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An updated assessment on anticancer activity of screened medicinal plants in Jordan: Mini review

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Abstract
Since the ancient ages plant species have been used as key part in traditional medicine and curing practices. Recently a huge body of literature showed that medicinal plant species used by the Jordanian people for the treatment of cancer were screened for their potential as cytotoxic therapy at least *in vitro*. This review summarizes an updated evidence on different features of traditionally used chemotherapeutic plants in addition to the screened ones for their antiproliferative activity and to shed light on them for further investigation. Studies of screening for selective cytotoxicity and antiproliferative activity of plants are briefly discussed.

Keywords: Cancer, Proliferation, Medicinal plants, Jordan Flora, phytochemical, *In vitro*, *In vivo*

Introduction
As a second leading cause of death worldwide, cancer is a challenging area of research to discover new drugs (Bray *et al.*, 2018) [14]. Cancer is one of the biggest health problems that affect human and needs active approaches for therapy. Globally, about 1 out of 6 deaths are due to cancer and an estimated 9.6 million deaths in 2018 are from cancer (Bray *et al.*, 2018) [14]. Cancer or tumor are general names represent a group of diseases that can affect all part of the human body. Cancer is an abnormal, uncontrolled rapid growth of cells which can invade other parts of the body. Once cancer spread through the body uncontrollably it leads to death (Akaza, 2019) [7].

According to World Health Organization (WHO, Country-specific 2019) [15] the most commonly diagnosed cancer cases in Jordan for the year 2018 are; breast (19.7%), lung (10.5%), colorectum (10.1%), bladder (4.9%), Leukemia (4.8%) and other cancers (50%).

Medicinal plants are key tools in discovering new drugs and new chemical compounds. Plant and plant derived entities are safe and ecofriendly. It was proved that 50% of new chemical substances were natural products, semi-synthetic natural products, and semi-synthetic natural analogs (Sofowora, *et al.*, 2013) [20]. The importance of medicinal plants as a part of the health care system has been reported globally. A high percentage of people around the world depends on therapies of plant origin specially in the primary healthcare (Talib & Mahasneh, 2010) [21].

Jordan territory is diverse and composed of tropical and desert natural features. Jordan is divided into four biogeographic regions: the Mediterranean, Irano-Turanian, Saharo-Arabian and Sudanian. The four regions comprise thirteen vegetation types which provide the natural habitats for over 4,000 species of wildlife and vegetation from the terrestrial, marine and freshwater environments. (Moghbelli *et al.*, 2015-2020) [18].

Issa and Bushati have reported that Jordanians believe in herbs and natural preparations more than synthetic drugs and get their therapeutic information mainly from herbalists. Several plants have been used in traditional medicine for many years without enough scientific data to confirm their efficacy Issa & Basheti 2017) [17]. These plants may contain actual active compounds which could be used therapeutically and prepared in pharmaceutical formulations. Such plants should be evaluated as medicinal plants. Active ingredients which are called phytochemicals can be extracted and purified to be used clinically. For example, but not as a limitation, ginger, capsaicin, and curcumin for direct medicinal use; microscopic plants, e.g. fungi, actinomycetes that are used for isolation of drugs specially antibiotics and fibre plants, e.g. cotton, flax, jute which are used for the preparation of surgical dressings (Sofowora *et al.*, 2013) [20] as hemi-synthesis of medicinal compounds.

Many published studies indicated that several plant species are considered as remedies for the treatment of different cancer types (Abu-Dahab, *et al.*, 2012; Alhourani, *et al.*, 2018; Al-Samydai, *et al.*, 2019) [2, 11, 9].

In vitro evaluation of anticancer activity of many plants and plant derived compounds is considered as an important field of research. These experimental screening led to the introduction of several anti-cancer drugs to the market such as vinblastine, vincristine and paclitaxel (Iqbal *et al.*, 2017) [16].

Essential oils are one of the most popular constituents of aromatic plants. Continually, researchers investigate EOs for their activity as antiproliferative, antioxidant, and detoxifying agents. Essential oil are volatile, and odorous compounds produced by the secretory compartments of aromatic plants. In general, they are hydrophobic liquids with low boiling point components of plants, with a distinctive odour or volatile aroma compounds found in glands in several parts of the aromatic floras: roots, flowers, leaves, seeds, fruit, and barks (Al-Kalaldeh, *et al.*, 2010) [8]. Terpenes and terpenoids, and aromatic/phenolic components are the main group of the essential oil compounds that have a low molecular weight (Asbahani *et al.*, 2015).

