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ORIGINAL RESEARCH

The antioxidant and chemical properties of *Berberis vulgaris* and its cytotoxic effect on human breast carcinoma cells

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Abstract In this study we evaluated the biological activity of alcoholic and aqueous extracts from the fruit of *Berberis vulgaris*. The total antioxidant capacity of *Berberis* was characterized by FRAP, DPPH, Folin–Ciocalteu while the anthocyanins content was measured by pH differential method. Cell viability and apoptotic property were determined by MTT and DNA fragmentation assays, respectively. Alcoholic extract of *Berberis* was richer in antioxidants and anthocyanins compared to aqueous extract. Although both extracts significantly inhibited proliferation of breast cancer cells (MCF-7); these changes were not observed in normal human breast epithelial cells (MCF10-A). The alcoholic extract was more effective in inducing apoptosis as detected by DNA fragmentation in treated cancer cells. Our results suggest that *Berberis* has potent antioxidant properties and cytotoxic effects that can induce apoptosis. Therefore, *Berberis* can potentially be exploited for the development of therapeutics to fight against human breast cancer.

Keywords Breast cancer · *Berberis vulgaris* · Cytotoxicity · Antioxidant · Apoptosis

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Introduction

Breast cancer is the most common malignancy in women both in the developed and the developing countries (Wen et al. 2014). Its common treatments are surgery, radiation and chemo-hormone therapies. However, most of the patients suffering from the disease ultimately develop drug resistance and experience intense side effects. So, it is required to apply effective therapies without side effects. In this context, the use of natural components such as herbs may find a new safe way for breast cancer treatment (Wen et al. 2013; Shafi Sofi et al. 2013; Fathi Najafi et al. 2007).

Reactive Oxygen Species (ROS), i.e. free radicals are one of the major causes for the conversion of normal cell to cancerous cells (Rajkumar et al. 2011). Herbs protect human body against ROS and reduce oxidative damage to DNA in cancer initiation or promotion. Antioxidants of herbs may mediate these biological effects by directly reacting with ROS, free radical scavenging or catalytic metals chelating (Kaliora et al. 2006; Koncic et al. 2010). Furthermore, medicinal plants with antioxidant potential inhibit proliferation of different cancer cells via apoptosis induction (Samarghandian and Shabestari 2013; Bathaie et al. 2013; Hoshyar et al. 2012, 2013). Apoptosis

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or programmed cell death is an ordered cellular suicide process that occurs in both physiological and pathological conditions. Understanding apoptosis in cancer is very important not only in its pathogenesis but also leaves clues of cancer treatment (Samarghandian and Shabestari 2013; Wong 2011).

Berberis vulgaris L. from *Berberidaceae* family are grown in Europe and Asia, specially in Iran. The medicinal properties for all parts of this plant have been reported including antimicrobial, antiemetic, antioxidant and anticancer activities (Wen et al. 2013; Končić et al. 2010; Abd El-wahab et al. 2013). The aim of the present study was to examine and compare the biological in vitro activities (antioxidant, anticancer and apoptotic properties) of alcoholic and aqueous extracts of *Berberis* fruits in human breast cancer cells, MCF-7 in comparison with the normal human epithelial cells (MCF10-A).

Materials and methods

Chemicals and cell culture

Human breast cancer (MCF-7) and normal breast epithelial (MCF10-A) cell lines were provided from Iranian Biological Resource Center (IBRC, Teheran, Iran). RPMI-1640 and DMEM: Ham's F-12 media, fetal bovine serum (FBS), phosphate buffered saline (PBS), trypsin/EDTA solution, cell lysis buffer and 3-(4,5-dimetylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide (MTT) and dimethylsulfoxid (DMSO) were purchased from Gibco BRL (Grand Island, NY, USA) and Sigma (St. Louis, MO, USA), respectively.

Preparation of extracts of *Berberis vulgaris*

The *Berberis* fruits were collected in the *South Khorasan* province of *Iran*, dried at room temperature while keeping away from direct sunlight and then powdered. To prepare aqueous extract, *Berberis* fruit powder was added to boiling water and brewed for 45 min. For preparation of alcoholic extract, *Berberis* fruit powder was added to ethanol 70 %, and incubated overnight in the shaker at room temperature. Then extracts were filtered by Whatman No. 1. The alcoholic extract was obtained by using vacuum rotary evaporator. Finally both alcohol and water extracts were completely dried using freeze drying method.

