

Egyptian Medicinal Plants and Cancer Disease

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ABSTRACT

Cancer is a major public health burden in both developed and developing countries. Plant derived agents are being used for the treatment of cancer. Several anticancer agents including taxol, vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, and etoposide derived from epipodophyllotoxin are in clinical use all over the world. A number of promising agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol are in clinical or preclinical development.

Keywords: *Allium sativum*; *Azadirachta indica*; *Calotropis procera*; *Echinacea purpurea*; *Juniperus phoenicea* L; *Thymus vulgaris*; *Withania obtusifolia*; Anti-cancer agents

Introduction

Natural products from plants are rich sources of chemical diversity and most of the pharmacological active principals currently used as drugs, including anticancer agents are plants products. Egypt, a semi-arid region has abundant plants resources. Which are used traditionally for various disorders? In conclusion, some natural products from Egyptian flora used as therapeutics for diseases, such as cancer. Egyptian flora, the most diverse in the world, has become an interesting spot to prospect for new chemicals leads or hits due to its species diversity.

From 3000 to 6000 years ago, the ancient Egyptians have invented an efficient pharmacological collection of numerous curing materials obtained from natural resources. By far the most common form of treatment recommended in the medical papyri was the use of drugs, drawn from a very wide range of animal, mineral, and vegetable materials and administered in a variety of ways. The ancient Egyptians were renowned for their skill in this respect. The ancient Egyptians have written one of the earliest known records on Ebers Papyrus that dated to 1500 BC, which contains information on over 850 plant medicines, including garlic, juniper, cannabis, castor bean, aloe, and mandrake. The Egyptian physicians prescribed sedatives, analgesics, gastrointestinal disorder remedies, and medicines for urinary tract diseases and the common cold. Plant extracts were prepared and taken internally, applied topically, and administered by fumigation and vapor inhalation. The Egyptians also credited with the early medicinal use of wine, castor oil, marijuana, opium, mints, and beer made from barley and wheat. Oakes and Gahlin pointed out that the Egyptians were the first people to use some drugs that modern studies have proved would have been medicinally. The present review article clarifies some Egyptian plants, *Allium sativum*, *Azadirachta indica*, *Calotropis procera*, *Echinacea purpurea*, *Juniperus phoenicea* L, *Thymus vulgaris* and *Withania obtusifolia* on cancer disease.

Various Egyptian Plants

Allium sativum

Garlic (*Allium sativum*) is among the oldest of all cultivated plants. It used as a medicinal agent for thousands of years. It is a remarkable plant, which has multiple beneficial effects such as antimicrobial, antithrombotic, hypolipidemic, antiarthritic, hypoglycemic and antitumor activity. In this review, we will discuss particularly the largely preclinical use of this agent in the treatment and prevention

of cancer. A number of studies have demonstrated the chemo preventive activity of garlic by using different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of organosulfur compounds derived from garlic. The chemo preventive activity attributed to the presence of organosulfur compounds in garlic. How this achieved not fully understood, but several modes of action proposed. These include its effect on drug metabolizing enzymes, antioxidant properties and tumor growth inhibition. Most of these studies carried out in the animal models. In addition, recent research has focused on the antimutagenic activity of garlic. Recently, it observed that aged garlic extract, but not the fresh garlic extract, exhibited radical scavenging activity. The two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine, had the highest radical scavenging activity. In addition, some organosulfur compounds derived from garlic, including S-allylcysteine, found to retard the growth of chemically induced and transplantable tumors in several animal models. Therefore, the consumption of garlic may provide some kind of protection from cancer development [1].

Azadirachta indica

Neem (*Azadirachta indica*), a member of the Meliaceae family, is a fast growing tropical evergreen tree with a highly branched and stout, solid stem. Because of its tremendous therapeutic, domestic, agricultural and ethnomedicinal significance, and its proximity with human culture and civilization, neem called the wonder tree and nature's drug store. All parts of this tree, particularly the leaves, bark, seed-oil and their purified products are widely used for treatment of cancer. Over 60 different types of biochemicals including terpenoids and steroids purified from this plant. Pre-clinical research work done during the last decade has fine-tuned our understanding of the anticancer

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properties of the crude and purified products from this plant. The anticancer properties of the plant studied largely in terms of its preventive, protective, tumor-suppressive, immunomodulatory and apoptotic effects against various types of cancer and their molecular mechanisms. *A. indica* contains a wide range of biological active compounds, including nimbin, nimbidin, nimbolide, and limonoids. The first polyphenolic flavonoids from fresh neem leaves were quercetin and β -sitosterol. Atawodi and Atawodi, added that All of previous compounds occupy essential places in cancer development and mana. From many published papers, concluded that neem tree extracts and compounds have great potential for the prevention of cancer [2,3].

