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Evaluating the Anti-Migratory Effect of Fucoxanthin in Human Cisplatin-Resistant Ovarian Cancer Cells

Fatemeh Valinezhad Sani[1], Shiva Ghofrani [2], Safa Kamalian [2], Melika Ehtesham Gharaee [2] Fatemeh Mosaffa [3*]

1. *Department of Laboratory Sciences, School of Paramedical and Rehabilitation Sciences, Mashhad University of Medical Sciences, Mashhad, Iran*
2. *Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*
3. *Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*

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Corresponding Information:
Fatemeh Mosaffa, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
E-Mail: Mosaffaf@mums.ac.ir

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ABSTRACT

Background & Objective: Ovarian cancer ranks among the most prevalent gynecologic cancers in women with the majority of patients experiencing a recurrent type and developing treatment resistance. Resistance to chemotherapy drugs has been observed to trigger epithelial-mesenchymal transition (EMT), which leads to the acquisition of metastatic properties. Thus, targeting the molecular mechanism of EMT may lead to novel interventions against metastatic disease. In this research, the suppressive impacts of fucoxanthin, as a natural compound, were examined on cell migration and expression of key EMT-related markers in ovarian cancer cells which were sensitive and resistant to cisplatin.

Materials & Methods: To determine the non-toxic concentrations of fucoxanthin for migration assay, the MTT assay was conducted. To assess the anti-migratory capacity of fucoxanthin in ovarian cancer cells which were sensitive and resistant to cisplatin, a wound-healing migration test was done in the presence of non-toxic concentrations of fucoxanthin. RT-qPCR was utilized to examine the impact of fucoxanthin on the mRNA expression of E-cadherin, vimentin and α- SMA (as EMT-related markers) in ovarian cancer cells.

Results: Fucoxanthin at concentrations of (1 and 2.5 µM) downregulated the expression of α–SMA in cisplatin-resistant ovarian cancer cells and inhibited migration in ovarian cancer cell lines.

Conclusion: Fucoxanthin exhibited remarkable efficacy in inhibiting migration in in ovarian cancer cells which were sensitive and resistant to cisplatin. However, more research is required to ascertain the clinical advantages linked to utilizing fucoxanthin in the treatment of cisplatin-resistant ovarian cancers.

Keywords: Fucoxanthin, Ovarian cancer, EMT marker, Cell migration

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1. Introduction

Epithelial ovarian cancer (EOC) is a lethal gynecologic cancer with the highest case-fatality rate in women (1). Platinum-based therapy initially shows effectiveness in treating EOC. However, when the disease recurs, it often becomes resistant to treatment, leading to high mortality rates. Furthermore, resistance to chemotherapy drugs has been observed to trigger epithelial-mesenchymal transition (EMT), which leads to the acquisition of metastatic properties. EMT is a multifaceted developmental program which facilitates the transformation of cancer cells by suppressing their epithelial characteristics and adopting mesenchymal traits. This transition empowers cells with increased mobility and the ability to migrate away from their original location (2). Lately, there has been a focus on studying the potential connection between drug resistance and the invasion as well as spread of cancer. It has been shown that certain tumor cells that have developed resistance to drugs exhibit a higher degree of invasiveness and metastatic potential compared to their non-resistant parental cells. Furthermore, in certain instances, secondary tumors that are more prone to metastasis demonstrate greater resistance to chemotherapeutic drugs when compared to primary tumors (3). EMT is closely controlled through signaling pathways between tumor cells and their

