CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3582978

Available online at: http://www.iajps.com *Research Article*

ANALYSIS OF PTEROSTILBENE IN INDUCTION OF APOPTOSIS THROUGH DOWN REGULATION OF CASPASE ACTIVATION IN OVARIAN CANCER PATIENTS

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Abstract:

The basic aim of the study is to elucidate the mechanism of action of pterostilbene against ovarian cancer cells. This cross sectional study was conducted at Midcity Hospital, Lahore during January 2019 to July 2019. The 5cc blood was drawn for the analysis of ROS. Reactive oxygen species was determined using fluorescent probe DCF-DA. Pterostilbene-induced ROS generation was measured by DCF-DA. The results showed that pterostilbene-induced ROS generation at 120%, 134% and 157% in 12, 24 and 48 h,-respectively. The present study demonstrates for the first time that pterostilbene- induces apoptosis in ovarian cancer cell line, through ROS generation, mitochondrial depolarization, activation of caspase 9 and 3.

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Please cite this article in press Shair Ali Khan et al., ***Analysis Of Pterostilbene In Induction Of Apoptosis Through Down Regulation Of Caspase Activation In Ovarian Cancer Patients.,*** *Indo Am. J. P. Sci, 2019; 06(12).*

INTRODUCTION:

Pterostilbene is a natural dietary compound present in the blue berries[1]. It is a methylated analog of resveratrol with increased bioavailability and lipophilicity compared to that of resveratrol. So, recent research has been into much focus on this compound[2]. Pterostilbene is an excellent antioxidant compound, which has been reported for various pharmacological properties like antifungal, anti-inflammatory, anti-diabetic and anti- cancer properties[3]. The anti - cancer role of pterostilbene has been reported in different cancers such as breast, gastric, prostate, hepatic etc., by both *in vitro* and *in vivo* studies[4]. The mechanism through which pterostilbene exerts anti- cancer potential has been reported to include both apoptosis and autophagy. Although it has been studied for its anti-cancer property in different cancers, its role in ovarian cancer has not been explored[5].

Pterostilbene (trans-3,5-dimethoxy-40-hydroxystilbene) is a naturally occurring phytoalexin identified in the genus Pterocarpus, leaves of Vitis vinifera, and some berries and grapes[6]. It has multiple pharmacologic activities, including antioxidant and cancer prevention activity and the capability to inhibit DNA synthesis[7]. Pterostilbene is also cytotoxic to various types of cancer cells, including breast cancer, melanoma, colon cancer, liver cancer, and gastric cancer. Although anti-proliferative and pro-0064apoptotic activities of pterostilbene have been demonstrated in vitro, the ability of pterostilbene to induce apoptosis in drug-resistant lymphoma cell lines[8].

Objectives of the study

Thus the present study was designed with an aim to elucidate the mechanism of action of pterostilbene against ovarian cancer cells.

MATERIALS AND METHODS:

This cross sectional study was conducted at Midcity Hospital, Lahore during January 2019 to July 2019. The 5cc blood was drawn for the analysis of ROS. Reactive oxygen species was determined using fluorescent probe DCF-DA.

Total antioxidant capacity **(**TAC) in the cells treated with pterostilbene was determined by the specific method. After an appropriate treatment period, the cells were sonicated and the cell lysate was used for the assay. The principle involves measurement of hydroxyl radical formation between the antioxidants in the sample against free radicals.

Statistical analysis

The data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. All biochemical experiments were performed thrice in triplicates to ensure reproducibility.

RESULTS:

Pterostilbene-induced ROS generation was measured by DCF-DA. The results showed that pterostilbene-induced ROS generation at 120%, 134% and 157% in 12 , 24 and 48 h,–respectively. Further results from Ca^{2+} levels also showed that pterostilbene caused significant levels of calcium release with maximum levels upto 180% ($p<0.001$) when compared to control cells (Figure 1).