Calotropis procera

Ibrahim studied the ethyl acetate fraction of the methanolic extract of the root barks of *Calotropis procera* (Asclepiadaceae) from Egypt. Bioassay-directed fractionation and final purification of the extract resulted in the identification of a new cardenolide glycoside named proceraside A (1) together with two known compounds, frugoside (2) and calotropin (3). Their structures elucidated by extensive NMR studies and very spectrometric data. They studied in vitro cytotoxicity of the isolated compounds evaluated against A549 non-small cell lung cancer, U373 glioblastoma and PC-3 prostate cancer cell lines. They showed potent activity against the tested cancer cell lines with IC50 ranging from 0.005 to 0.3 μ g/mL. Cisplatin used as positive control [4].

Echinacea purpurea

Chamomile is one of the oldest garden herbs, whose reputation as a medicinal plant shows little signs of abatement. Considered a universal remedy by the ancient Egyptian, chamomile continues to be used today to battle illness, promote calm and relieve anxiety at bedtime. As a tisane (herbal tea), it is naturally caffeine-free. The finest varieties of chamomile, of which our tea is a great example, continue to come from Egypt. If you have yet to try it, you pleasantly surprised by its superior flavor. Chamomile is one of the most important medicinal and aromatic plants cultivated in Egypt. In Egypt, many of the big farmers have been switching to the cultivation of chamomile plants especially in Menia, Fayoum, Benisuef and Assuit governorates. The net return (L.E.) for chamomile is 2095 L.E./feddan (hectare = 2.34 feddan) yearly. A relaxing honey- sweet infusion made from the flower heads of the highest grade Egypt grown chamomile.

Juniperus phoenicea L

Juniperus phoenicea L. listed as threatened tree by IUCN Red List. In Egypt, *J. phoenicea* L. is the only conifer tree that is restricted to the three mountains of northern Sinai: Gabal El-Halal, Gabal El-Maghara and Gabal Yelleq. Mediterranean region included in a national list as target for conservation and management. To provide baseline information for the development of a conservation strategy, the present study aims at comparing the isolated populations of *J. phoenicea* and their associated plant composition and diversity at the three mountains. The application of TWINSPAN and DCA analysis techniques resulted in identifying of four vegetation types associated with juniper and each related to a specific geomorphologic habitat on a topographic gradient. Juniper shows generally poor conditions of vitality at higher elevation (600–960 m) with a higher proportions of old and recent dead trees, and with the predominance of male individuals, as compared with the populations of Gabal El-Maghara and Gabal Yelleq. In contrast, the juniper populations at lower

elevation (350–470 m) of Gabal El-Halal proved to be in best condition with mostly living foliage and reproductive branches. The differences in rock types and elevation among the three mountains reflect serious limitation on recruitment of *J. phoenicea* due to moisture availability. The results of this study showed that *J. phoenicea* is an endangered species and its conservation in northern Sinai Mountains is a priority. For a successful conservation of this community, it is highly recommended to preserve in particular the suitable habitats at Gabal El-Halal, but also the other stands merit conservation measures [5].

Thymus vulgaris

The genus *Thymus* is one of the eight most significant genera within the Lamiaceae family and its importance lies in its wide range of medicinal and non- medicinal purposes and its increasing economic importance for North America, Europe and North Africa. In Egypt, certain species of thyme including *T. capitatus*, *T. bovei* and *T. ducussatus* grow wild, while others are cultivated, such as *T. vulgaris* and *T. serpyllum*. *Thymus vulgaris* is included in many pharmaceutical preparations, with no less than 30 local pharmaceutical products in Egypt alone. *Thymus vulgaris* oil has been reported to be among the top 10 essential oils of significant anti- bacterial, anti- mycotic, anti-oxidant and natural food preservation. The phenolic monoterpenoids, thymol and carvacrol, constituting the main components of the thyme oil believed to play the main role in the above biological activities [6-8].

