Medicinal Plants from Jordan in the Treatment of Cancer: Traditional Uses vs. *In vitro* and *In Vivo* Evaluations – Part 1

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- traditional medicine
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Abstract

Plant species have long been used as principal ingredients in traditional medicine. Different surveys showed that ethnomedicinal plant species used by the inhabitants of Jordan for the treatment of cancer are inadequately screened for their therapeutic/chemopreventive potential and phytochemical findings. In this mini review, traditional herbal medicines pursued indigenously with their methods of preparation and active constituents are listed. Studies of random screening for selective cytotoxicity and antiproliferative activity of local spices, domesticated greens, or wild plants are briefly discussed. Recommended future directives for the design and conduct of comprehensive trials are pointed out to validate the usefulness of these active plants or bioactive phytoconstituents either alone or in combination with existing therapies or complementing pharmacologies.

Introduction

The Hashemite Kingdom of Jordan's habitat is unique in that the intersection of dense forest, arid desert, and tropical geography endows the country with a rich variety of plants and microorganisms that can be studied efficiently in a relatively small land area (**Fig. 1**) [1]. More than 2500 wild plant species from 700 genera exist; of these, there are approximately 100 endemic species, 250 rare species, and 125 very rare species [1–3]. In the Mediterranean basin, there seems to be a wealth of ethnobotanical studies providing a new and key tool for a quest after invaluable phytopharmaceuticals or the development of functional foods or nutraceuticals [4–12]. Traditional medicine practices are part of the Jordanian culture. Despite modern medicine accessibility, herbal medicine has often maintained popularity [13]. The percentage of reliability on herbal medicine varies from rural and desert areas to urban ones [14–16]. Crucially, the folk phytotherapy is "aging" or "vanishing" in the sense that knowledge of medicinal plants persists mainly in elderly rural people with little schooling [17]. In the last decades negative human impacts also affected the ecosystem, adding more plants to the list of endangered species, thus calling on the urgent need for community-based programs promoting their national conservation and sustainability [18].

In a survey carried out with the herbalists in Jordan, none of the interviewed herbalists mentioned any plants for the treatment of cancer [15]. On the other hand, literature surveys based on the published studies indicated that in Jordan and in the neighboring countries, 27 plant species are considered as traditional remedies for the treatment of the different types of cancers [14, 19–23]. This article summarizes information on different aspects of chemopreventive-therapeutic plants as well as randomly screened plants for the antiproliferative activity to stimulate interest in these herbs which are of importance in Jordan and other countries of the semi-arid tropics.

Results and Discussion

Cancer is a leading cause of death worldwide. More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030 [24].

Running second after heart diseases, cancer is a major cause of morbidity among the Jordanian population, with an estimated incidence rate of

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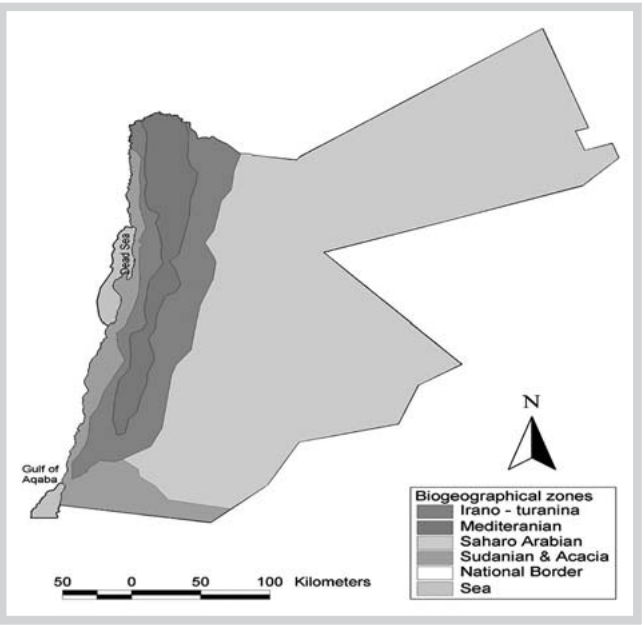

Fig. 1 Biogeographic zones of Jordan.

