

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

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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

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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

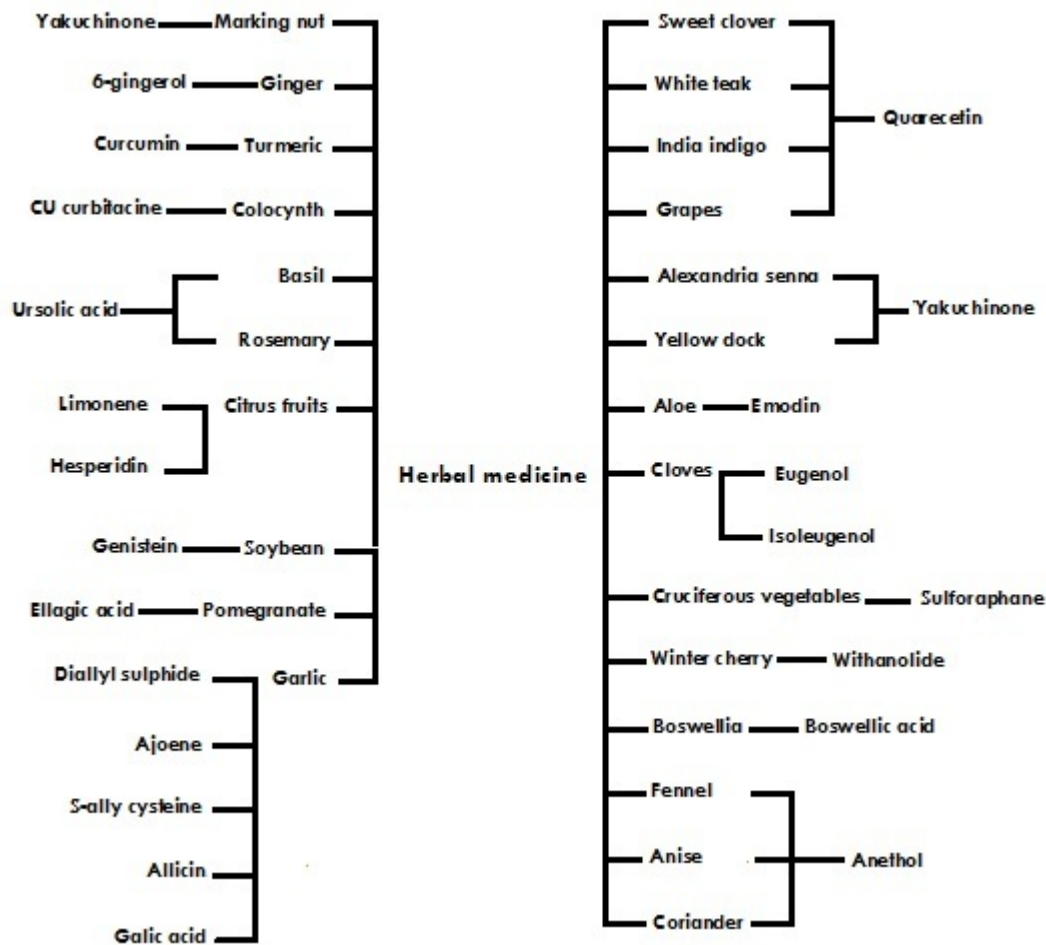


Figure 1. Active components from herbal medicine

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 taraxacum 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