Withania obtusifolia

Medicinal plants from the Egyptian Sinai Peninsula are widely used in traditional Bedouin medicine to treat a range of conditions including cancer, and as such are a promising resource for novel anti-cancer compounds. Various parts of *W. somnifera* especially the roots with its unique contents proved effective against different kinds of cancers. The most active components withanolides and withaferins along with a few other metabolites including withanone (WN) and withanosides have been reported effective against different types of cancer cell lines. This herb holds an important place among various anticancer medicinal plants [9].

Discussion

Various researches have shown that *Allium sativum* and organosulfuric compounds reduce the risk of cancer in breast, larynx, colon, skin, womb, gullet, bladder, and lung. In other research, we refer to the role of the most important *Allium sativum* compound, that is, Allicin, and the antitumor characteristics of this compound on breast and prostate cancer proved. This compound induces planned death of cells and has anticancer role. When *Allium sativum* is crushed and cracked up, Allicin 1, under the effect of an enzyme, changes to Allicin 2. Allicin is a proliferation inhibitor of malignant human cells. Ajoene is another compound that suppresses proliferation of leukemia and will cause planned death of cell [10].

Hemerson evaluated the cytotoxic potential of stem organic extracts from *Calotropis procera* (Asclepiadaceae) against cancer cell lines by MTT assay. The tested subsequently, samples considered cytotoxic for antimetabolic activity on sea urchin egg development and for in vivo antiproliferative activity in mice bearing Sarcoma 180 tumor. They added that among the five extracts (hexane, dichloromethane, ethyl acetate, acetone and methanol), ethyl acetate and acetone extracts displayed higher cytotoxic potential against tumor cells, with IC50 ranging from 0.8 to 4.4 μ g/mL, while methanolic extract was

weakly cytotoxic. They added that cytotoxic extracts also exhibited cell division inhibition capacity by antimetabolic assay, revealing IC50 values lower than 5µg/mL. Meanwhile in vivo antitumor assessments, ethyl acetate- and acetone-treated animals showed tumor growth, inhibition ratios of 64.3 and 53.1%, respectively, with reversible toxic effects on liver and kidneys.

Steffani indicated that the organic extract of *E purpurea* root decreased the proliferation of BT-549 in comparison to the DMSO-control cells. The dosage range of the organic extract was 70µg/µl to 700µg/µl, for 96hr. The proliferation of the BT-549 cells decreased significantly starting at 280µg/µl and continued to decrease as the concentration of the organic extract of *E purpurea* root increased. They added that the BT-549 cells that treated with DMSO continued to proliferate as the concentration of DMSO increased as well. Cells were plated at 3x10⁵ cells per well in a 6-well plates and treated for 96hr. While the results of the effect of the organic extract of *E purpurea* leaf indicated that, the extract decreased the proliferation of BT-549 in comparison to the DMSO-control cells. The dosage range of the organic extract was 70µg/µl to 700µg/µl, for 96hr. The proliferation of the BT-549 cells decreased significantly starting at 210µg/µl and continued to decrease as the concentration of the organic extract of *E purpurea* leaf increased.

Afaf isolate three biflavonoids (essuflavone (1), amentoflavone (2), and sumaflavone (3)), four diterpenoids (13- epi- cupressic acid (4), imbricatolic acid (5), 3- hydroxy- sandaracopimaric acid (6), and dehydroabietic acid (7)), and one lignan [β- peltatin methyl ether (8)] from the cytotoxic fractions of the extracts of the leaves of *Juniperus phoenicea* L. The structures of these compounds elucidated by spectroscopic means. They found that Cytotoxicity of compounds 1–6 were assessed against the human lung cancer cell line A549 using the MTT assay. They found that compounds 1 and 3 showed cytotoxicity against the A549 cells (IC50 = 65 and 77 µM, respectively), whereas compound 2 did not show any activity. Diterpenes 4–6 exhibited weak cytotoxicity against the A549 cells with the IC50 values of 159, 263, and 223 µM, respectively. They evaluated cytotoxicity of each compound compared with the anticancer drug, etoposide (IC50 = 61 µM). Cupressuflavone (1) also evaluated for cytotoxicity against both the human PC3 cancer cell line and the normal prostate cell line (PNT2), they added that this compound revealed a high degree of cytotoxic selectivity towards the prostate cancer cells (PC3), with IC50 value of 19.9 µM, without any evidence of cytotoxicity towards the normal prostate cell line (PNT2) [10].

