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اثر ضد تکثیر و القای آپوپتوتیک سزکوی ترپن لاکتون پارتنولید بر روی رده سلول سرطانی پستان انسان لاین MDA-MB- 231

Anti-proliferative effect and apoptotic induction of sesquiterpene lactone parthenolide in a human breast cancer cell line MDA-MB- 231

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چکیده

پارتنولید یک متابولیت ثانویه است که به طور طبیعی در گیاه بابونه کبیر (*Tanacetum parthenium*) وجود و اثر درمانی دارد. عملکرد پارتنولید در مهار رشد سلولهای سرطانی، به تنهایی یا در ترکیب با سایر داروهای ضد سرطان، در چندین آزمایشگاه مورد بررسی قرارگرفته است. در این مطالعه، اثر پارتنولید استخراج شده از بابونه کبیر بر بیان هفت ژن (*BID, P21, PUMA, BAX2, P53, CASP8, BIM*) پرو آپوپتوتیک، مسیر سیگنالینگ NF-κB، در یک رده سلول سرطانی پستان بررسی شد. نتایج نشان داد که در پاسخ به درمان با پارتنولید، همه ژنهای مورد مطالعه به طور قابل توجهی و با درجات مختلف القا شده و تنظیم شدند. نتایج این بررسی اثبات کرد که پارتنولید بیان انواع ژن های دخیل در مسیر آپوپتوتیک را در رده سلولی MDA-MB-231 تغییر میدهد. ژنهای انتخاب شده به طور مستقیم یا غیرمستقیم توسط NF-κB تنظیم شدند و تأیید شد که هدف پارتنوپید مسیر NF-κB می‌باشد.

واژه‌های کلیدی

آپوپتوزیس،
رده سلولی MDA-MB- 231،
پارتنولید،
RT-PCR

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Abstract

Parthenolide is a secondary metabolite, which naturally occurs in the feverfew plant (*Tanacetum parthenium*) and is responsible for its healing power. The potential of parthenolide in inhibition of cancer cell growth, alone or in combination with other anti-cancer therapeutics, has been studied in several laboratories. In this study, the effect of extracted parthenolide on the expression of seven pro-apoptotic genes (*BID*, *P21*, *PUMA*, *BAX2*, *P53*, *CASP8* and *BIM)*, all of them were influenced by NF-κB signaling pathway, in MDA-MB- 231, a breast cancer cell line was investigated. The results indicated that in response to the parthenolide treatment, all of the selected genes were induced and up-regulated significantly with different degrees. We proved that parthenolide alters the expression of a variety of genes involved in apoptosis pathway in MDA-MB- 231 cell line. In conclusion, we provided evidence that parthenolide alters the expression of a variety of genes involved in apoptosis pathway in MDA-MB- 231 breast cancer cells. The selected genes are directly or indirectly were regulated by NF-κB and it is confirmed that NF-κB is an important target of parthenolide.

Keyword: Apoptosis, MDA-MB- 231 cell line, Parthenolide, Real time PCR

Introduction

Compared with synthetic analogues, plant derived natural products have relatively less side effects and renewed interest have been raised for use of natural products in pharmaceutical medications. Feverfew (*Tanacetum parthenium*), also known as wild chamomile, is an herb with anti-inflammatory properties and historically was used to prevent migraine and headaches, and mostly used as a fever reducer (from which the name is derived)(Ahmadi et al. 2018). Sesquiterpene lactone parthenolide, secondary metabolite, is the active ingredient, which is responsible for much of the healing power of feverfew and has high value in chemotaxonomy and medicine (Shahhoseini et al. 2019). Parthenolide a gemacranolide-type sesquiterpene lactone is the major constituent of European feverfew (Pooja et al. 2021). Parthenolide is also known for its exceptional anti-inflammatory and anti-cancer properties, which make it a promising candidate for further studies in drug development. Parthenolide has shown cytotoxic effects on cervical cancer (Jin et al. 2009) glioblastoma (Anderson et al. 2008) breast cancer (Nakshatri et al. 2004; Sweeney et al. 2005) leukemia (Guzman et al. 2005; Hewamana et al. 2008; Neelakantan et al. 2009) pancreatic cancer (Ramachandran et al. 2010) prostate cancer (Shanmugam et al. 2006; Sweeney et al. 2004) lung cancer, (Jin et al. 2009; Sun et al. 2020) melanomas (Kim et al. 2007; Suvannasankha et al. 2008) and colon cancer (Zhang et al. 2004) however, it does not affect normal cells.

