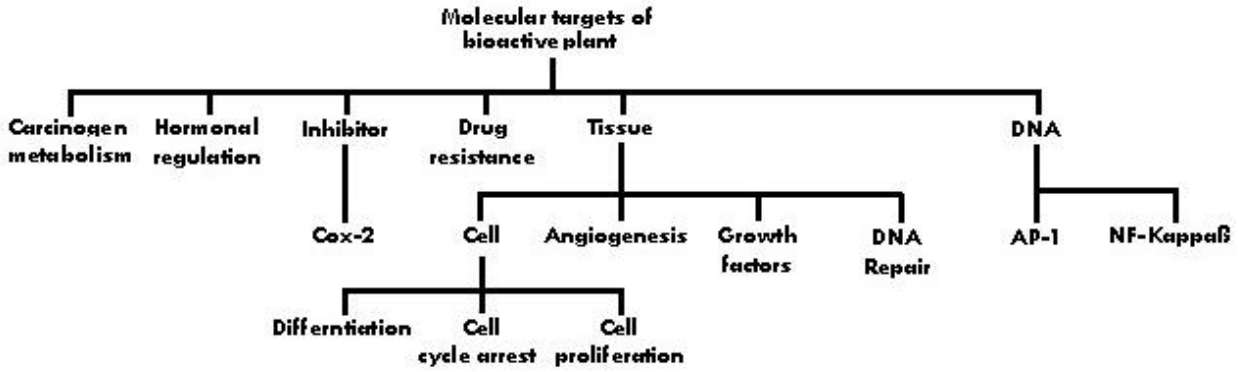

Figure 5. Molecular targets of chemopreventive compounds

carcinoma MDA-468 and breast adenocarcinoma MCF-7 cells compared to breast epithelial MCF-10A control cells [50].

Impact of herbal medicines on human breast cancer was studied by many research groups through reducing tumor burden by Resveratrol chemically modified extract [51], inhibition of estrogen-dependent gene transcription by Shikonin (gromwell)[52], cell cycle delay/arrest by Carcinosin, phytolacca, Conium and Thuja [53]and modulating signal pathway by cacalol which is a free radical scavenging compound from Cacalia delphinifolia plant [54]. Ganoderma lucidum, Astragalus mongholicus, polygonatum sibiricum, and Chinese sage herb, were observed to be effective on non-small-cell lung cancer for stage III or IV [55]. Rasagenthi Lehyam (RL) is a siddha medicine, which is a poly herbal formulation for the treatment of cancer in India. It is reported that the chloroform extract of RL inhibited the growth of prostate and lung cancers [56]; its governing mechanism is inhibition of pro-survival genes and up-regulating the pro-apoptotic genes.

Anti-proliferative effect of Melissa officinalis on human colon cancer cell line was well studied by Encalada et al. [57]. This herb's hydroalcoholic extract also showed significant antioxidative activities by free radical scavenging. Thymoquinone

(TQ) is the bioactive- constituent of the volatile oil of black seed whose anti-neoplastic and anti-inflammatory effects were studied by Gali-Muhtasib et al. [58]. The combination of TQ with clinically used anti-cancer drugs led to improvements in their