5000 new cases per year. Male to female ratio for cancer cases in Jordan is 0.97 : 1. The overall median age of cancer diagnosis in Jordan is 56 years (males: 60 years; females: 52 years). 43.15% of all newly registered cases occurred in the age of 60 years and above, and 11.6% occurred below the age of 30 years [25].

As recently updated by the Jordan National Cancer Registry (JNCR) statistics, the most commonly diagnosed cancers in a descending order in 2008 would be breast (18.8%), colon (7.7%), lung (7.7%), bladder (4.3%), and non-Hodgkin's lymphoma (4.8%) [25, 26].

The evidence-based practices of consuming plants and plant derived products in the treatment of cancer with the orthodox therapy were first reported by Afifi et al. [13]. In cooperation with the King Hussein Cancer Centre (KHCC), the researchers interviewed a total of 1138 randomly selected cancer outpatients, predominantly Jordanians. Among interviewees, the total number of complementary and alternative medicine (CAM) users was 404 (35.5%). All CAM users were either on chemotherapy or radiotherapy and preferred to use the crude extract in the form of infusions (n = 296, 73.3%) [13]. Crude extracts were prepared from coarsely powdered plant mixtures and none of the individual plants could be identified by the researchers. Therefore emphasis is given in the present review to the plants with claimed anticancer activities in the ethnopharmacological studies and to the findings of the random screening of the plant species from the local flora for their antiproliferative activities. **Table 1** lists the ethnopharmacologically promoted plants with the method of preparation; parts used and reported phytochemical constituents. Clearly, in half of them, experimental studies to prove their cytotoxicity properties, however unique, are negligible. The majority of the plants (78%), nevertheless, were tested for other pharmacological activities (**Table 1**).

In an attempt to screen the medicinal herbs from the Jordanian flora collected from each of the four biogeographic regions of Jordan, more than 120 ethanol, chloroform, and water extracts belonging to about 49 families representing 86 genera were evaluated for their antiproliferative activity. *Inula graveolens, Salvia dominica, Conyza canadiensis* and *Achillea santolina, I. viscosa, Lavendula officinalis*, and *S. syriaca* showed promising and potent antiproliferative activities on a breast cancer cell line (MCF-7) [27–29]. The most active plant was *I. graveolens* with an IC_{50} of 3.83 µg/mL [27]. Inclusive reporting of the selective cytotoxicity of *Rhus coriera* and *A. biberstenii* along with the preceding seven species were collectively presented at the 1st Annual World Cancer Congress 2008 Shanghai, China. The ethanol extracts of the active plants were further evaluated using T47D, ZR-75-1, and BT474 cell lines, as were some of their volatile fractions and isolated pure flavonoids [28].

Al-Kalaldeh et al. demonstrated the cytotoxicity activity for the ethanol extracts of *Origanum syriacum* (IC_{50} of 6.4 µg/mL), *Laurus nobilis* (IC_{50} of 24.5 µg/mL), and *S. triloba* (IC_{50} of 25.3 µg/mL) against MCF-7 cell lines [30]. These were among many other commonly used culinary spices or edible domesticated greens proven for their therapeutic properties [31]. In a parallel line of work, Faris et al. illustrated the enhanced chemopreventive effect of cooked lentils against colorectal carcinogenesis [32]. Furthermore, compared to garlic-only treatment, combined supplementation of soy and garlic had a marked modulation of 7,12 dimethylbenzy-α-anthracene induced mammary cancer in female albino rats [33]. Additionally, aqueous extracts of *Nigella sativum, Allium sativum*, and *Onopordum acanthium* augmented significantly splenic natural killers' cytotoxicity against tumor targets *in vitro* and *in vivo* [34–36].

