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Cardiac Glycoside Oleandrin Suppresses EMT Ability in Endometrial Carcinoma Cells

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ABSTRACT

Endometrial carcinoma is one of the most common types of cancer among women. The progression of cancer occurs via the Epithelial- Mesenchymal Transition (EMT) pathway. Cells lose their epithelial properties and become mobile. For this reason, the EMT process is one of the most important step to be targeted in cancer treatment. Oleandrin is a cardiac glycoside and its use is limited due to its narrow therapeutic index. In this study, we aimed to evaluate effects of lower level Oleandrin doses on EMT process in endometrial carcinoma. Oleandrin was administrated to Ishikawa endometrial adenocarcinoma cells at different doses and times. IC_{50} dose was determined by XTT proliferation test. Expression analysis of EMT-related genes was then performed by qRT-PCR. Invasion and colony formation abilities of cells were examined microscopically. Finally, the migration analysis of cancer cells was determined by the Wound Healing Assay. The IC_{50} dose of Oleandrin applied to Ishikawa cells was determined as 75.3 nM at the 48 h. According to qRT-PCR analysis, expression levels of ZEB1, FN1, ITGB1, VIM, SMAD2, SNAI1, SNAI2, SNAI3, and TGFB3 genes significantly decreased, but TIMP2, TIMP3, ITGAV and GSK3B genes significantly increased. In addition, Oleandrin significantly reduced colony formation and invasion of Ishikawa cells. According to the Wound Healing analysis, the migratory abilities of the Oleandrin-treated cells were reduced compared to the control. Low dose Oleandrin suppresses the EMT pathway in Ishikawa cells. It has been shown that Oleandrin significantly suppresses the cell's colony formation, invasion and migration ability both in gene expression analyzes and microscopically.

Keywords: Oleandrin, endometrial carcinoma, invasion, migration

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Introduction

Endometrial carcinoma (EC) is the fourth most common cancer type in women in developed countries after breast, lung and colorectal cancers (1,2). Additionally, the incidence of EC is increasing day by day (3). EC are tumors that contain the uterine body of the uterus, which is the female reproductive organ, and originate from the endometrium (4). In carcinomas developing from epithelial cells, metastasis begins with epithelial-mesenchymal transition (EMT), which means that cells with epithelial features first begin to exhibit mesenchymal features. Acquiring a mesenchymal identity is achieved by the cells undergoing some changes. These changes include loss of cell-cell connectivity, resistance to apoptosis, increased migration and invasion ability (5). EMT occurs naturally in processes such as embryonic development, postnatal development, wound healing and it is terminated reversibly. EMT is accompanied by changes in the expression of transcription factors such as SNAIL, TWIST or ZEBs. These changes cause downregulation of E-cadherin, ZO1, cloudins and occludins and upregulation of extracellular matrix (ECM) components such as N-cadherin, collagens, fibronectin and matrix metalloproteases (MMPs) (6,7). The separation of cells from the primary tumor is a process mediated by cadherin and integrins (8,9). Then, the surrounding tissue is invaded and MMPs are released, the ECM is reshaped and access to the vascular and lymphatic system is provided. A very small part of the circulating tumor cells survive and adhere to the endothelium at distant sites (10). As a result, cells extravasate and invade the surrounding tissue and cause distant metastasis (11).