surrounding extracellular matrix as well as the tumor microenvironment. A significant event in EMT is the occurrence of various cellular changes, particularly the disruption of cell-cell adhesion which is based on the decline of E-cadherin (4). Moreover, the increased expression of vimentin in epithelial cells not only enhances cell motility, but also leads to alterations in cell shape, disruption of cell-cell interactions, and a higher rate of turnover in focal adhesions (5). Another key component of EMT is α-SMA, the subtype of α-actin, which is recognized as a crucial component in cell mobility, as well as in maintaining cellular structure and integrity (6). Hence, targeting EMT and molecules that are responsible for cell adhesion, polarity, and interaction with the basal membrane may be an efficient strategy for treating metastatic tumors (7-11). Fucoxanthin, an orange-colored pigment, is the predominant carotenoid in brown macroalgae and diatoms (12). Extensive research has revealed that fucoxanthin possesses a multitude of biological activities and health-promoting properties, including reduction of body weight (13), plus anti-diabetic, antioxidant, and anti-inflammatory effects (14, 15). Furthermore, fucoxanthin has exhibited a broad spectrum of anticancer and anti-proliferative activities in various studies (16). It has been shown that fucoxanthin inhibited NF-κB activation in the human cervical cancer cell line (17). NF-κB is a transcription factor whose activation has been linked to various cancer-related processes such as inflammation, transformation, proliferation, and angiogenesis (18, 19). Huber et al showed preventing the NF-kappaB signaling pathway resulted in the inhibition of EMT in Ras-transformed epithelial cells. Conversely, activating this pathway facilitated the transition to a mesenchymal phenotype, independent of TGF-beta presence (20). According to the aforementioned observations, the purpose of this research was to investigate the impact of fucoxanthin on cell migration and expression of epithelial marker (E-cadherin) and mesenchymal markers (vimentin and α- SMA) in cisplatin-resistant ovarian cancer cells.

2. Materials and Methods

2.1 Cancer cell lines and reagents

The human ovarian cancer cells which were sensitive and resistant to cisplatin (A2780 and A2780RCIS respectively) were supplied by Institute of Pathology in Berlin, Germany. These cells were grown in RPMI-1640 medium with the addition of 10% FBS (Gibco, UK), 1% penicillin (100 units/mL), and streptomycin (100 mg/mL) in a humidified environment with 5% CO2 at 37 °C. Fucoxanthin, with purity ≥ 95%, was obtained from Sigma (USA). Fucoxanthin was dissolved in pure ethanol to obtain a 20 mM stock solution. Further, 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) was supplied by Lifebiolab (Germany).

2.2 Analysis of cell viability

To determine the non-toxic concentrations of fucoxanthin for subsequent experiments, the MTT assay was conducted to assess the effect of fucoxanthin on the proliferation of ovarian cancer cells. The cells were cultured in 96-well plates (5×10^3 cells per well) and incubated for 24 hours. Subsequently, the cells were treated with various concentrations of fucoxanthin (0-80 µM) for 72 hours. Following the treatment period, the cells were incubated with 10 µL MTT (5 mg/mL) for 4 hours. After removing the medium, DMSO (100 µL/well) was added. The spectrophotometric absorbance was assessed at a test wavelength of 570 nm and a reference wavelength of 630 nm. Cell viability percentage was determined by calculating the ratio of OD test to OD control, and the results expressed as the mean ± standard deviation (SD).

2.3 Real-time polymerase chain reaction

To determine the impact of fucoxanthin on the mRNA expression level of EMT-related markers, quantitative Real-Time PCR (qRT-PCR) was conducted in Real-Time PCR instrument as previously reported (21). The β-actin gene served as an endogenous control. Table 1 reports the sequences of primers utilized in this study (21).

Table 1. The Sequences of primers used for RT-qPCR assay

Gene	Forward primer	Reverse primer
E − cadherin	5′- CGG GAA TGC AGT TGA GGA TC -3′	5′- AGG ATG GTG TAA GCG ATG GC-3′
Vimentin	5′- GAG AAC TTT GCC GTT GAA GC-3′	5′- GCT TCC TGT AGG TGG CAA TC-3′
α –SMA	5′-CCG ACC GAA TGC AGA AGG A-3′	5′- ACA GAG TAT TTG CGC TCC GAA-3′
β-actin	5′-TCA TGA AGT GTG ACG TGG ACA TC-3′	5′-CAG GAG GAGCAA TGA TCT TGA TCT-3 ′

2.4 Wound healing migration test

To conduct the wound healing migration test, 2.5 × 10^5 cells were cultured in each well of a 96-well plate, and a single scratch was created after 90% of the wells were filled. Next, the cells were exposed to 1 and 2.5 µM of fucoxanthin and incubated for 72 h. The cells that migrated to the wounded area were captured at 0, 24, 48, and 72 h. Thereafter, the rate of cell migration was quantified by measuring the cell-free area in captured images using Image J software and the following formula (21):

$\frac{(At0-Atn)treated}{(At0-Atn)control} \times 100\%$, At_0 = the initial wound area at zero time, and Atn = the wound area after n hours of the initial scratch.