Evaluation of antioxidant activity of *Berberis vulgaris*

Ferric Reducing Antioxidant Power (FRAP) assay

The total antioxidant capacity of *Berberis* extracts was determined by FRAP assay (Benzie and Strains 1996). The results were expressed in M Fe(II)/g dry weight of plant extracts (DW).

Folin–Ciocalteu assay

The total phenolic contents of herbal extracts were measured using the Folin–Ciocalteu method (Rakitzis 1975). The data were expressed as milligram Gallic acid equivalents (GAE)/g dried weight of plant extracts (DW).

DPPH radical-scavenging activity

Effect of the herb extracts on 1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radical was measured, based on previous study (Brand-Williams et al. 1995). The percentage of DPPH free radical scavenges ability of *Berberis* is reported as (%).

Determination of Total monomeric anthocyanins (TMA)

The TMA have been estimated by a pH differential method (Giusti and Wrolstad 2005) using UV–Vis spectrophotometer. Results were expressed as mg of cyanidin-3-glucoside equivalents per liter of *Berberis* extracts.

Evaluation of anticancer effects of *Berberis vulgaris* on cells

Cell culture and cell viability assay

The MCF-7 and MCF-10A cells were cultured in RPMI-1640 and DMEM: Ham's F-12 media, respectively. Cultures supplemented with 10 % FBS serum, 100 units/mL penicillin and 100 mg/mL streptomycin. Both cell lines were grown at 37 °C in humidified atmosphere containing 5 % CO_2. The cells were seeded in 96-well plates (5×10^3 cells/well) and allowed to attach overnight. Before treatment, the cells were grown to 90 % confluency and starved by incubation in a basal medium for 24 h to

synchronize cells to the resting stage. Then the synchronized cells were treated with different concentrations of *Berberis* (0–6 mg/ml) at various time intervals (0–72 h).The cytotoxic effect of *Berberis* extracts against MCF-7 and MCF-10A cells was evaluated by MTT assay. For analysis of the cytotoxic efficiency, the IC_{50} value of *Berberis* was calculated using the dose- and time-dependent curves by linear interpolation (Hoshyar et al. 2013).

DNA fragmentation assay

Biochemically, apoptosis is characterized by the activation of a nuclear endonuclease that cleaves DNA into multimers of base pairs and can be visualized as an oligosomal ladder by standard agarose gel electrophoresis. In brief, MCF-7 cells were treated with alcoholic extract of *Berberis* (1.5 and 3 mg/ml) for 48 h. DNA samples were isolated after cell lysis according to previous studies (Aghbali et al. 2013; Samarghandian and Shabestari 2013). The samples were analyzed by electrophoresis on 1.5 % agarose gel in TAE buffer containing 0.5 µg/ml ethidium bromide. Fragmented DNA of treated cells was compared with untreated cells as control, by UV illuminator.

Statistical analysis

All experiments were accomplished in triplicate and the data were expressed as mean ± standard error of the mean (SEM). Results were analyzed using one-way ANOVA followed by Tukey's post hoc test using SPSS version 16 software. Differences at $p < 0.05$ were considered to be significant.

Results

Total antioxidant activity (TAA)

The FRAP values of adequate concentrations of both aqueous and alcoholic *Berberis* extracts (2.5 g/l) indicated that the reducing power of the alcoholic extract was higher compared to aqueous extract (Table 1).

Total phenolics contents (TPC)

The results of total phenolic values of *Berberis* extracts are presented in Table 1. The amounts of total phenolic content of equal concentration of aqueous and alcoholic extracts of *Berberis* (2.5 g/l) were 184.1 ± 5.30 and 291.22 ± 2.52 GAE/g DW, respectively.

Table 1 The total antioxidant activity, total phenolics and total anthocyanins of both *Berberis* fruits extracts

Antioxidant contents	Aqueous extract	Alcoholic extract
TAA[1] (M Fe(II)/g DW)	397.68 ± 7.11	542.93 ± 6.32
TPC[2] (GAE/g DW)	184.1 ± 5.30	291.22 ± 2.52
TAC[3] (mg cy-3-glu/l)	602 ± 6.8	785 ± 9.2

Data are mean ± standard error of the mean (SEM; n = 3)

[1] Total antioxidant activity expressed in M Fe(II) per gram dry weight (DW) of plant extracts

[2] Total phenol content expressed in milligrams of Gallic acid equivalents (GAE) per gram dried weight (DW) of plant extracts

[3] Total monomeric anthocyamins expressed as mg cy-3-glu per liter of plant extracts

Total anthocyanins contents (TAC)

Total monomeric anthocyanins of *Berberis* extracts are shown in Table 1. The data illustrate that TMA of ethanolic extract was higher than that of water extract of this herb.