Cardiac glycosides are secondary compounds found in plants. Oleandrin is a type of cardiac glycoside obtained from *N. oleander* (12). Other well-known cardiac glycosides are digoxin and digitoxin. These compounds have common chemical structures: a lactone, steroid, and sugar ring (13). The lethal dose of oleander leaves for cattle is 50 mg/kg (14), whereas other research found a semi-quantitative risk of 3–10 mg/kg (15). It has been observed that the fatal dose of oleander for sheep is 250 mg/kg (16). Overall, clinical indications of Oleander toxicity are similar in humans and other animals, despite disagreements regarding the exact lethal dose. Clinically used cardiac glycosides have cardiovascular toxicity, so their narrow therapeutic index limits their therapeutic use (17). Primary immune cells were used in a study with samples taken from six different blood donors and it was determined that Oleandrin increased the immune response, especially in Natural Killer (NK), T-lymphocytes and monocytes. 31.3 ng/mL and 125 ng/mL Oleandrin provided statistically strong results (18). Low doses of Oleandrin increased the activation of immune cells against cancer. It has been shown that Oleandrin both induces apoptosis and increases ER stress in breast cancer cell lines MCF7, T47D and MDA-MB-231 cells (19). Its extraordinary pharmacotherapeutic potential has been described as antioxidant, antibacterial, neuroprotective, anti-HIV, anti-inflammatory, and anticancer (20).

The anti-proliferative and anti-metastatic effects of Oleandrin on cancer cells without causing cardiovascular damage are still being investigated. The main goal of our study is to investigate the effect of oleandrin on the EMT ability.

Materials and methods

Chemicals

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Commercial Oleandrin (99% HPLC) was obtained from Sigma (USA). RPMI 1640, PBS, penicillin/ strepto-mycin, XTT kit and FBS were purchased from Biological Industries. QIAzol and cDNA synthesis kits were obtained from Qiagen and Bio-Rad, respectively.

Cell Culture

Ishikawa human endometrial adenocarcinoma cell line was obtained from European Collection of Authenticated Cell Cultures (ECACC). Ishikawa cells were proliferated in RPMI medium containing 10% FBS, 2 mM L-glutamine and 1% penicillin/streptomycin in an incubator containing humidity with 5% CO_2 atmosphere and 37 °C.

XTT Proliferation Assay

Cytotoxic activity of Oleandrin was detected in Ishikawa cells by using XTT colorimetric based assay to calculate IC_{50}. Oleandrin was dissolved in methanol. Ishikawa cells were seeded as $1x10^3$ cells/well in a 96-well plate. The cells were treated with various doses of Oleandrin (7.5, 15, 30, 40, 50, 100 and 150 nM) for 24, 48 and 72 hours. Then, amounts of cell viabilities were determined at wavelength 450 nm using a microplate reader to calculate cell viability (%).

qRT-PCR Analysis

Total RNA isolation from Ishikawa cells and cDNA synthesis were conducted with QIAzol (Qiagen) and Transcriptor First-Strand cDNA Synthesis Kit (Bio-Rad) using manufacturer's manuals, respectively. The primer sequences of genes used in this study for qRT-PCR analysis were designed with IDT PrimerQuest (https://eu.idtdna.com/site) and were presented in Table 1. The qRT-PCR reaction mix was prepared for each gene. Briefly, each reaction contained 2 µL cDNA, 5 pmol of forward and reverse primer and 5 µL 2X SYBR Green Supermix (Bio-Rad). qRT-PCR protocol was performed as initial denaturation at 95 °C for 10 minutes, denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds and extension at 72 °C for 30 seconds, respectively. PCR reaction was performed as 40 cycles. qRT-PCR analysis was conducted using Bio-Rad CFX ConnectTM Real-Time System. Melting curve analysis was performed by progressive heating from 65 °C to 95 °C on the PCR products. GAPDH were used as reference gene in the study.

Colony Test

For colony formation analysis, Ishikawa cells were digested with trypsin, counted using trypan blue dye exclusion test, and seeded in 6-well plates at a density of 10^3 cells/well. The medium was changed every 3 days for 10 days until visible colonies formed. Colonies were fixed with methanol for 10 min and stained with crystal violet.