2.5 Statistical analysis

The mean ± SD from three independent experiments was used to present all results. Statistical analyses were conducted using Prism version 6, employing one-way ANOVA with Dunnett's multiple comparisons test or t-test. Statistically significant differences were determined by P values < 0.05.

3. Results

3.1 The effect of fucoxanthin on the viability of ovarian cancer cell lines

The sensitivity to cisplatin between two cell lines and the effects of fucoxanthin on cell proliferation were measured by MTT assay based on the previous study (22). According to Figure 1, fucoxanthin revealed a similar inhibitory pattern in both cisplatin-resistant and sensitive ovarian cancer cells. The proliferation of ovarian cancer cell lines gradually diminished with an increase in the concentration of fucoxanthin. However, the concentrations of 1 and 2.5 µM had no significant impact on the viability of A2780 and A2780RCIS cells. Thus, these specific concentrations of fucoxanthin were taken in the subsequent experiments.

3.2 The effect of fucoxanthin on EMT gene expression

The mRNA expression level of EMT- related markers was evaluated in ovarian cancer cells. In the previous study, we observed the expression level of E-CAD was downregulated while the expression level of α–SMA was upregulated in A2780RCIS cells compared to A2780 cells (21). When A2780RCIS cells were treated with non-toxic concentrations of fucoxanthin (1 and 2.5 µM), the expression of α–SMA was significantly downregulated in these cells (Figure 2).

3.3 The effect of fucoxanthin on cell migration

The impact of fucoxanthin on the migratory capacity of ovarian cancer cells is depicted in Figure 3 and 4. Fucoxanthin exhibited an inhibitory effect on cell migration in cisplatin-sensitive ovarian cancer cells and its resistant variant compared to the control.

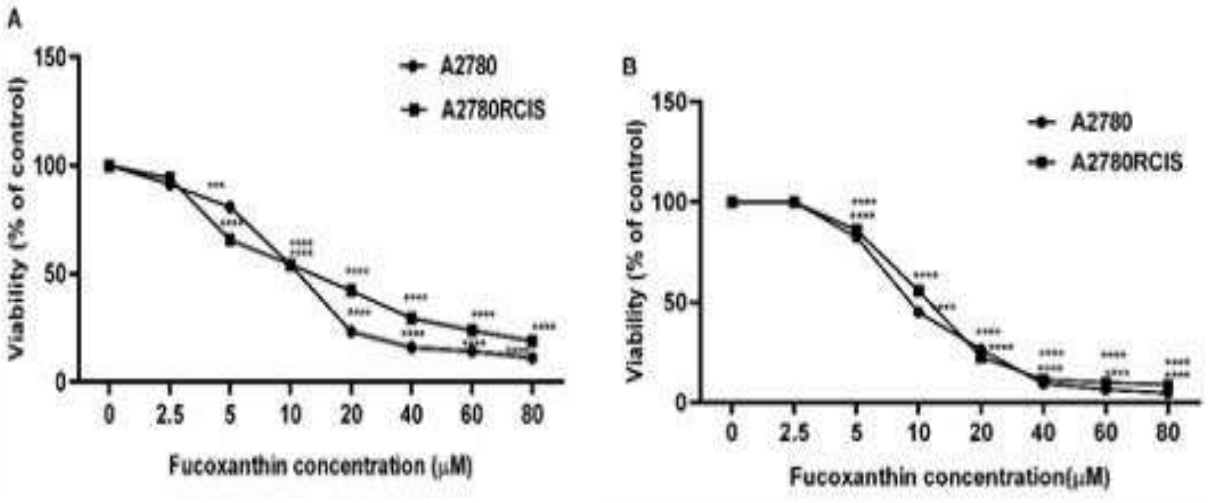


Figure 1. The effects of fucoxanthin on the viability of ovarian cancer cell lines. After exposing the cells to several concentrations of fucoxanthin for 48 (A) and 72 h (B), the cell survival percentage was detected using MTT assay, and the results were shown as mean ± SD. ***P < 0.001, ****P < 0.0001 compared to untreated control cells.

