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The Analysis of Egyptian Medicinal Plants for the Treatment of Cancer Disease

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Review Article

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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.

INTRODUCTION

Cancer is the second leading cause of death worldwide. Although great advancements have been made in the treatment and control of cancer progression, significant deficiencies and room for improvement remain. A number of undesired side effects sometimes occur during chemotherapy. Natural therapies, such as the use of plant-derived products in cancer treatment, may reduce adverse side effects. Currently, a few plant products are being used to treat cancer. However, a myriad of many plant products exist that have shown very promising anti-cancer properties *in vitro*. Natural products from plants are rich sources of chemical diversity and most of the pharmacological active principles 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 [1]. 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 Sumner. The Egyptian physicians prescribed sedatives, analgesics, gastrointestinal disorder remedies and medicines for urinary tract diseases and the common cold [2].

LITERATURE REVIEW

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. Although there are several proposed modes of action, how this was achieved is not fully understood.These include its effect on drug metabolizing enzymes, antioxidant properties and tumor growth inhibition. Most of these studies carried out in the animal models [3]. 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 [4].

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, Nakagawa et al. 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 [5].

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 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[6]. *Azadirachta 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 Alzohairy. Atawodi and Atawodi added that all of previous compounds occupy essential places in cancer development. From many published papers, concluded that neem tree extracts and compounds have great potential for the prevention of cancer.

Calotropis procera

Ibrahim et al. 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 together with two known compounds, frugoside and calotropin[7]. 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 IC_{50} ranging from 0.005 to 0.3 µg/mL. Cisplatin used as positive control.

Hemerson et al. evaluate 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 antimitotic activity on sea urchin egg development and for *in vivo* anti proliferative 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 IC_{50} ranging from 0.8 to 4.4 µg/mL, while methanolic extract was weakly cytotoxic. They added that cytotoxic extracts also exhibited cell

division inhibition capacity by antimitotic assay, revealing IC_{50} values lower than 5 µg/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 [8].

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. You will be impressed by its superior flavour profile if you've never tried that one yet. 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.

Steffani et al. indicated that the organic extract of *Echinacea purpurea* root decreased the proliferation of BT-549 in comparison to the DMSO-control cells. The dosage range of the organic extract was 70 µg/µl to 700 µg/µl, for 96 hr. The proliferation of the BT-549 cells decreased significantly starting at 280 µg/µl and continued to decrease as the concentration of the organic extract of *Echinacea 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 3^5 cells per well in a 6-well plats and treated for 96hr. While the results of the effect of the organic extract of *Echinacea 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 70 µg/µl to 700 µg/µl, for 96 hr. The proliferation of the BT-549 cells decreased significantly starting at 210 µg/µl and continued to decrease as the concentration of the organic extract of *Echinacea purpurea* leaf increased [9].

Juniperus phoenicea L

Juniperus phoenicea L listed as threatened tree by IUCN Red List. In Egypt *Juniperus 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 *Juniperus phoenicea L* 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 *Juniperus phoenicea L* due to moisture availability. The results of this study showed that *Juniperus phoenicea L*

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.

Afaf et al. isolate three biflavonoids (essuflavone 1, amentoflavone 2 and sumaflavone 3, four diterpenoids (13-epi-cupressic acid (4), imbricatholic acid (5), 3-hydroxy-sandaracopimaric acid (6), and dehydroabietic acid (7)], and one lignan [β-peltatin methyl ether (8)] were isolated from the cytotoxic fractions of the extracts of the leaves of the Libyan 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 (IC_{50}=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 IC_{50} values of 159, 263, and 223 μM, respectively. They evaluated cytotoxicity of each compound compared with the anticancer drug, etoposide (IC_{50}=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 IC_{50} value of 19.9 μM without any evidence of cytotoxicity towards the normal prostate cell line (PNT2).

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 *Thymus capitatus, Thymus bovei* and *Thymus* grow wild, while others are cultivated, such as *Thymus vulgaris* and *Thymus serpyllum* (Boulos, 1999). *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 Dorman and Deans 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 (Baser).

Mohamed et al. 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 G_2/M-phases accompanied by an increase in apoptotic cell death. Additionally, Nargenine 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.

Zahra et al. 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 *Thymus 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 Thymus *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 *Thymus 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 bio-functionalized *Thymus vulgaris* AgNPs' cytotoxicity properties showed that T47D human breast cancer cells were more sensitive than *Thymus vulgaris* extract.. Besides, the anti-oxidant activity of the TVAgNPs clarified a higher anti-radical-scavenging activity compared to *Thymus vulgaris* extract. They demonstrated that the bioorganic compounds present in the extract enhanced the potential biological activities of the bioactive constituents of *Thymus vulgaris* through bio-functionalized *Thymus vulgaris* AgNPs.

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 [10]. Various parts of *Withania obtusifolia* 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.

DISCUSSION AND CONCLUSION

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 (Shafik and Elseesy). 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.

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