Radical scavenging activity

The results of DPPH assay showed (Fig. 1) that various concentrations (1.25, 2.5 and 5 mg/ml) of alcoholic extract of *Berberis* exhibited greater free radical scavenging activity (33.17, 56.97 and 88.9 %, respectively) than that of its aqueous extract with 20.55, 43.02 and 74.71 %. All results were compared with ascorbic acid as a control.

Cytotoxic activity

The cytotoxic effects of various concentrations of alcoholic and aqueous extracts of *Berberis* on MCF-7 and MCF-10A cells for 24, 48 and 72 h were determined by MTT assay. As shown in Fig. 2 the viability of treated cancer cells was significantly reduced in a time- and dose-dependent manner compared to untreated cancer cells. Also the IC_{50} values (minimum concentration of extract to reduce cell viability to 50 %) of alcoholic and aqueous

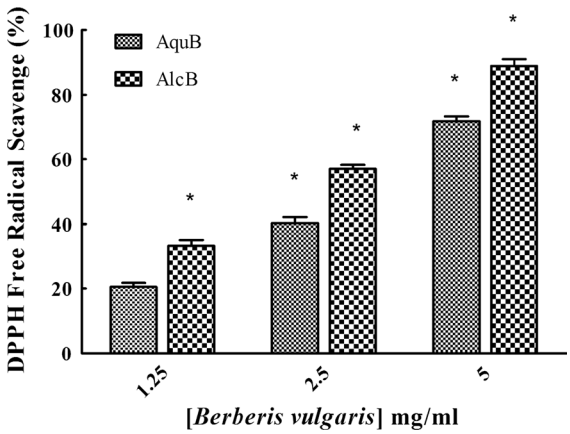

Fig. 1 Percentage of DPPH radical quenching activity of various concentrations of alcoholic and aqueous extracts of *Berberis* compared to lowest concentration of water extract (1.25 mg/ml, as a reference). Data are expressed as mean ± SEM (n = 3) and the histograms marked with *asterisk* are significantly different at $P < 0.05$

extracts of *Berberis* after incubation for 24, 48, and 72 h are reported in Table 2. The inhibitory effect of the alcoholic extract on cell proliferation was significantly superior to that of aqueous extract. Parallel treatment of the normal cells with this herb demonstrated a much less inhibitory effect on the viability of MCF-10A cells (Fig. 3).

DNA fragmentation is a qualitative hallmark of apoptosis. To show *Berberis*-induced apoptosis in MCF-7 cells, DNA of untreated cells and cells treated with effective doses of the alcoholic extract (1.5 and 3 mg/ml) for 48 h was analyzed by agarose gel 1.5 % electrophoresis. DNA of treated cells was fragmented whereas control cells did not show typical DNA fragmentation (Fig. 4).

Discussion

The mortality due to breast cancer is increasing in many countries (Taghavi et al. 2012). Cancer cells reproduce uncontrollably; loose sensitivity to anti-growth signals, get resistant to apoptosis and are enabled to replicative immortality (Hanahan and Weinberg 2011).

There are many evidences that commercially available anticancer drugs are derived from medicinal plants (Kitagishi et al. 2012; Zong et al. 2012). The antitumor effects of herbs are associated with