Few more reports on selective evaluation of the traditionally used plants for their cytotoxicity activities were obtainable [23, 37, 38]. Talib and Mahasneh screened 16 plants for their antiproliferative activity against Hep-2, MCF-7, and Vero cell lines and demonstrated that methanol fractions of *Ononis hirta* and *I. viscosa* exerted their antiproliferative activity by inducing apoptosis in cancer cell lines [23]. *In vitro* antiproliferative activities of several *Salvia* species against different cancer cell lines were tested by Fiore et al. [37]. Their findings showed promising cytotoxic activity for *S. menthefolia, S. spinosa, S. sclarea*, and *S. dominica* [37]. In a panel of fibrosarcoma L929sA cells, breast cancer cells MDA-MB231 and MCF-7, organic extracts of *Withania somnifera, Psidium guajava, L. nobilis*, and *S. fruticosa* also displayed remarkable antitumor cytotoxicity [38]. Withaferin A, a major constituent of *W. somnifera*, was further characterized among a novel class of NF-κB inhibitors, holding promise in cancer treatment [39]. As part of serial studies on the unique and under-explored biodiversity of Jordan, the colchicinoids of *Colchicum spp*. (Colchicaceae) were pursued [40–44]. Alkaloids of the colchicinoid structural class are well known from this genus, particularly (−)-colchicine, and these compounds have been investigated extensively for both toxicological and potential medical properties, exhibiting potent cytotoxicity against a human cancer cell panel [45]. Nevertheless, the pyrrolizidine alkaloids recovered from *Echium glomeratum* (Boraginaceae) by the same research group lacked any anticancerous cytotoxicity [46].

Nowadays, it is well accepted that plant constituents possess cancer-preventive and cancer-therapeutic activities and natural product chemistry has already contributed to 60% of all anticancer drugs [47–49]. Chemoprevention research has gained momentum through the US FDA approval of tamoxifen and raloxifene for breast cancer risk reduction. Various epidemiological and preclinical findings and the results of several early clinical studies convincingly argue for a definitive role of selected dietary products in the treatment and prevention of cancers. Many of these agents target multiple signal transduction pathways; mod-

Table 1 Indigenous medicinal plants of Jordan used for the treatment of cancer in folk medicine; major ethnopharmacological surveys, their phytochemical constituents, and latest common pharmacological findings.