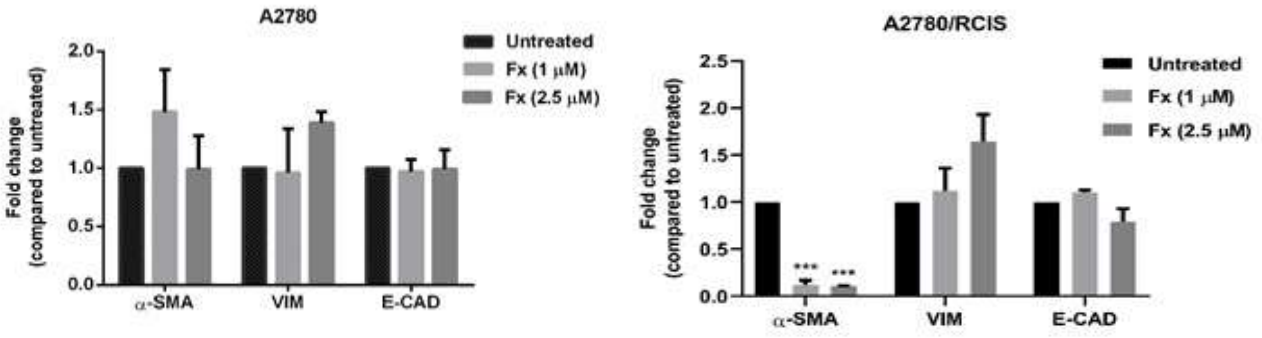


Figure 2. The effects of fucoxanthin on the expression levels of EMT genes in ovarian cancer cells. After treating the cells with fucoxanthin (1 and 2.5 μM) for 72 h,the mRNA expression of ECAD, VIM and α–SMA was analyzed by means of qRT-PCR and - the data is presented as mean ± SD. ***P < 0.001 compared to control cells.

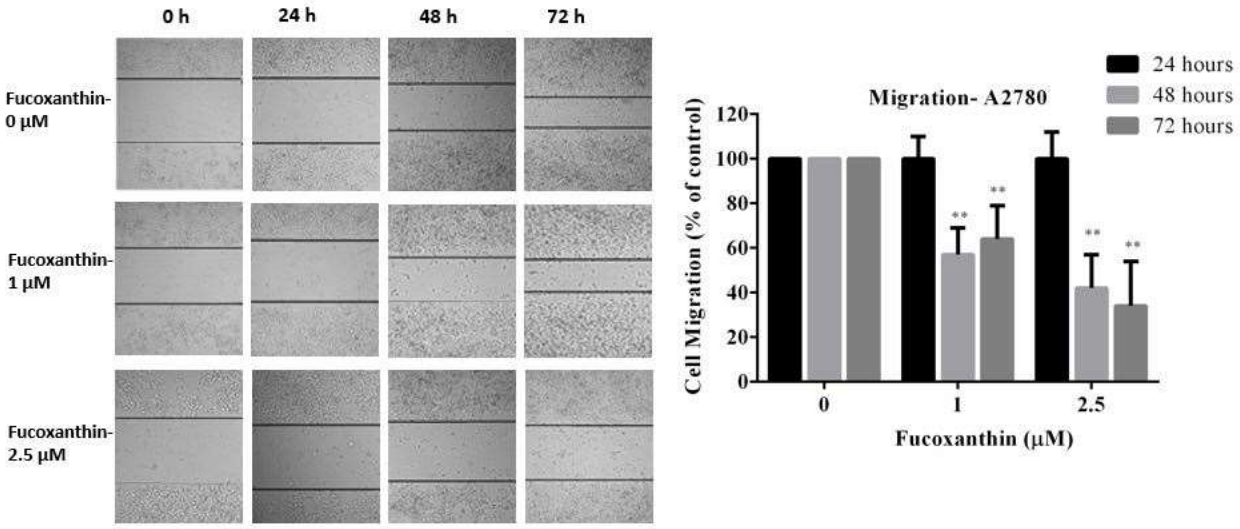


Figure 3. The scratch wound healing test was conducted to investigate the anti-migratory capacity of fucoxanthin in A2780 cells. After treating the cells with 1 and 2.5 μM concentrations of fucoxanthin, the images of the identical scratch area were captured at 0, 24, 48, and 72 hours, using a phase-contrast microscope, and the data is presented as mean ± SD. **P < 0. 01 compared to untreated control cells.

