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Review article ■

Contribution of Selected Medicinal Plants for Cancer Prevention and Therapy

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SUMMARY

Since time immortal, plants have been used for maintaining health and curing disease. With cancer being a widespread threat to humanity, plants play an important role in cancer prevention, as well as in therapy. Medicinal plants provide new active chemopreventive molecules. In addition, treatment with plants can ease side-effects as well as provide support to the fears and anxieties of the sick.

In this review, methods of exploring new plants and new active plant-derived compounds are described, including ethnobotanical research and screening procedures. Three newly researched medicinal plants, native of Israel, are selected, and new research findings related to their anticancer activities are presented.

The plants are: *Crocus sativus, Vitex agnus-cactus and Withania somnifera.*

All three plants are known in traditional medicine and their therapeutical uses are documented. Most findings are preliminary and further studies are required for clinical applications.

Key words: **ethnobotany, medicinal plants, cancer prevention, anticancer compounds, chemoprevention**

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INTRODUCTION

The plant kingdom is playing an important role in cancer prevention and therapy in a number of ways:

A: Medicinal plants represent a vast potential source for anticancer compounds. These compounds are extremely complex molecular structures, which would be difficult to synthesize (or conceptualize) in the laboratory. The antitumour activity of medicinal plant derived compounds may result via a number of mechanisms, including effects on cytoskeletal proteins which play a key role in cell division, inhibition of DNA topoisomerase enzymes, antiprotease or antioxidant activity, stimulation of the immune system, etc. (1).

B: Plants can delay or even prevent cancer onset.

C: Plants can support the immune system, thus improving body resistance to the disease and its treatments.

D: Plants can prevent and decrease side effects of conventional treatments.

E: Plants can provide nutritional, as well as psychological support.

Therefore, it is a two-sided approach: One - plant-derived molecules are used by conventional medicine as anti-cancer drugs. Secondly, plants are used as a part of complementary treatment, offering psychological, nutritional and physical support, thus increasing the quality of life (2).

Methods of exploring new active and potential useful plants

1. Ethnobotanical search

Ethnobotany is the scientific study of human interactions with plants and environment. This includes the study of how traditional and modern cultures across the globe interact or have interacted with plants.

The study is based on locating and interviewing healers using traditional medicine. An example of a list of required information is given in Figure 1.

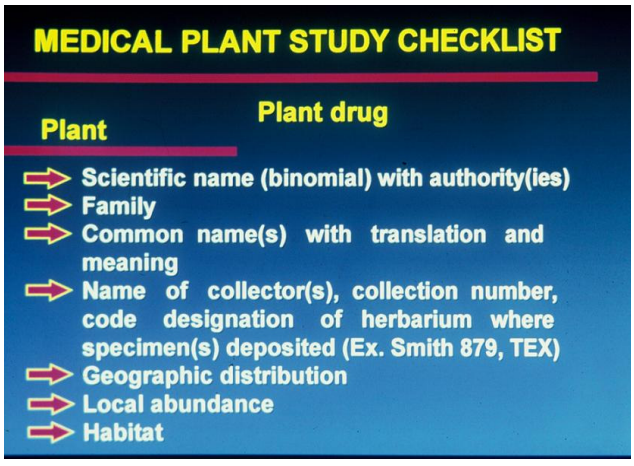

Figure 1. *Medicinal plant study checklist*

Figure 1 illustrates the importance of plant identification and of the geographic distribution of the medicinal plant being studied.

During data collection, attention is being paid to the part of plant collected, preferred time of collection and the stage of development, as well as methods of storing, extracting and preparing the traditional drug (3, 4).

2.Target-oriented search

The search is goal-oriented. The goal is to find new active molecules in plants, with the ability to stop and prevent the growth of cancer cells. Although plants have the potential to synthesize extremely complex molecular structures, extensive screening procedures are required to identify, isolate and purify these compounds.

Examples of plant-derived compounds with anticancer activity used clinically include: the *Vinca* alkaloids (which induce metaphase arrest by interfering with microtubule assembly) vinblastine, vincristine and vincamine derived from *Vinca rosea,* and their synthetic derivates vindesine and vinorelbine; the topoisomerase inhibitors campothecin, an alkaloid isolated from *Campotheca accuminata*, and etoposide, a semi-synthetic derivative of podophyllotoxin, an antineoplastic glucoside obtained from *Podophyllum peltatum*; the taxoids paclitaxel (taxol) and the synthetic analogue docetaxel (taxotere), which stabilize microtubules and disrupt mitosis. The various compounds described above are associated primarily with the treatment of breast cancer, but are also active against other forms of malignancy. For example, recent phase II/III trials have established docetaxel as the most active single agent in the treatment of advanced metatsatic breast cancer, whilst paclitaxel and platinum compound combination therapy is used as the standard regimen in the treatment of ovarian cancer and both agents are active in the treatment of lung cancer (1).