Anti-tumor activity of parthenolide has been shown to be strongly linked to the reactive oxygen species (ROS) generation and inhibition of transcription factor nuclear factor-kappa B (NF-κB) (Zhang et al. 2020). In combination with several common chemotherapy agents, parthenolide augments the cancer cells' response to the therapeutic agents, induces potent apoptosis and restores the cell sensitivity to the cells that developed resistance to chemotherapy.

It has been reported that the inhibition of NF-κB leads to change in the expression of apoptosis regulator target genes (Barkett and Gilmore 1999; Karam et al. 2021; Kolenko et al. 1999). In the present study, we evaluate the effect of Parthenolide on the expression of a group of pro-apoptotic target genes in MDA-MB-231 breast cancer cell line using real time PCR.

MATERIALS AND METHODS

Parthenolide purification

Tanacetum parthenium L.schulz Bip. Plant was collected from Hamadan province (34.7982º N,

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48.5146º E) in Iran and was identified and registered by deposit number 006420 in herbarium of Tehran University. The amount of 5 g flower was isolated and ground to a fine powder in liquid nitrogen. Parthenolide Extraction was performed with 15 ml methanol: formic acid (1000:1 v/v) method of Majdi accordingly (Majdi et al. 2011). Purification of parthenolide was carried out using a preparative HPLC system equipped with a photodiode array detector and mobile phase water (A) and acetonitrile: methanol (9: 1) (B) (Avula et al. 2006)Jafari et al. 2018).

Cell culture

MDA-MB-231 cell line was donated by Dr. Mosa Gardaneh (NIGEB, Iran). MDA-MB-231 cells were maintained in DMEM medium with 100 U.mL-1 of penicillin, 100 $\mu g.mL^{-1}$ of streptomycin, and 10% fetal bovine serum (FBS), at 37 ˚C containing 5% humidified CO_2. Culture medium was replaced with a fresh one every two days.

Anti-proliferative assay

The effect of different concentrations of parthenolide (0.5, 1, 1.5, 2, 2.5, 5, 10 and 20 µM) on the MDA-MB-231 breast cancer cell line viability was carried out by Methylthiazol Tetrazolium (MTT) for 24 hours (Jafari et al. 2018).

Annexin-V-FLUOS assay

The annexin-V-FLUOS assay was performed to measure the percentage of apoptotic and necrotic cells under the Parthenolide treatment using Annexin-V-FLUOS staining kit (Rosche, 11988549001). MDA-MB-231 cells were treated with the minimum lethal dose (2µM) that kills approximately 50% of cells (IC_{50}), obtained by MTT test, for 24 h. The cells were stained by FITC-conjugated Annexin-V-FLUOS and PI labeling solution according to the manufacturer's recommended concentrations and time and analyzed by fluorescent microscopy. The positive cells for annexin-V and PI were considered to be apoptotic and necrotic, respectively.

Real-time PCR

Total cell RNA was extracted using RNX-plus kit (Cinna Gen, RN7713C), after cDNA synthesis using reverted first strand cDNA synthesis kit (Thermofisher scientific, 00168871) and by using random primer, Real time PCR amplification reactions were performed using SYBR Fast qPCR kit (Roche, 03515869001) with appropriate primers (table1).

