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ORIGINAL RESEARCH

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# Apigenin inhibits the proliferation and aerobic glycolysis of endometrial cancer cells by regulating the PI3K/Akt signaling pathway

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## Abstract

This study investigated the effects of apigenin on endometrial cancer cell proliferation, apoptosis and aerobic glycolysis. The cell viability and cell proliferation of endometrial cancer cells were detected using Cell Counting Kit-8 (CCK8) kit and5-ethynyl-2′-deoxyuridine (EDU) staining. Flow cytometry analysis was used to detect the rate of apoptosis in endometrial cancer cells. Lactate production, glucose consumption, and Adenosine triphosphate (ATP) levels were also measured. Western blot was used to detect the expression of Bcl2-Associated X (BAX), B-cell lymphoma 2 (BCL-2), Cleaved Caspase-3, phosphoinositide 3-kinase (PI3K), p-PI3K, rapamycin (mTOR), p-mTOR, Phosphatase and tensin homolog (PTEN), protein kinase B (Akt) and p-Akt. The results showed that, apigenin inhibits cell viability, cell proliferation, promotes the rate of apoptosis, and the expression of BAX, Cleaved Caspase-3, and inhibits the expression of BCL-2 of endometrial cancer cells in a dose-dependent manner. In addition, apigenin suppressed lactate production, glucose consumption, and ATP levels and inhibited the phosphorylation of PI3K and Akt in a dose-dependent manner. Finally, apigenin inhibited the proliferation and aerobic glycolysis of endometrial cancer cells and promoted cell apoptosis by blocking the PI3K/Akt signaling pathway.

## Keywords

Endometrial cancer; Apigenin; PI3K/Akt; Cell proliferation; Apoptosis; Aerobic glycolysis

## 1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy and the sixth leading cause of cancer-related mortality in women. EC risk is elevated by genetic predisposition, age, obesity and race [1, 2]. Due to the advancements in medical therapies, there has been a recent increase in the 5-year relative survival rate of endometrial cancer. The prognosis for people with advanced disease remains unfavorable [3]. The present clinical management of endometrial cancer patients is extremely challenging due to the disease's high propensity for recurrence and resistance to therapy. Thus, the discovery of effective natural remedies provides new opportunities for advancing research on endometrial cancer [4].

Tumor cells exhibit heightened biosynthesis and possess the capacity to uptake glucose and generate lactate via the aerobic glycolytic pathway. Consequently, they are recognized for their rapid proliferation and metastatic potential [5]. The dysregulation of aerobic glycolysis has a major impact on the proliferation and invasion of cancer cells, especially in the case of endometrial cancer [6]. Thus, inhibiting aerobic glycolysis could serve as a beneficial therapeutic approach to halt the metastasis of cancer.

Apigenin, a naturally occurring flavonoid, is edible and can be found in a wide variety of fruits and vegetables. Prior studies have shown that apigenin possesses a wide range of biological actions, including anti-inflammatory, antioxidant, antibacterial, antiviral, anticancer and cardio-protective properties [7]. Apigenin has lower mutagenicity and toxicity towards normal cells compared to other flavonoids, indicating its potential as a beneficial adjunct in cancer therapy [8]. Additionally, it has the ability to precisely induce cell cycle arrest and death in cancer cells [9]. Research has shown that apigenin suppresses the activity of hypoxia inducible factor 1, alpha subunit (HIF-1$\alpha$), Myelocytomatosis viral oncogene homolog (c-Myc), phosphorylated epidermal growth factor receptor (p-EGFR), and glucose metabolism in non-small cell lung cancer. As a result, it hinders the process of autophagic flux and triggers apoptosis [10].

Apigenin reduces the activity of nuclear factor kappa-B (NF-$\kappa$B)/HIF-1$\alpha$, which leads to a decrease in glycolysis. This, in turn, reduces cell stemness and impairs DNA damage repair. As a result, the radiosensitivity of subcutaneous gliomas in mice is increased [11]. Apigenin inhibits the PI3K/Akt/mTOR signaling pathway, hence preventing osteosarcoma cells from displaying aerobic glycolysis and


  

stem cell-like properties [12]. Experimental studies have focused on apigenin's anticancer effect on different forms of cancer. However, there is limited documentation about the use of apigenin in endometrial cancer, and its mechanism of action remains uncertain.

The purpose of this study was to determine whether apigenin could control endometrial cancer cell growth, apoptosis, and aerobic glycolysis via the PI3K/Akt signaling pathway.