Medicinal plants continue to be the subject to extensive screening worldwide, in an attempt to develop more effective anticancer treatments. In many cases, the structure of these active compounds has been determined, and in some cases the potential mechanisms of action elucidated. However, the anticancer activity of these compounds has (in general) been established in cultured cell systems only, and their *in vivo* anticancer potential in animal model systems or human studies has yet to be established. In this review, we have focused on the novel anticancer activity of compounds derived from three medicinal plants, ***Crocus sativus,*** (Saffron) ***Vitex agnus-cactus*** (Chaste tree) ***and Withania somnifera*** ("ashwagandha"). All three plants are native of Israel, all known in traditional medicine. Their botanical characteristics, their uses in traditional medicine, as well as the new findings regarding their anti-cancer properties are reviewed.

3. Selected medicinal plants for cancer prevention and therapy

A. Crocus sativus - Saffron

Saffron is a small perennial plant of oriental origin. It grows from a bulb and flowers in the fall with white, lilac or violet flowers (Figure 2).

Figure 2. *Crocus sativus in flower*

The dried stigmas are used as a spice, for flavoring and coloring food, as a dye and as an ink. It is also very popular in traditional medicine (whole filaments, cut filaments, powder) (5) (Figure 3).

Figure 3. *Stigmas of Crocus sativus*

The stigmas have an aromatic odor, and a slightly bitter and pungent taste. Due to the high demand and manual work involved in collecting the stigmas, it is considered the most expensive spice (1gm=150 dried stigmas!)

The main components are carotenoids: Crocin, responsible for the orange color, and picrocrocin (bitter taste). The aroma is due to safranal, the main component of the essential oil (5).

History

Saffron is an ancient plant. It was used as a spice and as a medicine in Mesopotamia since the 4th millennium before the Common Era. Ancient Egyptian medicine used saffron for kidney problems, stomach problems and as an aid in delivery of babies (6). Saffron is mentioned in the Bible, as well as in old Jewish Manuscripts. Traditional therapeutical uses include: treatment of cough, flatulence, stomach disorders, insomnia, colds, fever, and heart problems. In China, saffron is used to treat depression, fear and pain.

Saffron and Cancer

There is a growing volume of scientific publications indicating the effect of saffron extracts on the inhibition of tumor formation and the retardation of tumor progression in a variety of experimental *in vivo* and *in vitro* systems. Some examples are cited in the text to follow. In a review published by Abdullaev and Espinosa-Aquirre (7), the biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials are described. This review provides an updated summary of *in vitro* and *in vivo* investigations focused on the anticancer activity of saffron (*Crocus sativus L.*) and its principal ingredients. Studies in animal models and with cultured human malignant cell lines have demonstrated antitumor and cancer preventive activities of saffron and its main ingredients. More direct evidence of anticancer effectiveness of saffron as chemopreventive agent may come from trials that use actual reduction of cancer incidence as the primary endpoint.This work suggests that future research be warranted that will define the possible use of saffron as effective anticancer and chemo preventive agent in clinical trials (7).

Recently a review has been published by Gutheil *et al*. (8) entitled: "Crocetin: an agent derived from saffron for prevention and therapy for cancer." The authors claim that crocetin, an important carotenoid constituent of saffron, has shown significant potential as an antitumor agent in animal models and cell culture systems. The authors suggest the possible mechanism of action: Crocetin affects the growth of cancer cells by inhibiting nucleic acid synthesis, enhancing anti-oxidative system, inducing apoptosis and hindering growth factor signaling pathways.

A research paper, titled: "Use of *in vitro* assays to assess the potential antiproliferative and cytotoxic effects of saffron, (*Crocus sativus* L.) in human lung cancer cell line." has been published recently (9). The authors showed that the ethanolic extract of saffron decreased cell viability in malignant cells as a concentration and timedependent manner. Their conclusions were that the extract exerts proapoptotic effects in a lung cancer-derived cell line and could be considered as a potential chemotherapeutic agent in lung cancer.