Table1. Primers used for real time PCR

Product size	Annealing temperature	Primer sequence	Gene name	Accession numbers
256	59	F- GTCAGTGGTGGACCTGACCT R- CACCACCCTGTTGCTGTAGC	*GAPDH*	XR002004287.1 XM0199661648.1
362	60	F-GACAAGAATCCGACCAAATGGCAAA	*BIM*	LM463826.1
		R-AAAAGGATCCATGAGAAATCCTTGTGG		XM019021358.1
133	60	F-GAGGTTGGCTCTGACTGTACC	*P53*	XM019944223.1
		R-TCCGTCCCAGTAGATTACCAC		XM004058511.1
180	60	F-ATTAGGGACAGGAATGGAACAC	*CASP8*	XM002004922.1
		R-GGAGAGGATACAGCAGATGAAG		XM019838464
175	60	F-TGCCTCAGGATGCGTCCACCAA R-CCCCAGTTGAAGTTGCCGTCAG	*BAX*	XM0040611100 XM019978503.1
100	60	F-CCTTGCTCCGTGATGTCTTTC R-TCCGTTCAGTCCATCCCATTT	*BID*	XM003988294.4 XM016939651.1
101	60	F-GACGACCTCAACGCACAGTA R-AGGAGTCCCATGATGAGATTG	*PUMA*	AF354655.1 XM019934993.1
90	60	F-GGAGACTTCTCAGGGTCGAAAAC R-GGGCTTCCTCTTGGAGAAGATC	*P21*	XM19780435.1 XM015237492.1

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A two step program was used as follows: 3 min at 95˚C; 40 cycles of 10s at 95˚C, 30s at 60˚C which was followed by a melting curve analysis step in the Rotor-Gen 3000 Real-time DNA analysis system (Corbett, RO80902).
The relative expression ratio (RER) was measured based on the expression ratio of the target gens (Table 1) versus a reference gene (Glyceraldehyde-3-Phosphate Dehydrogenase (*GAPDH*). The relative gene expression ratio was calculated by following mathematical model.

ΔC_t treatment = C_t (Target Gene, treatment) – C_t (*GAPDH*, treatment)

ΔC_t control = C_t (Target Gene, control) – C_t (*GAPDH*, control)

RER = $2^{-\Delta\Delta C_t}$ (Livak and Schmittgen 2001).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) software was used to Statistical analysis. T-test was performed for finding significant differences in gene expression values. Differences with *P* values < 0.01 were considered as significant. Orthogonal comparisons were used to evaluate the significant difference between the means of treatments compared to the control.

RESULTS AND DISCUSSION

Studies have shown that in Feverfew (*Tanacetum parthenium)*, parthenolide accumulates in flower (Majdi et al. 2011). Accordingly, we extracted parthenolide from flower head and then purified with HPLC-Preparative (Figure 1-A).

Programmed cell death or apoptosis is one of the major animal cell death types which is characterized by many changes in morphological and molecular level, including cell shrinkage, nuclear condensation, plasma membrane blebbing, and differentially expression of many genes related in the apoptosis related pathways (Zhang et al. 2009).

Herein, the MTT assay results, confirmed that the purified parthenolide behaves as an apoptotic inducer for MDA-MB-231 cells (IC_{50} value= 1.5 µM) (Figure 1-B). This result verified by the Annexin-V-FLUOS staining (Figure 2).

Describing the molecular mechanisms of this apoptotic induction may be applicable to improve the chemotherapeutic strategies for breast cancer.

Several studies have recognized that induction of apoptosis by parthenolide is associated with inhibition of NF-κB (Pozarowski et al. 2003; Saadane et al. 2007; Yip-Schneider et al. 2005) and increased reactive oxygen species (D'Anneo et al. 2013). For instance, Liu and et al showed that parthenolide can decrease the protein expression level of anti-apoptotic *BcL2* and increase protein expression of pro-apoptotic *BAX* in pancreatic cancer cells (Liu et al. 2010). Both *BcL2* and *BAX* are regulated by NF-κB.