Table 1. Laboratory Experiments of Herbs Anticancer Effects

Type of Cancer	Model	Herb	Mechanism
HNSCC	SCC-25 and KB cell lines, four nude mice with s.c. inoculation of KB cells	Scutellaria baicalensis	Inhibition of cell growth in vitro and in vivo, inhibition of PGE2 synthesis via suppression of COX-2 expression
	KB, KB v200 cell lines	Asiaticoside	Induction of apoptosis and enhancement of the anti-tumor activity of Vincristine
Leukemia	U937 cell line	Mylabris phalerlata, Scutellaria barbata,	Induction of apoptosis
	NB4, HL60 cell line	Red orpiment	Induction of apoptosis
	AKR/J mice	Echinacea purpurea	Enhancement of nonspecific immune or cellular immune systems (or of both).
	CCRF-CEM,CEM/E1000, CEM/VLB(100)cell lines	Artesunate(ART), Bufalin	ART significantly increased Daunorubicin accumulation in CEM/E1000 cells, but not in CEM/VLB (100) or CCRF-CEM parental cells, Bufalin caused a small, but significant increase in Daunorubicin accumulation in CEM/VLB (100) and CEM/E1000 cells.
	NB4 cell line	Arsenic trioxide	Induction of apoptosis
	HL-60 cell line	Hydrolysable tannis from Eugenia jambos L.	Induction of apoptosis
	HL-60,NB4,U937 and THP-1 cell line	PC-SPES	Inhibition of growth, induction of differentiation and apoptosis.
Colorectal Carcinoma	CoLo205 cell line	Magnolol	Induction of apoptosis
	Mice bearing colon26/ clone 20 carcinoma cells	Coptidis rhizome and Berberine	Reduction of IL-6 mRNA levels and protein levels in tumors and sera
Gastric Cancer	MGC-803 cell line	Isoliquiritigenin	Induction of apoptosis
		Astragali(AR)	Cytostatic
	AGS cell line	Anemarrhena asphodeloides	Induction of apoptosis
	MNK45 and KATO-III cell line		
Hepatic Cancer	Hep-G2 cell line	Mognolol	Induction of apoptosis
	SMMC-7221 cell line	Isoverbascoside	Induction of differentiation
Lung Cancer	A549 cell line	Bupleuri radix	Inhibition of telomerase activity and activation of apoptosis
	Lung cancer cells	Triptolide	Induction of apoptosis in combination with Apo2L/ TRAIL
Breast Cancer	95-D cell line	Acutiaporberine	Induction of apoptosis
	F344 rats	Anticancer-number-one	Increasement of NK cell activity increasing and inhibition of tumor metastasis.
	MCF-7 cell line	Rosemary	Reversing MDR
	MCF-7cell line	Tea and tea polyphenols	Suppression of fatty acid synthase (a key enzyme in lipogenesis)
	MCF-7 and MCF-7/ADM cell line	Asiaticoside	Enhancement of the anti-tumor activity of Vincristine

Ovarian Cancer	SKOV3,CAOV3 and OVCAR-cell lines	Scutellaria barbatae	Induction of apoptosis
Prostate Cancer	LNCaP cell lines	PC-SPES	Activation of the JNK/c-Jun/AP-1 signal pathway resulting in growth arrest and apoptosis of prostate cancer cells
	Prostate carcinoma cells	Equiguard	Down-regulation of expression of androgen receptor and prostate- specific antigen, induction of apoptosis
	Embryoid bodies and multicellular DU-145 prostate tumor spheroids	Baicalein, Epicatechin, Berberine,Acteoside	Down- regulation of MMp expression, inhibition of angiogenesis.
Glioma	Rat C6 glioma cells	Saikosaponin a,b	Induction of differentiation
	Mice that injected with LZEJ-C3 cells subcuta-neously	Dang-gui-bu- xai-tang	increasing the population of activated T helper cells (CD4+CD25+)in spleen and TDLN

HNSCC: head and neck squamous cell carcinoma; PGE2: prostaglandin E2; COX-2: cyclooxygenase 2; EC: endotheliocytes; CTLs: cytotoxic T lymphocytes; TDLN: tumor-draining lymph nodes.
Anticancer-number-one: Panax ginseng, Poria cocos, Atractylodes macrocephala, Anglica sinensis, A. membranaceus, Curcuma zedoaria,Scutellaria baicalensis, Phellodenron chinense, Coptis chinensis, Glycyrrhiza uralensis, Crataegus pinnatifida, Hordeum õulgare, Salõia miltiorrhiza, Schisandra chinensis, Hedyotis diffusa, Ophiopogon japonicus, Lobelia chinesis lour, Scutellaria barbaba, Massa fermentata medicinalis; PC-SPES, Reishi mushroom, Baikal skullcap, Rabdosia, Dyer's woad, Chrysanthemum, Saw palmetto, Panax ginseng, and Licorice; Dang-gui-bu-xai-tang, Radix Angelicae sinensis and Radix Astragali membranaceus.

Table 2. Human Study of Herbs Anticancer Effects

Herb name	Cancer type	Reported outcome
Essiac	Prostate	Decrease PSA levels from 87.19 to 0.12 ng/ml
PC-SPES	Prostate	Less than 50% decrease in PSA level
PC-SPES	Prostate	Decrease PSA levels from 100 to 24 ng/ml and386 to114 ng/ml
PC-SPES	Prostate	Decrease PSA levels from 8.8 to 0.1 ng/ml
PC-SPES	Prostate	Increase serum PSA levels ranging from345% to 880% after discontinuation of PC-SPES
Chinese herbal medicine [a]	Lung	Complete regression
Oriental herbal medicine and Lyophyllum decates sing	Lung	Partial response
Ninjin yoei To (Traditional Chinese Medicine herbal medicine)	Lung	Decreased tumor marker levels CEA: 14.6 to11.3 ng/ml; CA19-9: 55 to39.2 U/ml
Chinese herbal extract (specific herbal component not identified)	CLL	Complete remission
Ganoderma lucidum	Gastric large B-cell Lymphoma	Complete regression
Green Tea	CLL	Partial response
Mixture of 36 herbs	Intracranial tumor(teratoid/rhabdoid tumor)	Complete response
Hochu-ekki-to	Lymphoma (Mycosis fungoides)	Partial improvement of skin eruption
Mistletoe	Malignant melanoma	Complete remission of liver metastasis