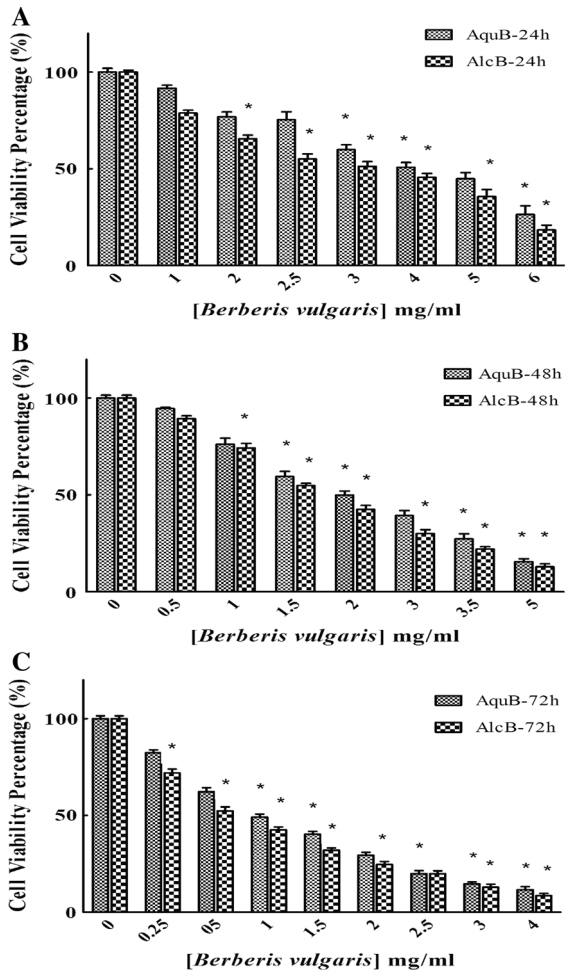

Fig. 2 Cytotoxicity of various concentrations of aqueous (Aqu) and alcoholic (Alc) extracts of *Berberis* (0–6 mg/ml) against MCF-7 cells after incubation for 24, 48 and 72 h (**a**–**c**). All tests were performed in triplicate and results are reported as the mean ± SEM. *$P < 0.05$, compared with untreated cells

Table 2 IC_{50} (mg/ml) values for both extracts of *Berberis* against MCF-7 cells after incubations for 24, 48 and 72 h

Time (h)	24 h	48 h	72 h
Alcoholic extract	4 ± 0.05	2 ± 0.03	1 ± 0.07
Aqueous extract	3 ± 0.08	1.5 ± 0.04	0.5 ± 0.02

Results are mean ± SEM of three replications

Induction of apoptotic DNA fragmentation by *Berberis* extracts

modulation of cell-cycle and induction of apoptosis (Pandey and Rizvi 2009; Kuno et al. 2012). It has been also illustrated that herb extracts possess antioxidant properties which neutralize production of free

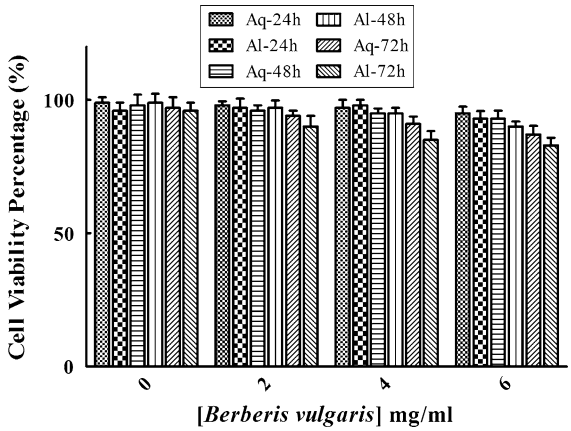

Fig. 3 Effect of *Berberis* on the viability of human epithelial MCF-10A cells. Cells were treated with different concentrations of aqueous (Aq) and alcoholic (Al) extracts of this herb (0–6 mg/ml) for 24, 48, and 72 h. Results are reported as the mean ± SEM

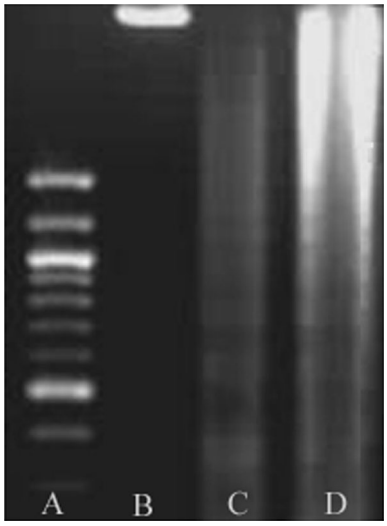

Fig. 4 DNA fragmentation after 48 h treatment with alcoholic extracts of *Berberis* (*C*: 1.5 mg/ml and *D*: 3 mg/ml) compared to untreated cells (*B*) and marker (*A*) values

radicals, prevent damage of DNA in cancer cells and reduced side effects of the most common types of cancer treatment (Charoensin 2014). *Berberis vulgaris* is one of these medicinal plants that have various biological properties including anti-proliferative, anti-migratory and antioxidant activities (Mahata et al. 2011; Wen et al. 2013). Previous studies mentioned that the phytochemical constituents of *Berberis* such as antioxidants and anthocyanins increased its bioactivity and was affected by different extraction procedures or the type of solvents used (Abd El-wahab et al. 2013; Annegowda et al. 2011).

