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Anticancer Activity and Phenolic Compounds of *Pistacia atlantica* Extract

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ABSTRACT

Recently a lot of studies have been conducted to identify natural compounds for prevention of the development and recurrence of cancers. The present study aimed to determine phytochemical content and anti proliferative activity of *Pistacia atlantica* extract. Ethanolic extract of *Pistacia atlantica* was prepared. The antioxidant activity, total phenol, flavonoid and flavonol content of the extract were evaluated. Cytotoxicity activity of extract on AGS and HeLa cell lines was evaluated by MTT assay 48 hours after treatment. The antioxidant activity of extract was 4.6±0.66 µg/ml while it was 25.41±1.89 µg/ml for butylated hydroxytoluene (BHT). The total phenol, flavonoid and flavonol contents were 269 mg GAE/g, 40.7 mg RUT/g and 88.12 mg RUT/g, respectively. The extract inhibited the proliferation of AGS, HeLa and HDFs cells with IC50 values of 382.3 µg/m, 332.3 µg/ml and 896.3, respectively. This study revealed that the extract of *Pistacia atlantica* can suppress the proliferation of gastric carcinoma and cervical cancer cells. The plant with high phytoconstituents could be a promising source of anticancer drugs.

Key Words: *Pistacia atlantica,* Cancer, Antioxidant, Proliferation.

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INTRODUCTION

Cancer, as one of the main reasons for mortality of the global population, causes more than 20% of the mortality in the world [1]. Base on the published report of the World Health Organization via the International Agency for Research on Cancer of in 2014, the incidence of cancers in the world has been approximately 14 million new cases. It has been projected to register 19.3 million in 2025 [2]. Gastric cancer, as a kind of gastrointestinal tract cancers, is the leading cause of cancer-related mortality in the world [3, 4]. The incidence of the gastric cancer has increased during the past decade. Furthermore, cervical cancer is one of the most common malignancies [5] that the causes a lot of deaths in women worldwide [6]. Despite advances in early diagnosis and treatment modalities due to the side effects of anticancer drugs, problems related to radiotherapy and chemotherapy, and development of drug resistance, recurrence of cancers remained unsolved. [7]. There are a variety of therapeutic approaches for treatment of the cancer; However, these approaches have many undesirable side effects [8]**.** Therefore it is necessary to discover novel and more effective drugs. In this regards, natural compound such as medicinal plants can be a rich resource.

Pistacia atlantica Desf. (*P. atlantica*) belonging to the Anacardiaceae family. It also is known as the Atlas Pistacio tree. *P. atlantica* is a key species of the Mediterranean and Western Asian areas [9, 10]. Data regarding the phytochemical composition of *P. atlantica* is very sparse [11]. A series of plant metabolites including triacylglycerols, tocopherols, sterols, and pigments has been found in this plants. Also caffeic acid, p-coumaric acid, cinnamic acid,

ferulic acid, , o-coumaric acid and vanillin, , has been identified in other species of this genus [12]. This study was conducted to evaluate poly phenolic content of *P. atlantica* extract and determine its antioxidant and anti proliferative activity.

MATERIALS AND METHODS

Preparation of hydroalcoholic extract

Pistacia atlantica was gathered from southwest region of Iran. Then, the genus and species of the plant were identified and confirmed in Herbarium of Medical Plants Research Center of Shahrekord University of Medical Sciences (Iran). The leaves were powdered (100 g) and dissolved in 70% ethyl alcohol for 96h at room temperature (RT). Subsequently, the mixture was filtered and concentrated under nearly vacuum pressure at 40˚C using rotary evaporator. The extracts were suspended at 37°C in dimethyl sulphoxide (DMSO) to give a stock solution of 25 mg/mL, dissolved in culture medium, and stored at 4°C until use. The remaining DMSO in the wells (maximal 0.2%) did not affect the experimental results [13].

Determination of the free-radical scavenging activity

The free-radical scavenging activity was measured by the 2,2 diphenyl-1-picrylhydrazyl (DPPH) method described by Moon and Terao, with some modifications [14]. Different amounts of the extract and methanol were added to a solution of 0.3 mg/mL methanolic solution of DPPH to make up a total volume of 3.0 ml. After 15 min at room temperature, the absorbance was measured at 517 nm using UV–Vis spectrophotometer (UNICO 2100: USA). Butylated hydroxytoluene (BHT) was used as positive control. Inhibition of free radical by DPPH was calculated as follows:

Antiradical activity (%) = (A control – A sample)/A control×100.

The IC_{50} value defined as the amount of antioxidant necessary to decrease the initial DPPH concentration by 50%. It was calculated based on linear regression of plots of the percentage antiradical activity against the concentration of the tested compounds [15]. The experiment was carried out in triplicate.

