



## Research Paper

# Cytotoxic activity evaluation of some medicinal plants, selected from Iranian traditional medicine Pharmacopoeia to treat cancer and related disorders



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## ABSTRACT

**Ethnopharmacological relevance:** By studying the Iranian Traditional Medicine (ITM) Pharmacopoeia, we have collected information about medicinal plants which had been used to manage cancer-like disorders over eight hundred years, from medieval to the early modern era. Exploring the ITM herbal knowledge, the selected species have been subjected to MTT assay for examining their in vitro cytotoxic activity.

**Materials and methods:** Cancer was reviewed through the ITM and some terminologies were acquired. Five ITM Pharmacopoeia in Arabic and Persian languages from 10th to 18th century AD were explored. These Pharmacopoeia contained the ITM plants which were used to cure cancer and cancer-like diseases. The ITM names were matched with the scientific names. Then the medicinal plants were collected, authenticated and were evaluated for cytotoxic activity using MTT assay, against MCF-7, HepG-2, A-549 and HT-29 cell lines. Finally, the apoptosis induction ability of the most cytotoxic medicinal plant was investigated by activated caspase 3 inspection in MCF-7 cell line.

**Results:** Six species of the evaluated medicinal plants revealed cytotoxic activity. The most cytotoxicity was observed in *Tanacetum polycephalum* subsp. *argyrophyllum* (K.Koch) Podlech with IC<sub>50</sub> values of 28.3 µg mL<sup>-1</sup>, 53.9 µg mL<sup>-1</sup> and 43.3 µg mL<sup>-1</sup> against MCF-7, A-549 and HT-29 cell lines, respectively. Caspase 3 activation was also observed in MCF-7 cells by *Tanacetum polycephalum* subsp. *argyrophyllum*. This is the first time that the cytotoxic activity of this species has been reported.

**Conclusion:** In the present study, some reliable references of ITM have been introduced and though many technical difficulties, linguistic problems and some other hindrances were encountered during the study, using traditional medicine texts for medicinal plant selection could be considered as a helpful starting point in the field of cancer drug discovery.

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## 1. Introduction

### 1.1. Aim of the study

The study has focused on the historical Pharmacopoeia of Iranian Traditional Medicine (ITM) to excerpt data on medicinal plants which had been used to manage cancer and related diseases over eight centuries, from medieval to the early modern era. The obtained data subsequently helped us to choose some medicinal plants and evaluate their cytotoxic activity. We have focused on

plants which were used specifically and in a long period of time to manage an especial disorder called cancer.

### 1.2. Background

Despite enormous technological development in recent years, a large number of people are diagnosed with cancer and consequently many deaths are reported. The statistics released by the American Cancer Society and the International Union against Cancer have shown probable 27 million diagnoses and 17 million deaths by 2030 worldwide (Aggarwal et al., 2009). Cancer treatments include surgery, radiotherapy and chemotherapy (Brundage, 2008). Chemotherapy in cancer care, as a term is: "a kind of therapy that uses chemical compounds to fight neoplastic diseases" (Schwab, 2001). In spite of low selectivity of

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cytotoxic agents to kill normal cells over cancerous ones, which is the cause of limitations, challenges and side effects, using such molecules to eliminate cancer cells and inhibit tumor growth are the original approach to the therapy (Priestman, 2012). A large number of natural and synthetic products are approved as anticancer agents and currently are in use (Kumar et al., 2013). Thus, setting up the beginning time for the treatment of an illness like cancer is too difficult because the herbal and other preparations have been used since antiquity (Baguley, 2002); thus, traditional herbal texts could provide a remarkable resource as the starting point for drug discovery (Buenz et al., 2004). ITM as a main subset of the medieval Islamic Medicine had a strong effect on the people of Iranian plateau for a long period of time and ITM scholars had created some important inscribed information such as *the Canon on Medicine* by Avicenna (dead 1037 AD) (Naghibi et al., 2014). Moreover, traditional medicine therapies are still attractive and practical and plant based health care systems are taking their parts in different cultures nowadays (Cragg and Newman, 2013).

In the present study, the cytotoxic activity of 19 medicinal plants has been evaluated through a micro-culture tetrazolium/formazan (MTT) assay. The medicinal plants were selected among some, which were traditionally used to cure cancer and related illnesses in ITM during 10th to 18th centuries AD. Furthermore, The apoptosis induction ability of the most cytotoxic plant has been evaluated by caspase 3 activation. This study has introduced medicinal plants for further cancer studies based on ITM manuscripts.