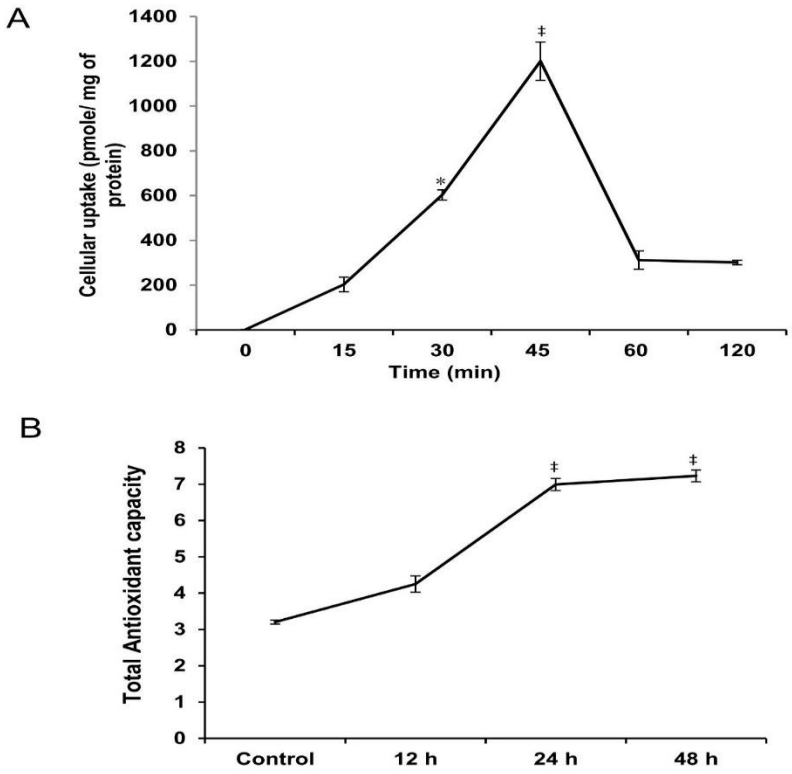

Figure 01: Pterostilbene enhances antioxidant status A)Cellular uptake of Pterostilbene in SKOV-3 cells. Time-dependent study (15 mins, 30 mins, 45 mins, 1 hr and 2 hr) on pterostilbene uptake showed maximum levels at 45 mins when compared to control cells. **B) Pterostilbene- enhanced TAC.** Cells treated with pterostilbene at different time points showed time dependent increase in antioxidant levels when compared to control cells (results shown as mean ± SEM).
*p<0.05, †p<0.01, ‡p<0.001; NS – non significant when compared to control

DISCUSSION:

Ovarian cancer is one of the common and lethal gynecologic tumors worldwide. Chemo resistance plays major roadblocks for the treatment of ovarian cancer[9]. Reports suggest that compounds which sensitize these cells to cell death could act as a therapeutic strategy. The present study showed the cytotoxic effect of pterostilbene against ovarian cancer at a level of 55 uM[10]. Further, increase in LDH release during pterostilbene treatment reveals that it causes membrane damage and subsequent cell death[11].

It has been well known that reactive oxygen species mediates cell death mechanisms. The present study evidenced that pterostilbene caused a significant increase in ROS generation in a time dependent manner. However, these increases in ROS, did not affect the antioxidant status; as we observed a consistent increase in antioxidant status. Thus, this level of antioxidant activity could be explained as cellular stress mechanisms evoked to combat the cell death. It is observed in many cases, where the antioxidant enzymes are upregulated during cellular stress responses[12].

CONCLUSION:

The present study demonstrates for the first time that pterostilbene- induces apoptosis in ovarian cancer cell line, through ROS generation, mitochondrial depolarization, activation of caspase 9 and 3. Dietary phenols and antioxidants play a major role in cancer prevention. However, compounds with increased biovailability have gained much importance.

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