Invasion Test

Invasion activities of control and dose groups of Ishikawa cells were determined according to the BioCoat Matrigel Invasion Chamber guide (BD Biosciences). The cells with serum-free RPMI 1640 medium were seeded at a density of 2×10^5 cells/well onto the upper chambers of Matrigel-coated filter inserts. The serum-containing RPMI 1640 medium (500 µL) was added to the lower chambers. Then, the cells were incubated at 37 °C for 24 h. After incubation, filter inserts were removed from the wells. The cells on the upper surface of the filter were wiped with a cotton swab. Filters were fixed with methanol for

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10 min and stained with crystal violet. The cells that invaded the lower surface of the filter were counted under a light microscope. Each experiment was repeated three times.

Table 1. Primers of EMT-related and reference genes used in this study.

No	Gene	Forward Primer (5'->3')	Reverse Primer (5'->3')	bp
1	CDH1	GAGAGCGGTGGTCAAAGAG	AGCTGGCTCAAGTCAAAGT	117
2	CDH2	GCTGACCAGCCTCCAAC	CATGTGCCCTCAAATGAAACC	112
3	ZEB1	CCCTGTGCAGTTACACCTTT	GGGCATTCATATGGCTTCTCT	205
4	ZEB2	TTTGCCCAACTGCTGACC	GCTACAGAGAGGGCAGGAA	123
5	FN1	CCCTAAAGGACTGGCATTCA	CTCGAGTAGGTCACCCTGTA	102
6	TIMP1	GCGTTATGAGATCAAGATGACCA	AACTCCTCGCTGCGGTT	141
7	TIMP2	GCTGCGAGTGCAAGATCA	CTCTTGATGCAGGCGAAGAA	136
8	TIMP3	GCAAGATCAAGTCCTGCTACTAC	GGATGCAGGCGTAGTGTTT	123
9	MMP2	TGGCAGTGCAATACCTGAA	GCATGGTCTCGATGGTATTCT	147
10	MMP9	GCAGACATCGTCATCCAGTT	ACAACTCGTCATCGTCGAAAT	139
11	ITGA5	AAGGCAGAAGGCAGCTATG	GGAGGGAGCGTTTGAAGAAT	124
12	ITGAV	CTTTCTTCCGATTCCAAACTGG	GCCTTGCTGAATGAACTTGG	120
13	ITGB1	ACAGATCCGAAGTTTCAAGGG	TCTCCTTTATTGAAGGCTCTGC	107
14	VIM	TCCAAGCCTGACCTCAC	CACCTGTCTCCGGTACTC	189
16	SMAD2	GCTAACTAGAATGTGCACCATAAG	GGGATCCCATCTGAGTTAATACTT	155
17	SMAD4	GGAAAGGATTTCCTCATGTGATCTA	ATGGATTCACACAGACACTATCAC	132
18	SNAI1	AAGATGCACATCCGAAGCC	GGCTTCTCGCCAGTGTG	113
19	SNAI2	TCAGTGCAATTTATGCAATAAGACC	GCTCACATATTCCTTGTCACAGTAT	127
20	SNAI3	AGCTGCACTGCCACCTG	GTGCGGATGTGCATCTTGAG	97
21	TGFB1	GCCTGGACACGCAGTACA	TTGCAGGAGCGCACGAT	172
22	TGFB2	AAAGACAGGAACCTGGGATTTA	TGTGGAGGTGCCATCAATAC	135
23	TGFB3	CTTGCAAAGGGCTCTGGT	GGATGCAGGCGTAGTGTTT	123
24	TWIST1	CCGCAGTCTTAACGAGGAG	TTGCTCAGCTTGTCCGA	137
25	GAPDH	TGAACGGGAAGCTCACTGG	TCCACCACCCTGTTGCTGTA	307

Wound Healing Assay

Wound-healing assay was applied to assess cell migration. Clear lines were created with a sterile 200 µL pipette tip after 24 h (21). Then the cells were continuously cultured. The wound areas were photographed at 0, 24, 48 hours. Scratch wound coverages were measured. Each experiment was triplicated.