Determination of total phenolic content

The total phenolic content of the *P. atlantica* extract was determined using Folin-Ciocalteu method [16]. Briefly, 0.1 ml of the diluted sample (1 gr/ml) was added to 0.5 ml of 10% (v/v) Folin–Ciocalteu reagent and kept at RT for 3-8 min. Subsequently, 0.4 ml of 7.5% (w/v) sodium carbonate solution was added to the mixture. After 30 min, the absorbance of the reaction mixture was measured at 765 nm using a UV–Vis spectrophotometer (UNICO 2100: USA). Amounts of total phenolic were calculated using a standard calibration curve of gallic acid. The results were expressed as gallic acid equivalents (GAE) g/g of dry plant matter.

Determination of total flavonoid content

The total flavonoid content of the extract was measured based on previously reported method with minor modifications [17]. Briefly, 0.5 ml of diluted plant material (1 gr/ml) was mixed with 0.1 ml of 10% (w/v) aluminum chloride, 0.1 ml of 1 M potassium acetate, and 2.8 ml of distilled water. Following incubation at (RT for 40 min, the absorbance of the reaction mixture was read at 415 nm using a UV–Vis spectrophotometer (UNICO 2100: USA). The results were expressed as mg of rutin equivalents of dry plant matter in comparison with the standard curve, which was made in the same condition.

Determination of total flavonol content

The total flavonol content was measured through a previously reported method with minor modifications [18]. Briefly, 0.5 ml of each diluted plant material was independently mixed with 1.5ml of methanol, 0.1 ml of 10% (w/v) aluminum chloride, 0.1 ml of 1M potassium acetate, and 2.8 ml of distilled water. After incubation at RT for 150 min, the absorbance of the reaction mixture was read at 440 nm using a UV–Vis spectrophotometer (UNICO 2100: USA). The results were expressed as mg of rutin equivalents of dry plant matter compared with the standard curve which was made in the same condition.

Cells and cell culture

AGS (human gastric carcinoma) and HeLa (cervix adenocarcinoma) cell lines were purchased from Pasteure Institute of Iran and Human dermal fibroblasts (HDFs) cell line was kindly provided by the Cellular and Molecular Research Center of Shahrekord University of Medical Science, Iran. The cell lines were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Invitrogen-Gibco, Carlsbad, California) supplemented with 10% of fetal bovine serum (FBS; Gibco), 100 µg/mL of streptomycin (Sigma-Aldrich Chemicals, St. Louis, MO, USA), 100 UI/mL of penicillin (Sigma) and 0.25 µg/mL amphotericin B (Gibco), at 37 °C in a humidified air atmosphere containing 5% (V/V) CO2.

MTT assay

The cells (6000 cells per well) were seeded on to 96-well plates (SPL Life Sciences, Korea) in a final volume of 100 µL per well. After incubation at 37 °C with 5% CO2 for 24 h, overlay medium was aspirated to allow the cells attach to the bottom of each well. Subsequently, the cells were incubated with 100 µL/well of various concentrations of the crude ethyl alcohol extract for 48 hours.

The number of living cells was determined by the ability to cleave the tetrazolium salt MTT [3-(4, 5-dimethylthiazol-2ol) 2, 5 diphenyl tetrazolium bromide] by the mitochondrial enzyme succinate dehydrogenase which develops a formazan blue color product. The procedure was as described previously [19]. Briefly, the supernatant was removed from the wells and 50 µL of MTT solution (1 mg·mL−1 in PBS) was added to each well. The plates were incubated for 4 h at 37 °C, and 100 µL of DMSO was added to each well to dissolve the MTT crystals. The plates were placed on a shaker (IKA Company, Staufen, Germany) for 15 min and the absorbance at 492 nm of each well

was read on an enzyme-linked immune sorbent assay (ELISA) reader (Stat Fax 2100, Awareness Technology, USA). Each experiment was carried out in triplicate and the percentage survival of the treated cancer and normal cultured cells was calculated according to the formula as follows: Percentage of survival (%) = (Absorbance of treated cells/ Absorbance of control) × 100

Statistical analysis

The 50% inhibitory concentration (IC50) was calculated by regression analysis and related models using the Probit regression model in the SPSS software (version 16.0).. All tests were done in triplicate. The data are expressed as Mean ± SD.

Table 1. DPPH radical-scavenging activity of the *Pistacia atlantica* extract

Samples	Concentration (µg/ml)	Scavenging of DPPH radical activity inhibition (%) (main ± SEM)	DPPH-radical scavenging activity IC_{50} / (µg/ml)
Pistacia atlantica extract	12.5	89.8±1.8	4.6±0.66
	6.25	57.5±2.2	
	3.125	29±2.6	
	1.56	15±2.3	
	0.78	3.9±1.9	
BHT	50	90.8±1.5	25.41±1.89
	40	78.3±1.2	
	30	55.5±0.7	
	20	40.09±1.7	
	10	22±1.06	

All data are presented as Mean ± SD of three assays; DPPH: 1,1-Diphenyl-2-picrylhydrazyl; BHT: Butylated hydroxytoluene.