No.	Family name	Species	Method of preparation of plant parts	Reported ethnopharmacological anticancer activity	Reported phytochemical constituents	Reported selective antiproliferative cytotoxicity or other pharmacologies
1	Amaryllidaceae	*Narcissus tazetta* L.[a,b]	Infusion of flowers	[23]	Alkaloids [55, 56], flavonoids, and terpenoids [57]	Antiviral [55, 58, 59]; cytotoxic constituents against a panel of cancer cell lines [56, 59], ethanol extract not cytotoxic against MCF-7 [23]; antimicrobial activity [57]
2	Araceae	*Arum dioscoridis* Sibth et Sm.[c]	Decoction of leaves	[19, 21]	None	None
3	Araceae	*Arum hygrophilum* Boiss.[b]	Decoction of leaves	[21]	None	Phytopathogenic fungicidal activity [60]
4	Araceae	*Arum palaestinum* Boiss.[a,b]	Decoction of leaves	[20, 21]	Pyrrole alkaloid [61]	Moderate antioxidant capacity [62]; dose-dependent suppression in the proliferation of breast carcinoma cells (MCF-7) and lymphoblastic leukemia cells (1301) by its ethyl acetate fraction [61]; ethanol extract not cytotoxic against MCF-7 [27]
5	Araliaceae	*Hedera helix* L.[b]	Decoction of leaves and berries	[14]	Saponins [63, 64]	Leishmanicidic activity [63]; anti-elastase and anti-hyaluronidase activities [65]; antispasmodic [66]; antimutagenic [67]; treatment of bronchial asthma [68]
6	Asteraceae	*Inula viscosa* (L.) Ait.[a,b]	Decoction of flower heads	[23]	Sesquiterpenes, sesquiterpenes acids [69]; azulenes, lactones, flavonoids, and essential oils [70]	Selective antiproliferative activity by inducing apoptosis in MCF-7 cancer cell lines [23]; anti-implantation and mid-term abortifacient effects in rats [71]; cytotoxic and genotoxic effects on *A. cepa* [72]; hypoglycemic activity in normal and diabetic rats [73]
7	Asteraceae	*Calendula arvensis* L.[b]	Infusion of dry flowering branches	[14]	Saponins [67, 74]; sesquiterpene glycosides [75]	Antimutagenic [67]; anti-inflammatory [74]; antiviral [75]
8	Asteraceae	*Anthemis pseudocotula* Boiss.[c]	Infusion of flower heads	[14]	Apigenin, apigenin-7-glucoside, scopoletin, and herniarin [76]	None
9	Cucurbitaceae	*Luffa cylindrica* L.[a,b]	Boiled seeds and aerial parts	[23]	Triterpenoids and saponins [77, 78]; flavone glycoside [79]	Although ethanol extract was noncytotoxic against MCF-7 [23], dose-dependent antiproliferative pro-apoptotic cytotoxicity of alpha-luffin towards tumor cells and its potential antitumor role [83, 84]; fibrinolytic [77]; antiviral, abortifacient, and cytotoxic activities [80, 81]; antioxidative [82] and immunomodulatory effects in Balb/C mice [78]
10	Ericaceae	*Arbutus andrachne* L.[b]	Decoction (oral), soaked in olive oil (external) of leaves, fruits, and roots	[20]	Arbutin, hydroquinone, beta-sitosterol, and ursolic acid [85]	Antityrosinase activity [85]
11	Euphorbiaceae	*Mercurialis annua* L.[a]	Decoction of leaves	[20]	Flavonol glycosides [86]	Ethanol extract lacked any antiproliferative efficacy in MCF-7 [27]
12	Fagaceae	*Quercus calliprinos* Decne[b]	Decoction of fruits and bark	[20]	Several fatty acids, lipids, and aromatic compounds [87]	High antioxidative capacity [62]; cattle toxicosis [88]
13	Globulariaceae	*Globularia arabica* L.[b]	Decoction of leaves	[14]	None	Fetotoxic potentials in female rats [89]; antimicrobial activity [90]; antiviral activity [91]
14	Lauraceae	*Laurus nobilis* L.[a,b]	Decoction of leaves	[20]	Flavonoid O-glycosides, flavonoid C-glycoside, catechin, and cinnamtannin B1 [92]	Antioxidant and acetylcholinesterase inhibition [93]; pro-apoptotic, antiproliferative properties on human melanoma cell lines [94]
15	Leguminosae	*Ononis sicula* Desf.[a]	Infusion (topical) of aerial parts	[23]	Flavonoids and terpenoids [23]	Selective antiproliferative activity against MCF-7 cancer cell lines [23]
16	Leguminosae	*Anagyris foetida* L.[a]	Decoction of leaves	[14]	Anagyrine, baptifoline, isorhamnetin [95]	Preliminary cytotoxicity against two tumor cell lines [95]; ethanol extract lacked such efficacy in MCF-7 [27]

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Table 1 Indigenous medicinal plants of Jordan used for the treatment of cancer in folk medicine; major ethnopharmacological surveys, their phytochemical constituents, and latest common pharmacological findings. *(continued)*