Herb name	Cancer type	Reported outcome
Mistletoe	CD 30+ cutaneous lymphoproliferative lymphoma	Complete regression
Morinda citrifolia (noni)	Gastric Cancer	Tumor suppression
Peruvian herbal tea	Barrett's adenocarcinoma	Seven year survival
Mixture of 9 herbs	Hepatocellular	Complete regression

PSA: Prostate Specific Antigen
[a] Components of Chinese herbal medicine: Herba Hedyotis diffusae, Maidony, Radix ophiopnis, pugongying Herba taraxaci, Sanqi Radix notoginseng, shancigu pseudobulbus, Cremastrae seupleiones, Xiyangshen Radix Panacis quinqufolii, Yuxingcao Herba houttuyniae, Zhebeimu Bulbus Fritillariae thunbergii, Zhibanxia Rhizoma pinelliae perparata.

therapeutic index and prevented non-tumor tissues from sustaining chemotherapy-induced damage.

Vinca alkaloids which are isolated from the periwinkle plant Catharanthus roseus, also known as Vinca rosea, possess many therapeutic effects including anti-tumor activity [59]. Vinca alkaloids are most commonly administrated weekly by short IV injection (1-15 min) more rarely by continuous infusion [60].

Other examples of plant-derived compounds fight cancer by inhibition of protein synthesis, and cell-cycle progression blocking are currently under investigation. Extracts isolated from the leaves and stem of Amoora rohituka, alkaloid isolated from Cephalotaxus harringtonia, β -lapachone which is a quinine obtained from the bark of the Lapacho tree (Tabebuia avellanedae)and Combretastatin A4 which is isolated from the stem wood of south Africa tree Combretum caffrum are the most important objectives of related researches [61]. Curcumin is one of the most studied chemopreventive agents. It is a natural compound extracted from the rhizome of Curcuma longa that allows suppression, retardation or inversion of carcinogenesis [62-85].Evidence from numerous in vitro and in vivo studies have confirmed Resveratrol's(a polyphenol found in numerous plant species including peanuts and grapes) ability to modulate various targets and signalling pathways [86].

Table1 demonstrates governing mechanism of some herbs including test model and cancer types [87].

In addition, some vivo (human) studies are summarized in table2; this table demonstrates herbal medicine effectiveness in cancer treatment [88].

Anticancer Herbs' Safety

Herb safety and herb-drug interactions are complex and controversial issues. With the increasing use of herbs, their potential abuse and toxicity effects should be considered legitimately. The safety of a drug, herb or a complex compound is always relative and contextual. Safety is determined by defining the conditions under which a substance is considered to be safe or dangerous and weighing potential benefits against possible short and long-term adverse effect.

As a matter of fact, compared to the record of approved pharmaceutical drugs with a few well-known exceptions, medicinal herbs are safer [89]. Common use of herbs is rarely associated with adverse effects that are not easily reversible. These effects are seldom serious and include such transient reactions as: hot flashes, dizziness, headache, indigestion and rashes that are rapidly abated by discontinued use or dose reduction [90].

The preponderance of evidence shows that when used as an adjunct to conventional medicine, herbs both enhance the desired effects and mitigate the harmful ones.

Conclusion

It is estimated that more than 70% of the world's population cannot afford modern cancer medicines. In addition to cost, current cancer therapies are minimally effective and exhibit toxicities that are intolerable in most cases.

By this review, evidence presents that agents derived from plants used in herbal medicine can be used not only to prevent cancer but also to treat it. Because of their pharmacological safety, these agents can be used alone or as adjacent to current chemotherapeutic agents to enhance therapeutic effects and minimize chemo therapy-induced toxicity.

This research indicates that the molecular targets of chemopreventive agents are similar to those currently used to treat cancer. It is also evident that more research is required on herbal medicine to ensure and reach their full therapeutic potential.

Acknowledgment

The authors thank Kish Sayan Herbal Company for funding this research.

Conflict of Interest

The authors have no conflict of interest in this article.

Authors' Contribution

Javad Tavakoli designed the study and wrote the manuscript. Solaleh Miar contributed to the data entry, literature review and writing-up process. Mohammad Majid Zarezadeh and Hossein Akbari contributed to searching process.

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