A review, dealing with new applications and mechanisms of action of saffron and its important ingredients, was published by Bathaie and Mousavi (10). The review documented saffron's application in a variety of disorders, involving neuronal, cardiovascular and other systems, as well as cancer. The cellular and molecular

mechanisms of its action are also under study. The more powerful components of saffron are carotenoids and monoterpene aldehydes. Structure-function relationship studies show that some properties are related to deglycosylated derivatives, while others belong to more glycosylated ones. Their study concludes that saffron has a wide range of usefulness in medicine, cosmetics, and coloring industries, so it can be used for new drug designs. However, more research about its mechanism of action is needed.

B. Vitex agnus-castus (Chaste tree)

Chaste tree is native of the Mediterranean region. It is a shrub with fragrant leaves and blue, violet and pink inflorescences (Figure 4).

Figure 4. *Vitex agnus-castus growing in Israel*

Vitex agnus-castus is used in traditional medicine in Israel as follows (11):

Tea made from the leaves is used for relieving headaches;, for joint pain - the black seeds are ground to powder, mixed with olive oil and spread over joints. Decoction of seeds is used for stomach pain; it is also used as a shampoo to stimulate hair growth; branches are used for basketry.

For over 2500 years, since the days of Hippocrates, chaste tree (*Vitex agnus-castus*) has been used for gynecological conditions. With a rich tradition of use, modern research supports historical wisdom, and has made chaste tree fruit preparations a phytomedicine of choice by the European gynecologists, for treatment of various menstrual disorders, PMS, and other conditions (12).

Vitex and cancer

Recently, a *Vitex agnus-castus* fruits (VACF) extract has been shown to exhibit antitumor activities in different human cancer cell lines (13). The scientists explored the antiproliferative effects of the fruit extract with a particular focus on apoptosis-inducing and potential cytotoxic effects. Three different human prostate epithelial cell lines representing different disease stages and androgen responsiveness were chosen. The extract inhibited proliferation of all three cell lines in a concentration-dependent manner with IC (50) values below 10 microg/mL after treatment for 48h. Cell cycle analysis and DNA fragmentation assays suggest that part of the cells were undergoing apoptosis. The VACF-induced decrease in cell number indicated a caspase-dependent apoptotic cell death. However, the concentration-dependent LDH activity of VACF treated cells indicated cytotoxic effects as well. These data suggest that VACF contains components that inhibit proliferation and induce apoptosis in human prostate epithelial cell lines. The extract may be useful for the prevention and/or treatment not only of benign prostatic hyperplasia but also of human prostate cancer.

Significant studies were done in Japan by a group of scientists who collected *Vitex* fruits in Israel and tested their effect on cancer cells (14). A crude extract was prepared with ethanol from dried ripened *Vitex agnus-castus* fruits growing in Israel (Vitex extract). Cytotoxicity of the extract against human uterine cervical canal fibroblast (HCF), ovarian cancer (MCF-7), cervical carcinoma (SKG-3a), breast carcinoma (SKOV-3), gastric signet ring carcinoma (KATO-III), colon carcinoma (COLO 201), and small cell lung carcinoma (Lu-134-A-H) cells was demonstrated.

It was concluded that the cytotoxic activity of *Vitex* extract may be attributed to the effect on cell growth, that cell death occurs through apoptosis, and that this apoptotic cell death may be attributed to increased intracellular oxidation by *Vitex* extract treatment.

Subsequently, the same group conducted a study on the cytotoxic effects of flavonoids from *vitex* against a human colon cancer derived cell line, COLO 201 (15). In this work, the mode of action was described. It was reported that the proliferation of this cell line, COLO 201, was effectively suppressed through apoptosis in the presence of flavonoids, an ethanol extract from *Vitex agnus-castus* fruits. The induction of apoptosis was not inhibited by the presence of an anti-oxidant, N-acetyl-L-cysteine, whereas only HO-1 gene expression levels increased among other typical oxidative stress-associated genes examined after Vitex treatment. These results suggest that *Vitex* treatment activates a pathway associated with HO-1 gene activation, resulting in the induction of apoptosis in COLO 201 cells. Results also implicate a potential clinical chemotherapeutic application of *Vitex* for the treatment of colon cancer patients.

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C. Withania Somnifera ("ashwagandha")

Withania is a short hairy shrub; its branches extend radially in a star pattern. Flowers are small and green. The ripe fruits are orange-red. The long brown tuberous roots are used for medicinal purposes. *Withania* grows in semi-tropical and temperate regions. It is native in Israel (Figures 5 and 6).