Statistical Analysis

Ct values of the genes analyzed in the study were normalized with the reference genes using the $2^{(-\Delta\Delta Ct)}$ method. Genes expression levels were evaluated using the "Multiple t test" by the GraphPad®Prism version 9.2.0 program. In all analyses, $p<0.05$ was considered as statistically significant.

Results

Oleandrin supressed cell proliferation

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Oleandrin decreased cell viability in Ishikawa cells (Figure 1). According to the results, the IC_{50} dose was determined as 75.3 nM at the 48 h.

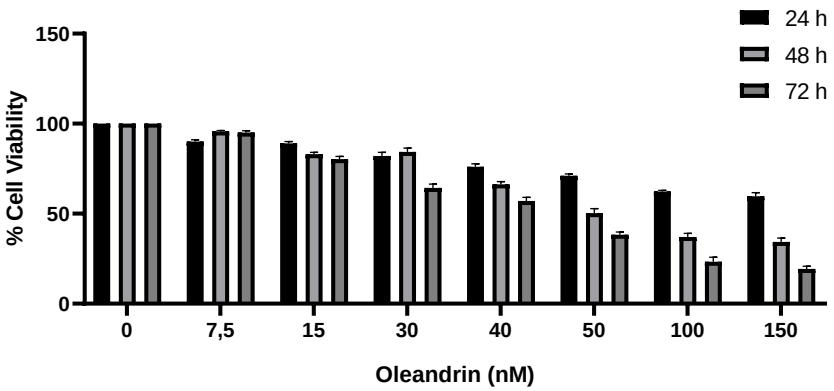


Fig. 1. Effect of Oleandrin on the Ishikawa cell viability. All experiments are triplicated.

Oleandrin alters expression of EMT-related genes

Oleandrin was found to be effective on EMT-related genes in Ishikawa cells. Especially, ZEB1, FN1, ITGB1, VIM, SMAD2, SNAI1, SNAI2, SNAI3 and TGFB3 genes were significantly downregulated. On the other hand, TIMP2, TIMP3, ITGAV and GSK3B genes were significantly upregulated (Figure 2.).

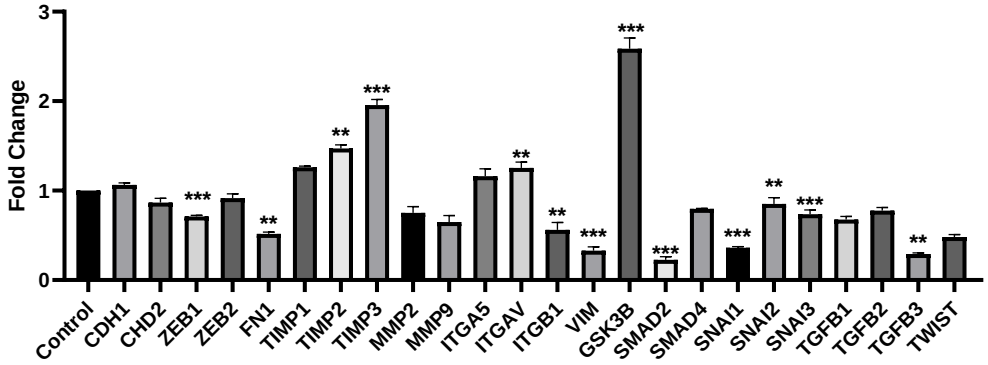


Fig. 2. The expression levels of EMT-related genes in Ishikawa cells after Oleandrin treatment.

Oleandrin inhibits colony formation

In our study, the effect of Oleandrin on colony formation was investigated. Accordingly, Oleandrin significantly reduced colony formation in Ishikawa cells (Figure 3).

Oleandrin reduces invasiveness

Oleandrin administration significantly reduced the invasion in Ishikawa cells (Figure 4).