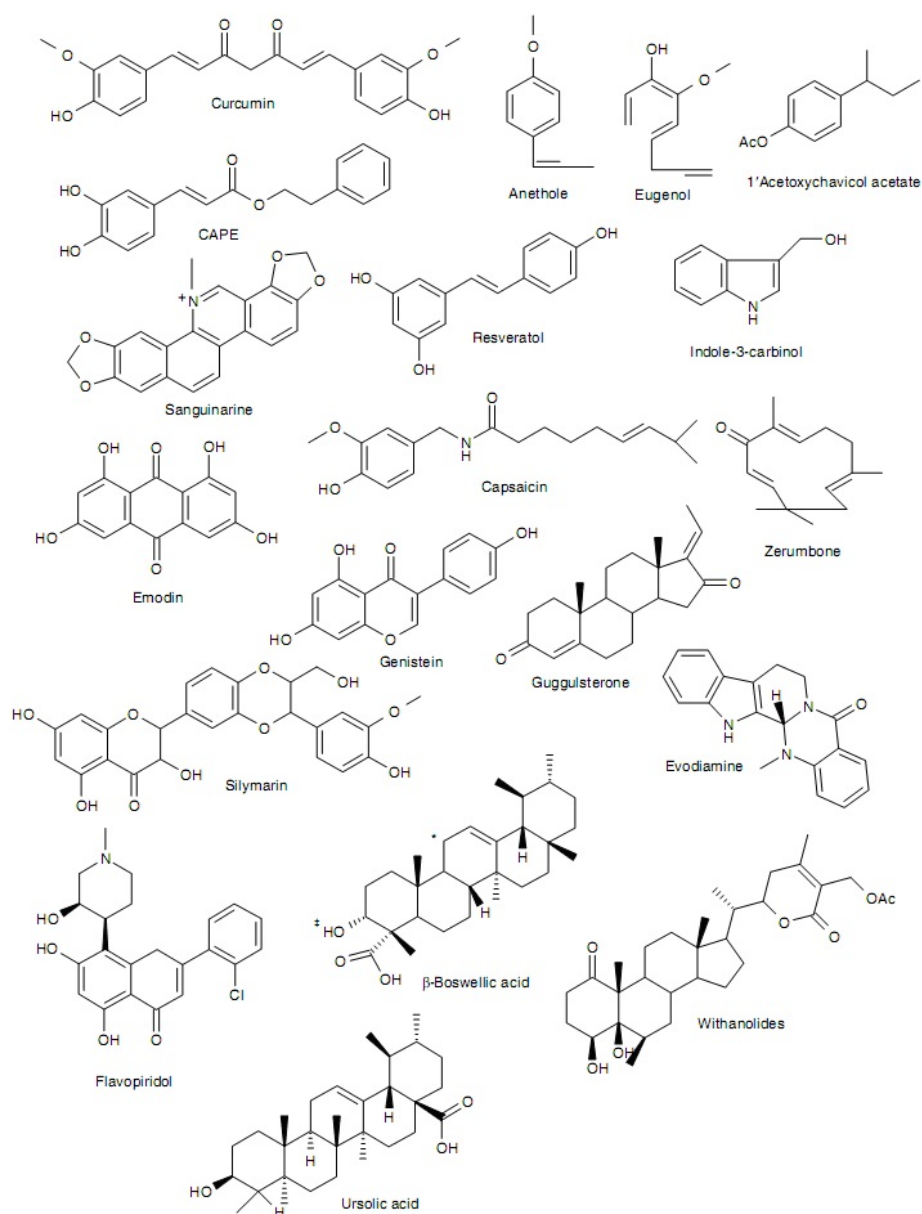


Figure 2. Chemical structures of selected active components in plants. (*can have a ketone group: 11-keto- β boswellic acid. ‡can be acetylated: acetyl- β boswellic acid. Both modifications together, result in acetyl- 11-keto- β -boswellic acid.)

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 *in 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 pilulosa*, *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