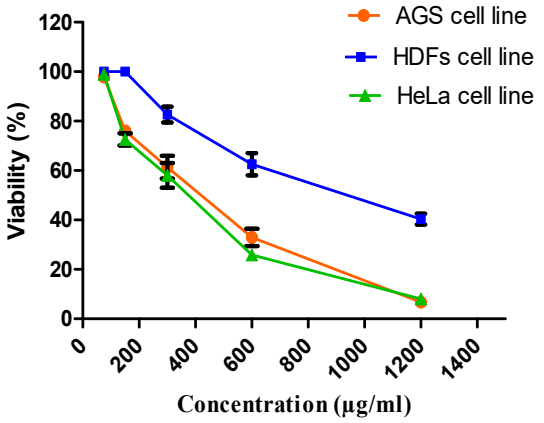

Figure 1: Antiproliferative activity of crude ethyl alcohol extract of *Pistacia atlantica* on AGS, HeLa (cancerous) and HDFs (normal) cell lines.
AGS, HeLa (cancerous) and HDFs (normal) cell lines were treated with different concentrations of the extract for 48 h and cell viability was determined using MTT assay. The probit regression model data curves showed that antiproliferative activity of the crude ethyl alcohol extract between normal and cancerous cell lines was significantly different (P<0.05); AGS: Human gastric carcinoma; HeLa: cervix adenocarcinoma; HDFs: Human dermal fibroblast.

RESULTS AND DISCUSSION

Poly phenolic compounds and antioxidant capacity

Total phenolic, flavonoid and flavonol amounts of *Pistacia atlantica* extract were 269 mgGAE/g, 40.7 mgRUT /g and 88.12 mgRUT /g respectively. The crude extract had IC50 value of 4.6±0.66 µg/ml. The IC_{50} of BHT was 25.41±1.89 µg/ml (Table1).

Anti-proliferative activity

The results showed that cell viability was significantly reduced in a dose-dependent manner following treatment with the extract (Figure 1). Based on Probit regression model, antiproliferative activity of the extract on three cell lines studied was significantly different (P<0.001). The IC50 value of the extract for AGS was 382.3 µg/mL/(CI95%: 339.1-430.9),and for HeLa was 332.3 µg/mL (CI95%: 293.8-375.9) The IC50 for the cell lines were lower than of HDFs cell line (896.3 µg/mL ; CI95%: 794.2-1011).

Medicinal plants have a long history of usage, especially in the treatment of various diseases [20]. Recent studies have also scientifically confirmed their effects in prevention [20, 21] and treatment[22, 23] of a wide variety of diseases such as cancer [24-26], cardiovascular [27, 28], diabetes [29, 30], hypertension [31, 32], and other diseases[33-41]. The plants and their active compounds exerted anticancer effects via removing free radicals and antioxidant effects, cell cycle arrest, induction of apoptosis, and inhibition of angiogenesis.

One of these plants is the mastic. The Genus of mastic is Pistacia and its family is Anacardiaceae. This genus has eleven species; some of them find in Asia and the Mediterranean area; They have many medical, social and economic importance[42]. In Iran, this plant is called Baneh. Our results indicated that *P. atlantica* is rich of the phenolic and flavonoid compounds and it has antioxidant activity higher than synthesis antioxidants. Various phytochemical compounds have been identified in Pistacia species. Phenolic compounds, catechin, epicatechin, and gallic acid with antioxidant activity have been detected in galls of *P. atlantica* [43]. Flavonoid compounds with antioxidant activity are also present in different parts of these species, including aerial parts of *P. atlantica* [44]. A flavone with anti-plasmodial activity (3-Methoxycarpachromene) has been isolated from aerial parts of *P. atlantica* [45]. Fatty acids such as palmitic, myristic, linolenic, palmitoleic, stearic, , arachidonic, and eicosanoic have been identified in this plant [46, 47].

Moreover, various parts from *P. atlantica* fruits and leaves have shown antioxidant activities [48, 49].

The fruit extract of *P. atlantica* sub. kurdica has revealed inhibitory activity on human colon carcinoma cells the same as Doxorubicin [50]. Interest in *P. atlantica* and its extracts has steadily increased in recent years, due to reported positive clinical effects. These include significant cyto/genotoxic effects on cancerous, as well as noncancerous cell lines, which are evoked by apoptosis and necrosis mechanisms [51], antioxidant [52], hypoglycemic [53], and pro-apoptotic effects in colon carcinoma HT29 cells [50]. Our results showed that cell viability of human cancer cell lines (AGS and HeLa) was significantly reduced following treatment with crude ethyl alcohol extract of *P. atlantica* with a dose-dependent manner. We think,

the phenolic compounds of the plant via cell cycle arrest and activation of apoptotic signal transduction pathways can cause its anticancer effects [54]. Also the previous studies have shown that medicinal plants can prevent of different diseases due to their effects on oxidative damages and inflammation [55-64].

CONCLUSION

Based on our findings, crude ethyl alcohol extract of *P. atlantica* suppress the proliferation of gastric carcinoma and cervix adenocarcinoma cells. Probably due to the phenolic and flavonoid compounds in this extract and its relatively high antioxidant activity, it is recommended to perform more study on this extract as the effective ingredient in the treatment of aforesaid cancers. Further researches are needed to fully understand the mechanism of action, in order to use in modern therapies as chemotherapy adjuvant in the treatment of cancers.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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