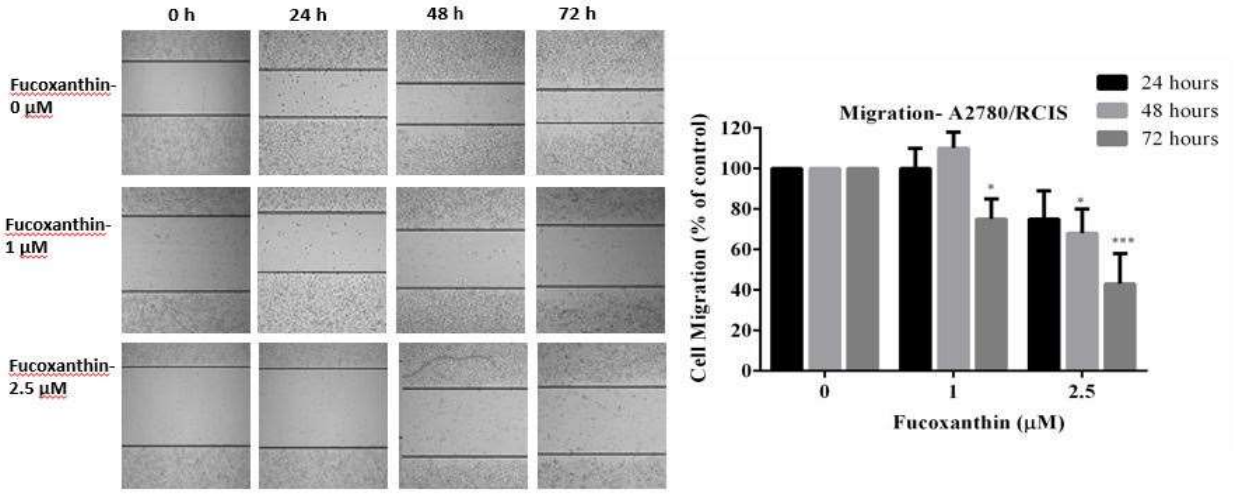


Figure 4. The scratch wound healing test was conducted to investigate the anti-migratory capability of fucoxanthin in A2780RCIS cells. After treating the cells with 1 and 2.5 µM concentrations of fucoxanthin, the images of the identical scratch area were captured at 0, 24, 48, and 72 hours, using a phase-contrast microscope, and the results were shown as mean ± SD. *P < 0.05, ***P < 0. 001 compared to control cells.

Discussion

Among all gynecological cancers, epithelial ovarian cancer ranks as the second leading cause of mortality in women (23). The diagnosis of ovarian cancer often occurs when tumors have already extensively spread within the peritoneal cavity, which reduces the effectiveness of debulking surgery and chemotherapy. Metastasis is crucial in advancing ovarian tumor growth and reducing patient survival (24). Therefore, implementation of various therapeutic strategies that target the detrimental communication between ovarian cancer cells and the metastatic tumor microenvironment holds promise for the advancement of more potent treatment modalities. These approaches can ultimately lead to improved clinical outcomes for patients with ovarian cancer (25).

Fucoxanthin, an orange pigment, is a prominent marine carotenoid in brown seaweeds. In some Southeast Asian countries and a few European nations, certain seaweeds containing fucoxanthin are commonly consumed as food (26). Fucoxanthin possesses an exceptional allenic bond in its molecular structure which is believed to be responsible for its anti-obesity, anti-diabetic, anti-cancer, anti-inflammatory, and various protective effects. These appealing properties have attracted significant attention from the food and health industry, leading to a surge in the global demand for fucoxanthin (27, 28). Several different mechanisms have been identified as potential contributors to the anti-cancer effects of fucoxanthin, such as the inhibition of angiogenesis, tubulogenesis, lymphangiogenesis, as well as the promotion of apoptotic proteins expression, cell-cycle arrest and nuclear fragmentations in some cancers (29). The down-regulation of Mcl-1, STAT3, and p-STAT3, along with the modulation of the JAK/STAT signaling pathway, results in the successful induction of apoptosis and cell-cycle arrest in gastric adenocarcinoma cells by fucoxanthin (30). Several studies have indicated that the cytotoxic effect of fucoxanthin was specific to cancer cells, sparing or minimally impacting normal physiological cells. Thus, fucoxanthin and its metabolites hold significant potential as therapeutic agents for treating cancer (31). In addition, other studies have shown that fucoxanthin and its metabolite exhibited a suppressive impact on NF-κB activation. Huber and her colleagues revealed that the NF-κB signaling pathway has an important role in EMT and metastasis, and the inhibition of NF-κB activation reduced the metastatic potential of Ras-transformed EpH4 cells (32). Furthermore, it is possible that treatment with some chemotherapy agents increased cancer invasion and metastasis, which require further investigation. In this research, we employed ovarian cancer cells that are sensitive and resistant to cisplatin to validate the potential impact of fucoxanthin on migration and expression of the main EMT-related markers. Our preceding findings indicated that fucoxanthin exhibited the same dose-dependent reduction in viability among A2780 and A2780RCIS cells (22). However, concentrations between 1 and 2.5 µM did not exert a significant impact on the proliferation of these cells.