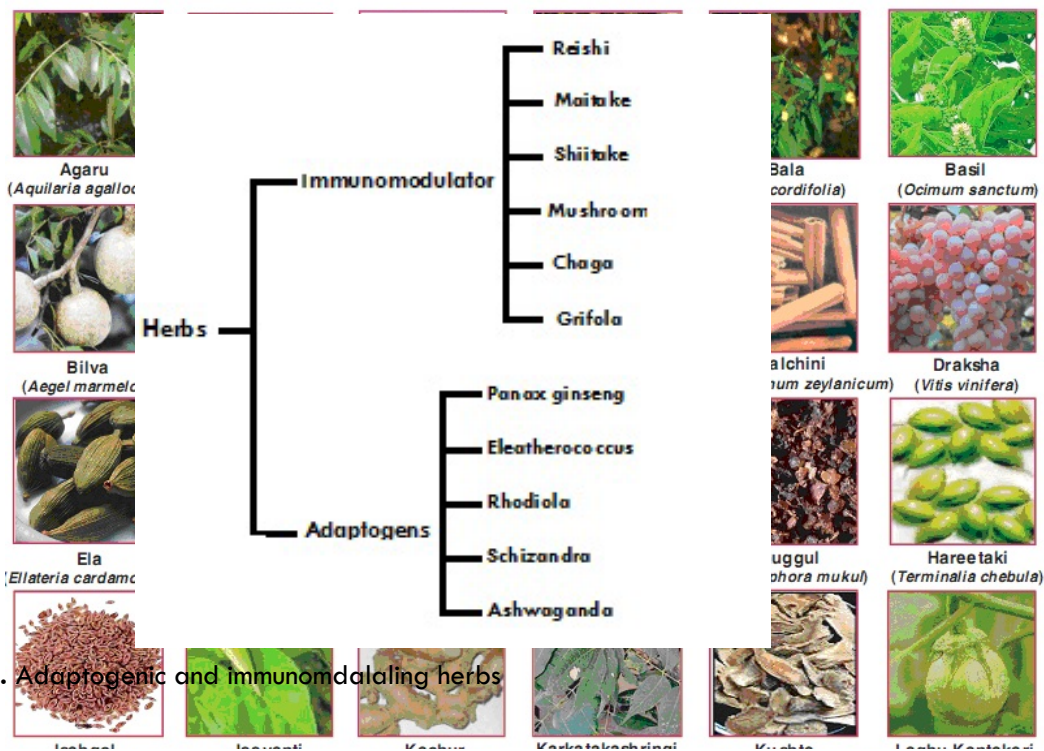


Figure 4. Adaptogenic and immunomodulating herbs

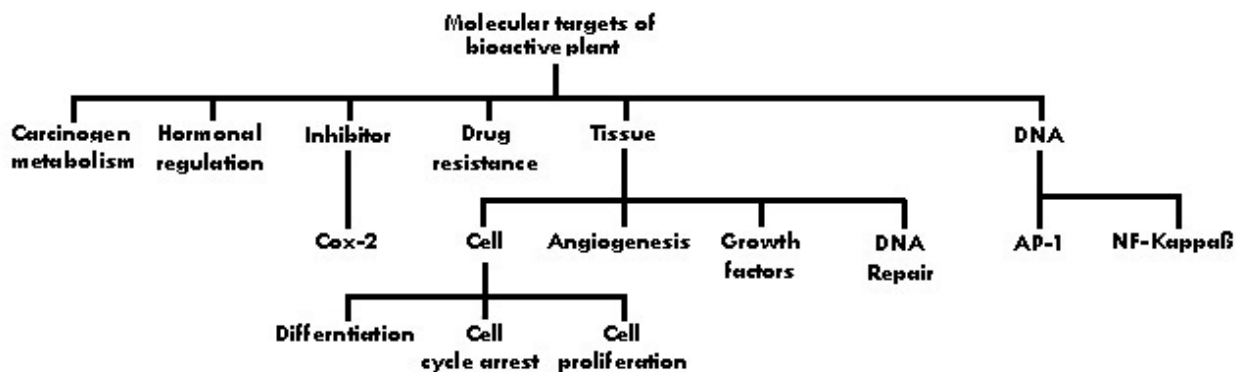


Figure 5. Molecular targets of chemopreventive compounds



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 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 Carcinisin, 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]. Rasagenti 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 | <i>Mylabris phalerlata</i> , <i>Scutellaria barbata</i> , | Induction of apoptosis |
| | NB4, HL60 cell line AKR/J mice | Red orpiment <i>Echinacea purpurea</i> | Induction of apoptosis 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 HL-60 cell line | Arsenic trioxide Hydrolysable tannis from <i>Eugenia jambos</i> L. | Induction of apoptosis 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 | <i>Coptidis rhizome</i> and Berberine | Reduction of IL-6 mRNA levels and protein levels in tumors and sera |
| Gastric Cancer | MGC-803 cell line | Isoliquiritigenin <i>Astragali(AR)</i> | Induction of apoptosis Cytostatic |
| | AGS cell line MNK45 and KATO-III cell line | <i>Anemarrhena asphodeloides</i> | Induction of apoptosis |
| 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 | Increase of NK cell activity increasing and inhibition of tumor metastasis. |
| | MCF-7 cell line | Rosemary | Reversing MDR |
| | MCF-7 cell line | Tea and tea polyphenols | Suppression of fatty acid synthase (a key enzyme in lipogenesis) |
| Ovarian Cancer | MCF-7 and MCF-7/ADM cell line | Asiaticoside | Enhancement of the anti-tumor activity of Vincristine |
| | 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 subcutaneously | 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: endothelial cells; CTLs: cytotoxic T lymphocytes; TDLN: tumor-draining lymph nodes.

Anticancer-number-one: Panax ginseng, Poria cocos, Atractylodes macrocephala, Angelica sinensis, A. membranacea, Curcuma zedoaria, Scutellaria baicalensis, Phellodendron chinense, Coptis chinensis, Glycyrrhiza uralensis, Crataegus pinnatifida, Hordeum vulgare, Salvia miltiorrhiza, Schisandra chinensis, Hedysotis diffusa, Ophiopogon japonicus, Lobelia chinensis Lour, Scutellaria barbata, 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 and 386 to 114 ng/ml |
| PC-SPES | Prostate | Decrease PSA levels from 8.8 to 0.1 ng/ml |
| PC-SPES | Prostate | Increase serum PSA levels ranging from 345% to 880% after discontinuation of PC-SPES |

| Herb name | Cancer type | Reported outcome |
|--|--|---|
| 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 to 11.3 ng/ml; CA19-9: 55 to 39.2 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 |
| 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 quinquefolii, Yuxingcao Herba houttuyniae, Zhebeimu Bulbus Fritillariae thunbergii, Zhibanxia Rhizoma pinelliae preparata.

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 administered 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].

Table 1 demonstrates governing mechanism of some herbs including test model and cancer types [87].

In addition, some vivo (human) studies are summarized in table 2; 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.

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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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