Figure 5. *Withania somnifera*

Figure 6. *Roots of Withania somnifera*

The main active constituents are alkaloids and steroidal lactones. Leaves contain withanolides, such as withaferin A. Recent research in mice suggests that withaferin A may have anti-metastatic activity (11).

Traditional medicine

Ashwaganda in Sanskrit means: horse's smell (odor of the roots). Somnifera means: "sleep-inducing". The roots are used for many purposes, including skin diseases, rheumatism, colds, fever, epilepsy, and as an aphrodisiac (11).

Withania and cancer

A review evaluating the scientific basis for the therapeutic use of *Withania somnifera* was published by Mishra *et al*. (16). Studies indicate that ashwagandha possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory, hemopoietic, and rejuvenating properties. It also appears to exert a positive influence on the endocrine, cardiopulmonary, and central nervous systems. The mechanisms of action for these properties are not fully understood. Toxicity studies reveal that ashwagandha appears to be a safe compound.

Yadav et al. (17), evaluated the anticancer activity of root, stem and leaves of *Withania Somnifera* against Various Human Cancer Cell Lines (17). Root, stem and leaves extracts showed cytotoxicity activity ranging 0-98% depending on the cell lines, but maximum activity was found in 50% ethanol extract of the leaves. This investigation is the first report of the anticancer activity in various parts of *Withania Somnifera.*

Withaferin A, the active component of Withania, shows the anticancer activity. It was reported (18) that Withaferin A (WA) induces p53-dependent apoptosis by repression of HPV oncogenes and upregulation of tumor suppressor proteins in human cervical cancer cells. Activity of WA was examined on human cervical cancer cells *in vitro* and *in vivo. In vivo,* WA resulted in reduction of nearly 70% of the tumor volume in athymic nude mice with essentially similar trend in the modulation of molecular markers as *in vitro*.

This is the first demonstration indicating that WA significantly down regulates the expression of HPV E6/E7 oncogenes and restores the p53 pathway, resulting in apoptosis of cervical cancer cells.

Medicinal plants in phytotherapy

A large number of plants are used as a support in the multisided side effects of cancer. These plants will be mentioned briefly, since this discussion is beyond the scope of this review.

Green tea, Ginseng and garlic gained the reputation of chemopreventive agents. *Capsicum annum* and *papaver somniferum* are used for pain relief. *Gingiber officinale Cannabis sativa, Mentha piperita* and *Cinnamonum cassia* are used to treat nausea and vomiting. For increasing vitality, *Panax ginseng, Siberian ginseng* and Ginkgo *biloba* are often used with great success (19).

CONCLUSIONS

The search for new pharmacologically-active compounds for drug development is an important issue, but not the only one, as the trend toward using standardized plant extracts of high quality, safety and efficacy will continue. Therefore, all efforts have to be targeted to reveal the chemical-pharmacological profiles of extracts and fixed combinations and to rationalize their therapeutic application. Whether in the future highly active, safe and causally-acting plant derived preparations will be able to replace some synthetic drugs, or in other cases are potent enough to be applied in combination with synthetic drugs, depends on the level of evidence-based therapeutic efficacy achieved.

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DOPRINOS ODABRANIH BILJAKA KOJE SE KORISTE U MEDICINSKE SVRHE U PREVENCIJI I LEČENJU KANCERA

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Sažetak

Zbog svoje otpornosti, biljke su se oduvek koristile kao preventiva, ali u i lečenju bolesti. U situaciji kada je kancer postao pretnja po čitavo čovečanstvo, biljke imaju važnu ulogu u prevenciji i lečenju kan-

cera. Biljke koje se koriste u medicinske svrhe poseduju nove aktivne hemopreventivne molekule. Pored toga, lečenje biljkama može da olakša nus pojave kao i da ublaži strahove i anksioznost bolesnika.

U ovom preglednom radu opisane su metode ispitivanja novih biljaka i aktivnih biljnih jedinjenja, pri čemu su uključena i etnobotanička ispitivanja i skrining procedure. Odabrane su tri nedavno ispitane biljke kojima je Izrael prirodno stanište i prikazani rezultati najnovijih istraživanja na temu antikancerogenih svojstava.

Ispitivane biljke su: Crocus sativus, Vitex agnus-cactus i Withania somnifera.

Sve tri biljke su poznate u tradicionalnoj medicini i ima podataka o njihovim terapeutskim svojstvima. Većina nalaza su preliminarni i potrebno je sprovesti dalja istraživanja kako bi njihova primena postala klinička.

Ključne reči: **etnobotanika, prevencija kancera, antikancerogena jedinjenja, hemoprevencija**