The analysis of EMT-related markers expression in a previous study revealed the down-regulation of E-cadherin expression and the up-regulation of α-SMA in A2780RCIS cells compared to parental A2780 cell lines. The data presented indicated that the invasive nature of the drug-resistant variant A2780RCIS surpasses that of the drug-sensitive ovarian cancer cell line A2780. E-cadherin is a molecule responsible

for cell-cell adhesion. E-cadherin expression has consistently shown to be lost at sites where EMT occurs, both in the context of development and cancer. Furthermore, there is often an inverse correlation between the level of E-cadherin expression and the grade as well as stage of the tumor (33). Lu et al. suggested that the increased invasive capability of MCF-7/Adr resistant breast cancer cell line compared to its parental cell line may be linked to the reduction in E-cadherin expression (34). Furthermore, studies have demonstrated that the administration of chemotherapy medication not only elevated the levels of certain ABC transporters responsible for multidrug resistance (MDR) but also enhanced the expression of markers associated with EMT, specifically in invasive breast cancer cells (35). Therefore, an effective approach to treating metastatic tumors could involve directing efforts toward EMT inhibition and the modulation of molecules involved in cell adhesion, polarity, and interaction with the basal membrane.

The analysis of EMT- related markers expression indicated that there was a notable decline in the expression of α-SMA after exposure to non-toxic concentrations of fucoxanthin in cisplatin-resistant A2780RCIS. However, fucoxanthin did not have any notable impact on the expression of these genes in the parental cell line. Other research indicated that the expression of α-SMA in cancer-associated fibroblasts (CAFs) was correlated with higher occurrence of lymph node metastases and unfavorable prognosis among cancer patients. Additionally, CAFs that test positive for α-SMA have been found to have an impact on tumor growth in vivo and are associated with an elevated presence of cancer stem cells. (6) Another research revealed that the expression levels of B7-H3 and α-SMA can act as indicators of an unfavorable prognosis for patients with gastric adenocarcinoma (36). The complexity of upstream and downstream signaling pathways of EMT induction illustrates that EMT is not simply characterized by changes in cell adhesion or cytoskeletal organization. Rather, it signifies a profound restructuring of various aspects of a cell's biology. (4) The result of the wound healing migration test indicated the inhibitory impact of fucoxanthin on cell migration in both A2780 cisplatin-sensitive cells and cisplatin-resistant A2780RCIS cells compared to the control. Scientists reported that fucoxanthin inhibited the invasion and migration of human glioblastoma cells by limiting the p38-MMP-2/9 pathway (37). Another study has demonstrated that fucoxanthin exhibited a preventive effect against breast cancer metastasis by intervening in the adhesion and transendothelial migration of circulating tumor cells (38). Ming and colleagues showed that fucoxanthin suppresses metastasis and improves the responsiveness of lung cancer to Gefitinib (39). This study and the other aforementioned preclinical evidence indicate that fucoxanthin may possess the capacity to combat cancer migration, making it a potential candidate for a novel therapeutic agent against ovarian cancer. Additional in-depth research is needed to elucidate the inhibiting effect of fucoxanthin on the dynamic cytoskeleton reorganization related to cancer progression and tumor microenvironment.

Conclusion

Despite the remarkable effectiveness of non-toxic concentrations of fucoxanthin in reducing migration in ovarian cancer cells, encompassing both cisplatin-sensitive and resistant variants, further comprehensive research, including animal studies, is necessary to ascertain any clinical advantages linked to application of fucoxanthin in the treatment of cisplatin-resistant ovarian cancers.

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Authors' Contribution

Fatemeh Valinezhad Sani: Investigation, Conceptualization, Writing Original Draft. Shiva Ghofrani: Investigation, Formal analysis. Safa Kamalian: Investigation, Formal analysis, Melika

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