For more clarification of the molecular mechanism of parthenolide-induced apoptosis, in this study seven pro-apoptotic genes were selected. Expression of these genes in the MDA-MB-231 cells to be studied when was treated by parthenolide and compared with control cells. All of the selected genes, including *BID*, *P21*, *PUMA*, *BAX2*, *P53*, *CASP8* and *BIM*, are affected by NF-κB activation. The results of real time PCR indicated the up-regulation of all genes in response to parthenolide treatment (Figure 3).

However, the increased amount is very different. Differences between the genes expression in before and after treatment were calculated according to Livak mathematical model. Changes were mostly observed in *BID* gene expression with almost 25-fold increase in the expression compared with control cells. *BID*, an acronym for BH3-interacting domain death agonist, is a pro-apoptotic *BCL-2* protein family. After cleavage with *CASP8*, activated *BID* translocates from cytosol to mitochondria and induces apoptosis by promoting *BAX* activation and mitochondrial outer membrane permeabilization, which results in the release of cytochrome c and other pro-apoptotic factors. It is shown that blockage of NF-κB signaling prevents the cleavage of *BID* (Danthi et al. 2010).

Studies have proven that targeting NF-κB through parthenolide could indirectly influence the pro-apoptotic activity of *P53* (Kim et al. 2009). Parthenolide can regulate *P53* activity by increasing MDM_2 ubiquitination (Gopal et al. 2009). *P21*, is a cell cycle inhibitor with a major role in growth arrest, and is tightly regulated by *P53*. The up-regulation of *P21* in *P53*-independent manner has also been described in response to certain stresses including DNA damage (Hosseini et al. 2017; Macleod et al. 1995).

Here, a five-fold increase was observed in *P21* expression while *P53* expression level compared with control cells, has changed slightly (~ 1.2-fold increase). Hence, it seems that Parthenolide, in this study, most likely up regulates the *P21* independently of *P53*.

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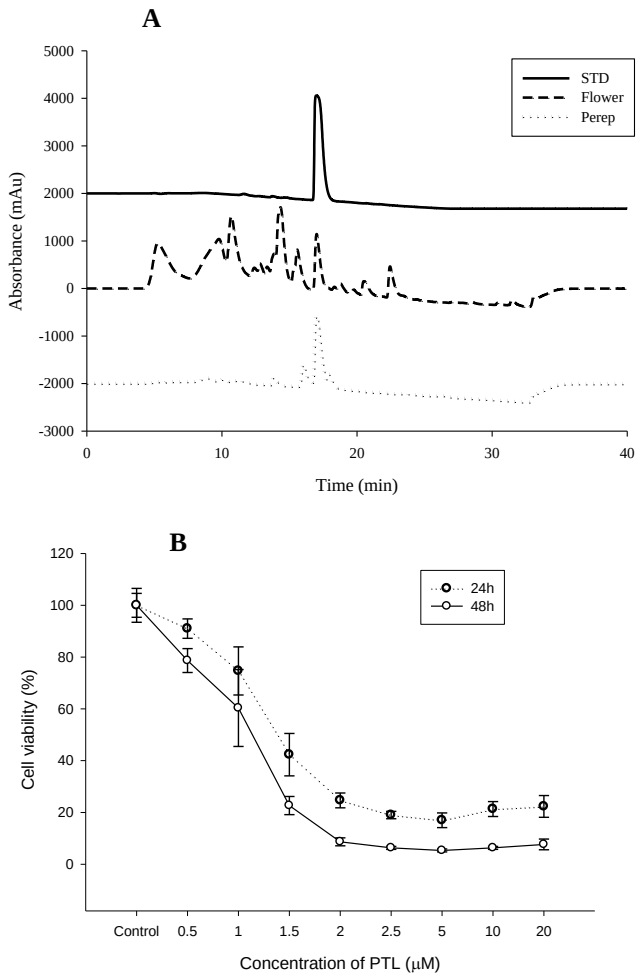


Fig 1. (A) HPLC chromatogram of parthenolide standard (STD), flower extract of feverfew (Flower) and purified parthenolide from feverfew by preparative HPLC. (B) MTT assay results. Viability of MDA-MB-231 cells treated with Parthenolide decreased in a dose dependent manner and the IC_{50} value for MDA-MB-231 was calculated 1.5 µM. Data are shown as means ± SD (n=3).