This review summarizes an updated evidence on different features of traditionally used chemotherapeutic plants in addition to the screened ones for their antiproliferative activity in order to shed light on them for further investigation.

Results and Discussion

Afifi *et al.*, (2011) [5] reviewed more than 100 articles and summarized data for plants cultivated in Jordan and traditionally tested and used for cancer. They listed the ethnopharmacologically used plants with the method of preparation; parts used and reported phytochemical constituents. Moreover, Affifi *et al.* declared that there is a need for inclusive research to investigate the promising Jordanian flora species alone or as adjuvants with other chemotherapies. This screening might lead to the discovery of a new natural compounds that eliminate or reduce the major influence of cancers. They concluded that these plants have unique potential as anticancer agents and candidates for chemotherapeutic leads. (Afifi, *et al.*, 2011) [5]. The most active plants found by Afifi are listed in table 1.

In 2013 Asaf and her group investigated the anticancer, anti-inflammatory, and antimicrobial activity of *Mercurialis annua* L., *Bongardia chrysogonum* L., and *Viscum cruciatum Sieb* S. which are traditionally used by herbalists in Jordan for hematopoietic neoplasms patients. *Viscum cruciatum Sieb* S. herbal methanolic extract showed high anti-cancer (IC_{50} 14.21 µg/ml on BJAB cells), anti- inflammatory (inhibited the release of IL-8) and anti-microbial potentials (specially against *Propionibacterium acne*). These findings might encourage the use of *Viscum cruciatum Sieb* S. for the treatment of diseases associated with some bacterial and fungal infections as well as for cancer and other immunotherapies (Assaf *et al.*, 2013) [13].

The anti-proliferative effect of the methanolic extract of *Chrysanthemum coronarium* L. was evaluated by Abu-Rish and her team against six human tumor cell lines (A375.S2, WM1361A, CACO-2, HRT18, MCF-7, T47D). C. *coronarium* extract showed cytotoxic activity against WM1361A and T47D antiproliferative in a dose-dependent manner (Abu-Rish *et al.*, 2016) [3].

Having antioxidant property indicates the possibility of anti-proliferative and anticancer activity of the plant. However, not all anti-oxidative plants can protect from oxidative DNA damage and prevent cancer development. In 2016, Alkofahi and others tested the ability of different plants to lower the oxidative stress status and protect against DNA damage. *Silybum marianum* A., *Pistachia palaestina* A., *Eucalyptus camaldulensis* M., *Salvia triloba* L., *Zizyphus spina-christi* R. and others, were extracted using five different solvents (water, ethanol, methanol, chloroform and hexane) and examined for their antioxidative DNA damage activity. The five extracts of *S. marianum* lowered significantly the marker used (8-OH-dG), only organic extracts of *P. palaestina* showed the potential to lower the oxidative damage, while only the ethanolic extracts of *E. camaldulensis*, *S. triloba*, and *Z. spina-christi* has antioxidative properties (Alkofahi, *et al.*, 2016) [12].

In another study, Afifi *et al.* explored the phytochemistry, antioxidative and antiproliferative activity of *Arum hygrophilum* A. They concluded that *A. hygrophilum*, like *A. dioscoridis* and *A. palaestinum*, was identified as an inhibitor of α-amylase/α-glucosidase but lacked antiproliferative effects in colorectal cancer cell lines HT29, HCT116, and SW620 (Afifi, *et al.*, 2017) [6].

In 2017, Al-Zereini prepered ethyl acetate extracts from *Ononis natrix* F. and *Salvia verbenaca* L. and assessed the antibacterial and cytotoxic activities of their phytoconsistuents. Both *Ononis natrix* and *Salvia verbenaca* have cytotoxic activity against MDA MB-231 breast cancer cells with IC_{50} of 28.75 ± 2.5 and 41.3 ± 4.8 µg/ml respectively, in a concentration-dependent manner (Al-Zereini, 2017) [10].

In vitro antitumor activity of the *Alkanna tinctoria* L and *Rubia tinctorum* L root ethanolic and methanolic extracts was investigated against eight different cell lines. Both ethanolic extracts showed very potent anti-cancer activity against MDA-MB-231 breast cancer cells (IC_{50} 2.98 µg/ml, 5.68 µg/ml for *A. tinctoria* and *R. tinctorum respectively*), and CAL-27 tongue squamous carcinoma cells (IC_{50} 3.75 µg/ml, 2.64 µg/ml for *A. tinctoria* and *R. tinctorum* respectively); methanolic extracts showed similar results as well (Rashan *et al.*, 2018).