In this study the antioxidant properties of alcoholic and aqueous extracts of *Berberis* were compared. A complete picture of total antioxidants capacity of both aqueous and ethanolic extracts of *Berberis* fruits determined was obtained via analysis by FRAP, DPPH and Ciocalteu assays. The results showed that the ethanol extract has a higher content in total antioxidants, total phenolices (Table 1) and free radical scavenging property (Fig. 1) than the aqueous extract. The high antioxidant capacity of *Berberis* fruit is primarily due to the high levels of phenolic and anthocyanin content found in this fruit (Ozgen et al. 2012). The best solvents for isolation of phenolic compounds from herbal extracts are organic solvents such as ethanol (Mohammedi and Atik 2011; Abd El-Wahab et al. 2013). Our FRAP, DPPH and Ciocalteu data confirmed these reports as indicated in Table 1 and Fig. 1.

One of the richest sources of anthocyanins is the purple-black of barberries which has strong antioxidant capacity (Ozgen et al. 2012). To investigate the difference of antioxidant activity between ethanolic and aqueous extracts, the anthocyanins amount was determined by spectrophotometry. It was found that the ethanolic extract was richer in anthocyanins compared to the aqueous extract. Previously, another study found that the ethanol extract of *V. vinifera* was richer in anthocyanins than the aqueous extract (Mansour et al. 2013).

The main biological property of cancer cells is uncontrolled and often rapid proliferation so arresting of tumor growth is considered as valid treatment option in different types of cancer therapies. The anti-proliferative effect of *Berberis* recognized in various cancers including breast, liver and colon cancers but its molecular mechanisms of action are not yet established (Kim et al. 2010; Mahata et al. 2011; Wang et al. 2009). In agreement with the last finding, our data showed that both aqueous and alcoholic extracts of *Berberis* significantly decreased cancer cell proliferation in a time- and dose-dependent manner (Fig. 3). The IC_{50} values strongly indicated that the effective doses of alcoholic extracts of *Berberis* were lower compared to aqueous extracts after different incubation times (0–72 h; Table 2). Therefore alcoholic extract of *Berberis* has inhibited growth of MCF-7 cells more effectively than aqueous extract. The cytotoxic effect

of ethanolic extract may be related to its higher content of phenolic and anthocyanin components. MTT results indicated that various concentrations of *Berberis* had no cytotoxic effect on normal (MCF-10A) cells after incubations of 24, 48 and 72 h (Fig. 3).

Induction of apoptosis is one the most important marker of antitumor agents. Apoptosis is characterized by morphological changes for instance, cell shrinkage, membrane blebbing, chromatine condensation, DNA fragmentation and loosing organelles position in cytoplasm (Aghbali et al. 2013; Galluzzi et al. 2007). It has been shown that some plants such as saffron, curcumin and Ginger suppressed carcinogenic progress through induction of apoptosis (Bakhshi et al. 2008, 2010, Hoshyar et al. 2013; Bathaie et al. 2013). In our study, *Berberis* extracts have caused main morphological changes in the treated cancer cells (data are not shown). Moreover, we examined the apoptotic activity of alcoholic extraction of *Berberis* by DNA agarose gel electrophoresis. The isolated DNA from apoptotic cells showed a typical pattern of DNA fragments (Fig. 4).

In conclusion, our data illustrated that various cytotoxic effect of ethanol and water extracts of *Berberis* related to different amounts of total antioxidant, phenolics and anthocyanin in herb. The ethanol extract exerted a higher level of phenolics and anyhocyanin, seems to be more effective against proliferation of cancer cells. Besides, ethanolic extract of *Berberis* induced apoptosis in MCF-7 cells that could be explained by its powerful antioxidant and free radical scavenging capacities. Thus, *Berberis* as a selective anticancer agent against MCF-7 cells is a potent phytodrug to be explored further for its cytotoxic property.

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Conflict of interest The authors have no conflict of interest to declare.

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