## 2. Materials and methods

### 2.1. Materials

Dulbecco's modified Eagle medium (DMEM), Fetal Bovine Serum (FBS), (Gibco, Auckland, New Zealand), RPMI1640 medium, Penicillin-Streptomycin, MTT ([3-(4, 5-dimethylthiazol-2-yl) -2, 4-diphenyl tetrazolium bromide]) (Sigma, St. Louis, MO, USA), DMSO (dimethyl sulphoxide) (Merck, Hohenbrunn, Germany) were used in the cytotoxic activity evaluation and methanol (Merck, Hohenbrunn, Germany) was used for plants extraction. NucView™ 488 Caspase 3 Assay Kit for Live Cells (Biotium, Hayward, CA, USA) and 5-FU (Sigma, St. Louis, MO, USA) were used in apoptosis assay.

### 2.2. Data extraction from ITM Pharmacopoeia

According to the defined cancer terminology in previous studies (Table 1), the ITM Pharmacopoeia were explored for

medicinal plants that were claimed to cure or relief cancerous states. The selected ITM medicinal plants names were matched to scientific names. Some former studies for identifying the scientific names were also studied (Amin, 2005; Dini, 2005, Ghahraman and Okhovvat, 2004, 2009; Mozaffarian, 2007). The goal was to achieve all ITM mentioned medicinal plants as far as possible. The considerations toward selection of every plant will be discussed later in this text. It should be noted that in some cases we had no choice but to substitute some plants because they had failed to grow or could not be found in their habitat due to climate changes, field utilization changes or over grazing.

### 2.3. Plant material

Nineteen plant species were collected from Zanjan, Azerbaijan, Ardabil, Gilan, Mazandaran and Alborz provinces, Iran (2012) and were authenticated by botanists at the Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. All voucher specimens were deposited at the TMRC herbarium for future reference. The plants were dried in shadow and ground.

### 2.4. Extraction and preparation for the assays

Dried powdered plants (10 g) were macerated with methanol at room temperature for 24 h for thrice. The extracts were concentrated using a rotary evaporator (40 °C) and the dried extracts were kept in 2–8 °C for future assays.

The extracts were dissolved in DMSO: 10 mg mL<sup>-1</sup> to make the stock solutions of each sample. Serial dilutions were prepared accordingly from the above stock solution to reach final concentrations (DMSO 1%).

### 2.5. Cell lines

MCF-7 (human breast adenocarcinoma), HepG-2 (hepatocellular carcinoma), A-549 (non-small-cell lung carcinoma) and HT-29 (colorectal adenocarcinoma) cells were obtained from the Pasteur Institute, Tehran, Iran. MCF-7 and HT-29 cell lines were cultured in DMEM with 5% FBS for MCF-7 cells and 10% FBS for HT-29 cells while the other two cell lines were cultured in RPMI1640 medium with 10% FBS to maintain the desired growth. All cell lines were treated with 1% penicillin-streptomycin and were kept in a humidified incubator at 37 °C in an atmosphere of 5% CO<sub>2</sub>.

**Table 1**

ITM cancer keywords used to search ITM Pharmacopoeia.

ITM terms (English translation) <sup>a</sup>	ITM term definition <sup>b</sup>
Cankers	Invasive hard to cure ulcers with disgusting appearance and thick red or green borders inclined to the edge of the lesion. The lesion caused decay.
Horrid ulcers	A kind of ulcer that was formed because of waste spoiled humors of the body. These humors could cause ulcers that would not or hardly be cured and might lead to death.
Chronic ulcers	Might cause chronic ulcers which would occasionally be cured or turned into the chronic black ugly ulcers and disperse.
The Pigs, Scrofula	A kind of tumor, stucked to the neighboring tissues. It might grow and new ones might be formed from the first one, just like warts. It mostly occurred around the neck and armpit. It was called Pigs because of the resemblance of the patient's neck to a pigs' neck. It had amplitude from benign to malignant tumors.
Fistula	An old sore with thick borders. The progression into the tissue was like a pipe and had permanent discharge.
Black bile tumors	Constructed from black bile, they showed no other signs of cancer except for hardness and dark appearance.
Crab, Cancer	A tumor, constructed from black bile. It was painful and fast growing. The blood vessels around the lesion made the appearance like a crab and it had the sense of beating.
Cold tumor	A tumor constructed from black bile or phlegm. Normally, it was non-invasive and benign. It had a slow growing rate. It was non-sensitive and had cool touch.
Hard, dense or solid tumor	Made from phlegm, black bile or the combination of both and were classified from benign to malignant tumors.

<sup>a</sup> The endeavor was to find the closest alternative in English language.

<sup>b</sup> The definitions were summarized from selected historical manuscripts of ITM (Naghibi et al., 2014).

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