Ruwad studied the immunomodulatory and anticancer activity of five herbal drinks consumed in Jordan. The antiproliferative activity, apoptosis induction macrophage function and splenocytes proliferation were evaluated. Breast cancer cell lines growth was inhibited by herbal drinks in dose dependent manner. They proposed that ginger and lemon verbena drinks affected cancer cells by induction of apoptosis and angiogenesis. Ginger and lemon verbena herbal drinks exhibit anticancer activities and stimulate the innate and acquired immunity (Ruwad, 2018) [19].

Essential oils were extracted from the aerial parts of *Tamarix aphylla* L., a wild plant in Jordan. Aqueous (AE) and ethanolic (EE) extracts were prepared from *T.aphylla* and their cytotoxicity against breast adenocarcinoma (MCF-7), colorectal adenocarcinoma (Caco-2), and pancreatic carcinoma (Panc-1) cancer cell lines was evaluated. The lowest IC_{50} (2.17 ± 0.10 μg/mL) was recorded for the AE of *T.aphylla* against MCF-7, they found that *T.aphylla* has antitumor activity comparable with cisplatin however, more selective to cancer cells since its IC_{50} against fibroblast was 79.99 ± 4.90 μg/mL (Alhourani *et al.*, 2018) [11].

Aerial parts of *Ajuga chia*, *Micromeria nervosa* and *Origanum dayi* were evaluated for their cytotoxicity against two different breast cancer cell lines MCF7 and T47D. The ethanolic extract of *O. dayi* had anIC_{50} of 99.4 ± 2.9 and 250 ± 4 µg/mL in both cell lines respectively (Yousef, *et al.*, 2018) [23].

Essential oils of *Ocimum basilicum* L. were extracted, the chemical composition of the oil was identified, and its

antitumor activity was assessed. *O. basilicum* essential oil has anticancer potential against triple-negative breast cancer cell line (MDA-MB-231), ER+ breast cancer (MCF7), and the glioblastoma (U-87 MG) with IC_{50} of 432.3±32.2, 320.4±23.2, and 431.2±15.3 µg/ml respectively (Aburjai, *et al*. 2020) [4].

In a short review, Ali Al-Samydai and his team summed up capsaicin anticancer activity against different cancer cell lines. *Capsicum annuum* L. is the natural source of capsaicin that has many therapeutic activities. Capsaicin was tested against *in vitro* T24 human bladder carcinoma cells, colon cells (SW480, HCT116, LoVo and Caco 2), gastric (MGC 803), and many others (Al-Samydai, *et al*., 2019) [9].

Conclusions and upcoming prospects

From this review we can conclude that plants and plants derivatives are promising and effective research zone for cancer treatment. It's worth mentioning that the main issue that remains unresolved is how researchers can best use medicinal plants for effective cancer prevention in people at risk. Due to the rising prevalence of cancer and the high price of its treatments, alongside various restrictions in the availability of therapy including high toxicity; thus arose the challenge for researchers to develop other biocompatible and cost-effective therapeutic approach. As a result of this situation, phyto-products are likely to alter cancer treatment in the future. The safety profile of plant ingredients and patient compliance have increased the value of phytochemicals in cancer therapy. It was reported that many phytochemicals defined in clinical trials such as thymoquinone, curcumin, epigallocatechin, isothiocyanates, gossypol, sulforaphane, garcinol…etc. are effective as cytotoxic and immunomodulatory agents. Moreover, more resources should be spent on these phytochemicals to assess their possible applications in cancer therapy either *in vitro* or *in vivo.*

Table 1: The most active plants screened for breast cancer cell line.

Plant name	Part used /extract	cancer cell line	IC_{50} (µg/ml)	Ref.
Inula graveolens, Asteraceae	Ethanol extract	MCF7	3.83 ± 0.177	1
Salvia dominica, Lamiaceae	Ethanol extract	MCF7	7.28 ± 1.150	1
Conyza canadiensis, Asteraceae	Ethanol extract	MCF7	12.76 ± 2.475	1
Achillea santolina, Asteraceae	Chloroform extract	MCF7	15.49 ± 1.45	1
Origanum syriacum, Lamiaceae	Ethanol extract	MCF7	6.40± 3.17	8
Laurus nobilis, Lauraceae	Ethanol extract	MCF7	24.49 ±8.17	8
Salvia triloba, Lamiaceae	Ethanol extract	MCF7	25.25 ± 1.21	8
Ononis hirta Fabaceae (aerial parts)	Methanol extract	MCF7	27.96 ± 0.54	21
Inula viscosa Asteraceae (flowers)	Methanol extract	MCF7	15.78 ± 0.59	21

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