Oleandrin suppresses cell migration

Wound healing at 0, 24 and 48 hours after Oleandrin application to Ishikawa cells was calculated by the migration of cells. Cells seems to lose their ability to migrate after Oleandrin administration (Figure 5).

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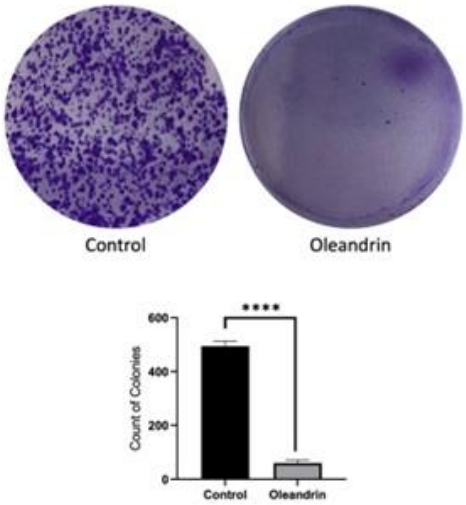


Fig. 3. Colony formation in Ishikawa human endometrial adenocarcinoma cells treated with Oleandrin (***p≤0.001).

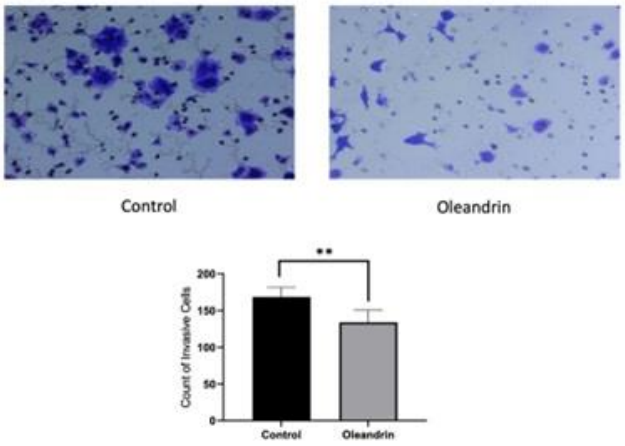


Fig. 4. Invasion ability in Ishikawa human endometrial adenocarcinoma cells treated with Oleandrin (**p≤0.01).

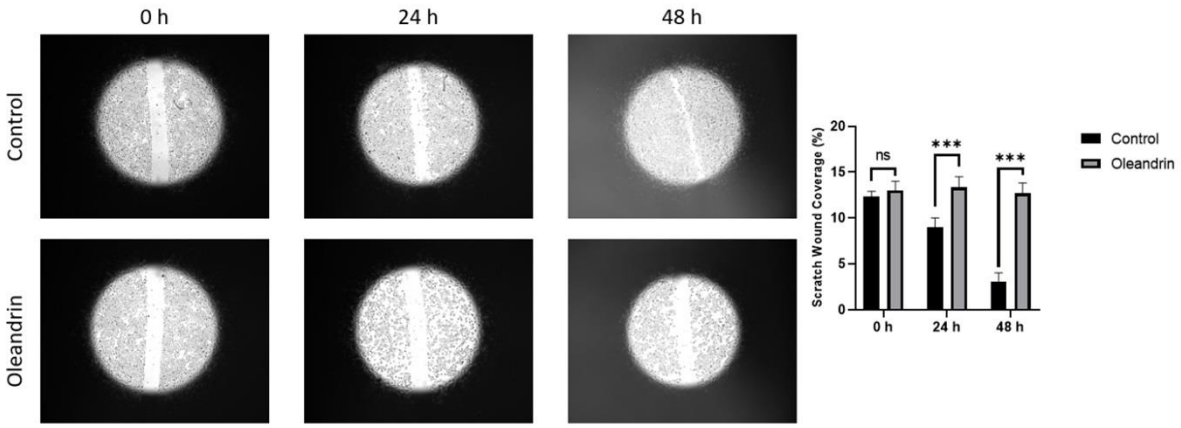


Fig. 5. Change in migration ability in Ishikawa human endometrial adenocarcinoma cell treated with Oleandrin at 0, 24 and 48 hours. All analyses were triplicated (***p≤0.001).