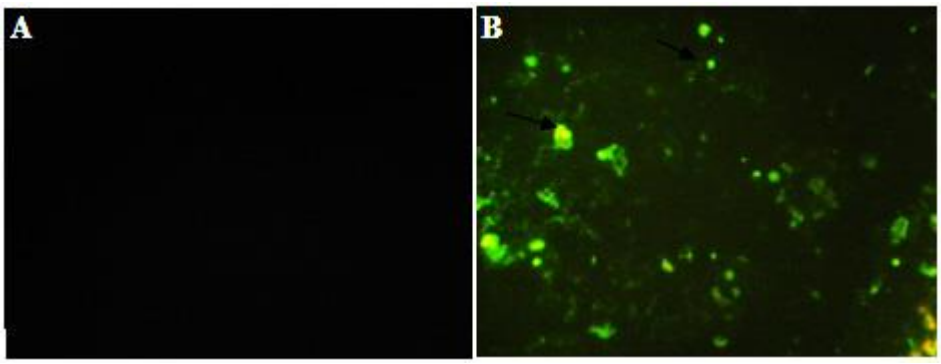
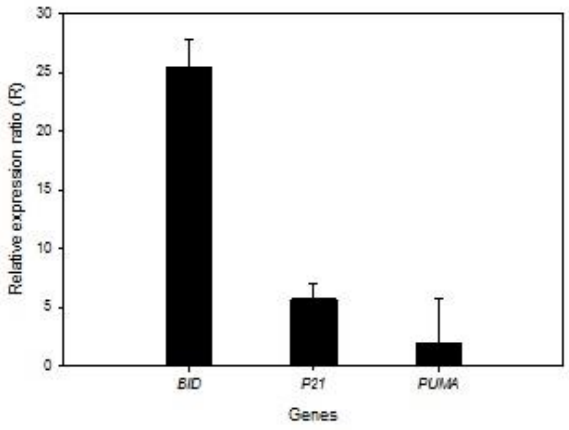


Fig 2. Annexin-V-FLUOS staining of MDA-MB-231 cells. (A)Untreated cells, and (B) treated cells with 2µM parthenolide for 24h. Early apoptotic cells were stained with green fluorescent Annexin V. No necrotic cells were detected.

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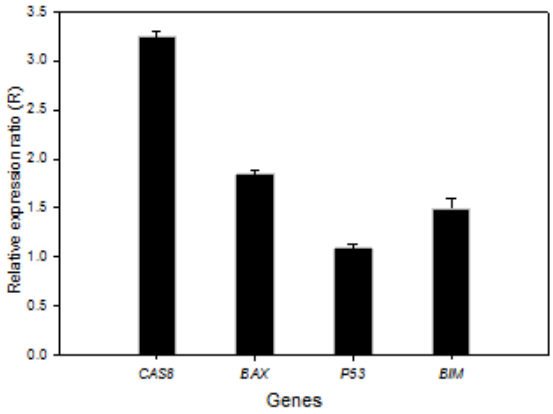


Fig 3. Real time expression analysis of *BID*, *P21*, *PUMA*, *CASP8*, *BAX*, *P53*, and *BIM* genes. The relative expression ratio (R) was measured based on the expression ratio of the target gens versus a reference gene (Glyceraldehyde-3- Phosphate Dehydrogenase (*GAPDH*) in control and treatment cells. The results showed that the expression of all selected genes in MDA-MB-231 cell treated with Parthenolide induced and up-regulated. Data are shown as means ± SD (n=3).

In conclusion, we provided evidence that parthenolide alters the expression of a variety of genes in treatment cells compared with control cells, involved in apoptosis pathway in MDA-MB- 231 breast cancer cells. The selected genes are directly or indirectly regulated by NF-κB and it is confirmed that NF-κB is an important target of parthenolide.

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Conflict of Interest Statement

The authors declare that no conflict of interest regarding the publication of this paper

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