No.	Family name	Species	Method of preparation of plant parts	Reported ethnopharmacological anticancer activity	Reported phytochemical constituents	Reported selective antiproliferative cytotoxicity or other pharmacologies
17	Liliaceae	*Urginea maritima* (L.) Baker[a,b]	Infusion of bulbs	[14]	Cardiac glycosides of the bufadienolide type [96, 97]	Insecticidal activity [98]; cytotoxic and genotoxic effects in *A. cepa* test [99]
18	Liliaceae	*Allium cepa* L.[a,b]	Decoction of raw bulbs and leaves	[19]	Flavonoid glycosides [100]; S-alk(en)yl cysteine sulfoxide metabolites [101, 102]; quercetin [103]; onionin A [104]	Antimutagenic [100]; antidiabetic [105]; antiplatelet aggregation effect [106]; chemopreventive in gastrointestinal, ovarian, and endometrial and skin cancers [107–110]; induction and augmentation of apoptosis [103, 111, 112]
19	Loranthaceae	*Viscum cruciatum* Sieb et Boiss.[a,b]	Decoction of external (pads) and leaves	[19, 22]	Diarylheptanoid [113]; triterpenoids and flavonoid aglycones [114]; polyphenols [115]	Antioxidative [115]; cytotoxic against larynx cancer cells [116] with a cytotoxic diarylheptanoid against a panel of cancer cell lines [113]
20	Menispermeaceae	*Cocculus pendulus* (J. R. & G. Forst.) Diels[b]	Infusion of leaves and branches	[14]	Several alkaloids [117–119]	Anticholinesterase activity [120, 121]
21	Poaceae	*Triticum aestivum* L.[a]	Decoction of shoots	[20]	Lignans, dietary fibers, and aleurone [122, 123]	Pro-apoptotic antitumor activity in colon cancer cells [122, 123]
22	Polypodiaceae	*Platanus orientalis* L.[a,b]	Decoction of leaves	[14]	Flavonoids and kaempferol glycosides [124, 125]	Antimicrobial [124]; cytotoxic against leukemic cell lines [125]
23	Ranunculaceae	*Clematis flammula* L.[b]	Infusion of leaves	[14]	Polyphenols [126]	Antioxidative capacity [126]
24	Rhamnaceae	*Zizyphus spina-christi* (L.) Desf.[b]	Decoction of fruits and leaves	[21, 127, 128]	Saponin glycosides [129]; flavonoids [130]	Insulinotropic hypoglycemic effects in diabetic rats [131–133]; cytoprotective against liver aflatoxicosis [134] and CCl4-fibrosis [135]; vasoconstrictive effect in rat aorta [136] antifungal [137]
25	Rosaceae	*Sarcopoterium spinosum* (L.) Spach.[b]	Infusion, decoction of leaves, seeds, and roots	[21]	Triterpenoids [138]	Antioxidative [62]; antidiabetic properties [139, 140]
26	Rosaceae	*Crataegus azarolus* L.[b]	Decoction of flowers and fruits	[20]	Polyphenols [141]	Antioxidative capacity [141]
27	Urticaceae	*Urtica pilulifera* L.[b]	Decoction of leaves	[20]	Phenolics [142]	Antioxidative [142]; hypoglycemic activity in diabetic rats [143]

[a] Plants with ethnotherapeutic claims and traditional uses subjected to critical antitumor cytotoxicity pharmacological appraisal. [b] Plants with ethnotherapeutic claims and traditional uses subjected to other critical pharmacological appraisals. [c] Plants with ethnotherapeutic claims and traditional uses not subjected to pharmacological appraisal

ulate cancer aneuploidy, tubulin binding, topoisomerases, and gene specific and aspecific targets, which vary widely depending on cancer origin [12, 50, 51]. The introduction of synthetic analogues of natural compounds may be a solution for potency and bioavailability limitations [52]. Some natural compounds have exhibited synergism with established chemopreventive agents or with other natural compounds [53]. Since drug associated toxicity remains a significant barrier for currently available chemotherapeutic and chemopreventive drugs, using natural compounds (with better safety profiles) as adjuvant therapy with current chemotherapeutic agents may help to mitigate drug associated toxicities [54]. The key challenge to researchers is how to best use this information for effective cancer prevention in populations with different cancer risks.

In conclusion, these studies, uniquely indicating the potential use of medicinal plants as antineoplastic agents, are among the very few that explored Jordanian flora from extreme environments such as the desert and near the Dead Sea (400 m below sea level) for pharmaceutical leads. Comprehensive research aiming at fully exploiting any of the promising species from the Jordanian flora, either alone or in combination with existing therapies, might lead to the discovery of new avenues for medicinal plants/natural compounds in reducing the public health impact of major cancers. Elucidation of molecular targets and mechanisms also constitutes another prerequisite.

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