Mohamed studied *Thymus vulgaris* ethanol extract and purified repeatedly to produce several compounds including the known flavanone. Nargenin, which identified using different spectral techniques. Nargenin shown to inhibit both human colorectal and breast cancer cell growth in a dose- and time-dependent manner through cell cycle arrest at S- and G2/M-phases accompanied by an increase in apoptotic cell death. Additionally, Nargenin altered the expression of apoptosis and cell-cycle regulatory genes by down-regulating Cdk4, Cdk6, Cdk7, Bcl2, x-IAP and c-IAP-2 and up-regulating p18, p19, p21, caspases 3, 7, 8 and 9, Bak, AIF and Bax in both colorectal and breast cancer cells. Conversely, it diminished the expression levels of the cell survival factors PI3K, pAkt, pIκBα and NFκBp65. Moreover, Nar enhanced the sensitivity of colorectal and breast cancer cells to DNA-acting drugs [4].

Zahra evaluated highlights the anti-oxidant and anti-cancer activities of bio-functionalized *Thymus vulgaris* silver nanoparticles (TVAgNPs)

and compared bioactive compounds using the human breast cancer T47D cell line. They evaluated aqueous ethanolic extract of *T. vulgaris* for chemical composition using the gas chromatography–mass spectrometer (GC–MS) analysis. They prepared TVAgNPs and determined by means of UV–Vis spectroscopy, FTIR spectroscopy, zeta potential, scanning electron microscopy, transmission electron microscopy, and energy-dispersed spectroscopy analysis. They studied *T. vulgaris* extract and TVAgNPs for their in vitro anti-oxidant property by 2, 2-diphenyl, 1-picryl hydrazyl (DPPH) assay. They added that Microscopic observations indicated spherical shaped and monodispersed nanoparticles and the average size of the nanoparticles was about 30 nm. Regarding the elemental composition profile of the TVAgNPs, the highest signal of silver (89.30%) detected followed by other elements. An absorption peak registered at 440 nm according to surface plasmon resonance (SPR) of the TVAgNPs in solution. A zeta potential of fabricated nanoparticles was approximately -12.6 mV, indicating higher stability of the bio-functionalized TVAgNPs. They evaluated *T. vulgaris* extract and synthesized TVAgNPs for their anti-cancer activity using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay and Annexin V double staining with propidium iodide (PI) flow cytometric analysis toward T47D cells. The cytotoxicity properties of the bio-functionalized *T. vulgaris* AgNPs revealed that the sensitivity of T47D human breast cancer cells high compared with *T. vulgaris* extract. Besides, the anti-oxidant activity of the TVAgNPs clarified a higher anti-radical-scavenging activity compared to *Thymus vulgaris* extract. They shown that the potential biological activities of the bioactive constituents of *T. vulgaris* enhanced through bio-functionalized *T. vulgaris* AgNPs due to the bioorganic compounds that exist in the extract.

Rahma isolated seven compounds from the leaves and fruits of Egyptian *Withania somnifera* dunal, (Family: Solanaceae). The identity of the compounds based on their spectroscopic data were as follows: two withanolides; withaperuvin C (1), phyperunolideF (2) and four lipids; 1,2-di-O-palmitoyl-3-O-(6''-sulfo-α-D-quinovopyranosyl)-glycerol (3), vaccenic acid (5), 1,3 dicaproyl,2-vaccenoyl-glycerol (6), vaccenolmonoglyceride (7) and β-sitosterol glucoside (4). All the isolated metabolites except (4) reported for the first time from this plant. Besides, this is the first report for isolation of compounds (6,7) in a pure form from a natural source. They added that Different fractions of the fruits of the Egyptian plant investigated for their anticholinesterase activities where the most potent ones found to be the aqueous, the light petroleum fraction in addition to a mixture of lipids.

Conclusion

Mohamed-Elamir cited that extracts derived from *Withania obtusifolia* (WO), *Jasania candicans* (JC), *Centaurea lippii* (CL), and (PU) were the most active ones among 76 extracts from 40 Egyptian medicinal plants. They added that they showed a significant reduction of cell viability on drug-sensitive CCRF-CEM leukemia cell line with IC50 values less than 7 µg/ml. Low cross-resistance degree observed in multidrug-resistant CEM/ADR5000 cells towards CL (1.82-fold) and JC (6.09-fold).

Acknowledgment

None

Conflict of Interest

The author's declared that they have no conflict of interest.

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