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Discussion

In order for cancer cells to metastasis, they must undergo some morphological changes and change their connections with other cells and the extracellular matrix (ECM; 22). It is known that there are improvements in survival in metastatic disease with treatments directed at metastasis and primary tumor (23). The metastasis process, which allows cancer cells to separate from the primary tissue and settle in distant places, has important stages. The most important of these stages is that cancer cells lose their epithelial identity and gain mesenchymal identity. This stage is called as EMT process, and many cellular connections are lost and the cells become mobile. Cells gaining mobility abilities migrate to distant tissues and settle. In addition, the EMT process has been shown to be effective in the formation of drug resistance (24). Although the EMT process is involved in metastasis in cancer, it is also the most effective process in embryonic morphogenesis, tissue fibrosis and wound healing under normal physiological conditions (25).

Oleandrin, a cardiac glycoside, is often avoided in different treatments due to its narrow therapeutic index. However, studies have shown that low doses of Oleandrin have a cytotoxic effect on cancer cells. In addition, the anti-carcinogenic effects of Oleandrin in cancer cells and molecular mechanism of this possible act are not well known yet. In our study, we found that Oleandrin suppressed invasion via the EMT pathway. In our previous study, it was shown that Oleandrin suppressed apoptosis and metastasis in A375 human melanoma cancer (26). EMT is a critical pathway for cancer pathogenesis. It has an important role in the treatment of aggressive cancers. Suppression of the EMT process may provide an alternative treatment option by suppressing the progression of cancer cells.

In this study, expression levels of ZEB1, FN1, ITGB1, VIM, SMAD2, SNAI1, SNAI2, SNAI3 and TGFB3 genes were significantly decreased. However, TIMP2, TIMP3 and ITGAV genes were significantly downregulated. SMAD proteins initiate the EMT process by activating ZEB, TWIST and SNAIL proteins.

The SNAIL family are ZINC finger transcription factors with various molecular mechanisms. This family consists of three members, called SNAI1 (Snail), SNAI2 (Slug), and SNAI3 (Smuc; 27, 28). Oleandrin significantly decreased the expression of all three SNAIL genes. SNAIL proteins have many binding sites on E-cadherin, indicating the importance of SNAIL proteins in the EMT process. They are also effective in the activation of matrix metalloproteinases MMP-2 and MMP-9. In addition, they induce upregulation of ZEB1 and ZEB2 (29). ZEB1 loses its epithelial cell properties and increases metastasis by binding to the promoter region of genes associated with cell-cell junctions, desmosomes and tight junction proteins (30, 31). In our study, it was observed that Oleandrin significantly reduced ZEB1 expression.

TIMP (metalloproteinase inhibitor) has a suppressor effect in the metastasis process, but different results have been obtained in studies. It has been observed that TIMP1 increases the EMT process in MCF10A human breast cancer cells through Twist-mediated metastasis (32). However, other studies have shown that TIMP2 inhibits metastasis in triple negative breast cancer (TNBC) models (33). In this study, TIMP2 and TIMP3 were found to be significantly increased.

Colony and invasion tests confirmed our gene expression analysis. While Oleandrin prevented cancer cells from forming colonies, it also reduced the invasion ability. In addition, wound healing analysis showed that Oleandrin treated cells decreased cancer cell migration.

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Clinical use of Oleandrin is limited because of its narrow therapeutic index. However, it has a potential that cannot be ignored in terms of cancer treatment. It can be used as an effective anti-carcinogen at non-toxic low doses. In this study, its effect on EMT in cancer cells was investigated *in vitro.* Further *in vivo* studies will allow us to obtain consistent results.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declared that this study received no financial support.

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