## 2. Materials and methods

### 2.1 Cell culture

Two human endometrial cancer cell lines, Ishikawa and human endometrial adenocarcinoma cells (HEC-1A), were taken from the American-type culture collection. The cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS) and 50 $\mu$g/mL diabody under 37 °C and 5% $CO_2$ conditions. The experimental groups are as follows: (1) 0 $\mu$mol/L apigenin (178278, Sigma Aldrich, St Charles, MO, USA); (2) 10 $\mu$mol/L apigenin; (3) 20 $\mu$mol/L apigenin; (4) 40 $\mu$mol/L apigenin.

### 2.2 Cell viability assay

$1 \times 10^4$ cells were placed in each well of a 96-well plate. After 24, 48 and 72 h, respectively, the reagents for the Cell Counting Kit 8 (CCK8, C0040, Beyotime, Nanjin, China) were added. The cells were then cultured for an additional hour. Using a microplate reader, determine the absorbance at 450 nm.

### 2.3 EDU incorporation assay

The Cell-Light 5-ethynyl-2-deoxyuridine (EDU, Sigma-Aldrich, BCK-EDU488, St Charles, MO, USA) kit was used to stain the cells. On glass slides, cells were sown, and EDU was added and cultured for 12 h. Next, the cells were permeabilized and fixed. Subsequently, Apollo® reaction mix was added and let to sit in light shielding for 30 mins. The cells were analyzed using a laser scanning confocal microscope (CKX41, Olympus, Tokyo, Japan) after counterstaining.

### 2.4 Annexin (annexin V-fluorescein isothiocyanate) V-FITC/propidium iodide (PI) assay

Using Annexin V-FITC/PI in accordance with the manufacturer's instructions, flow cytometry was used for detection. PI and Annexin V-FITC were gently mixed with the cells, and allowed to sit at room temperature in the dark for 15 mins. The cells were promptly assessed using flow cytometry.

### 2.5 Lactate production, glucose consumption and ATP levels analysis

Using a lactate colorimetric test kit (Cat. No. K627; BioVision, Palo Alto, CA, USA), seed $2 \times 10^5$ cells per well in a 6-well plate. The supernatant was collected in order to calculate the amount of lactic acid generated. A microplate reader set to 450 nm was used to test the lactate levels in the reaction mixture after it had been left at room temperature in the dark for 30 mins.

A glucose uptake colorimetric assay kit (Cat. No. K676; BioVision, Inc., Palo Alto, CA, USA) was used to measure the amount of glucose consumed. Following cell harvesting, the cells were treated for 40 mins in Krebs-Ringer-phosphate-N-2-hydroxyethylpiperazine-N-ethane-sulphonicacid (HEPES) buffer (100 $\mu$L), 20 mins in 10 $\mu$L 2-deoxyglucose (10 mM), and an hour in reaction mixture A. Each well was filled with 90 $\mu$L of extraction buffer, then incubated for 40 mins at 90 °C and placed on ice for 5 mins. After adding reaction mixture B to every well, a centrifuge was used to centrifuge the cells and the supernatant was collected for analysis. Using a microplate analyzer, the optical density (OD) value at 412 nm was ascertained.

Using an ATP Colorimetric Assay Kit (Cat. No. MAK1900; Sigma-Aldrich; Merck KGaA, St Charles, MO, USA) and following the manufacturer's instructions, ATP level measurements were carried out. The cells were collected and combined with 100 $\mu$L of ATP assay buffer. After centrifuging, the supernatant was used for the ATP assay. The supernatant was kept at room temperature for 30 mins in the dark. Using a microplate analyzer, the OD value at 570 nm was ascertained.

### 2.6 Western blot

Using Radio Immunoprecipitation Assay (RIPA) lysis buffer for 30 mins, total protein samples that were isolated from cells were obtained. Thermo Fisher Scientific, Inc.'s bicinchoninic acid (BCA) protein assay kit (P0009, Beyotime, Nanjin, China) was used to quantify the protein. The proteins in each sample were then transferred to a Polyvinylidene fluoride (PVDF) membrane by Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) using a 10% polyacrylamide gel. Membranes were blocked with anti-BAX (1:1000, ab32503, Abcam, Cambridge, UK), anti-BCL-2 (1:1000, ab182858, Abcam, Cambridge, UK), anti-Cleaved Caspase-3 (1:1000, ab32042, Abcam, Cambridge, UK), anti-phosphoinositide 3-kinase (PI3K, 1:1000, ab302958, Abcam, Cambridge, UK), anti-p-PI3K, (1:1000, ab283852, Abcam, Cambridge, UK), anti-p-Akt (1:1000, ab8805, Abcam, Cambridge, UK), anti-Akt (1:1000, ab283852, Abcam, Cambridge, UK), anti-mTOR (1:1000, ab134903, Abcam, Cambridge, UK), anti-p-mTOR (1:1000, ab109268, Abcam, Cambridge, UK), anti-PTEN (1:1000, ab267787, Abcam, Cambridge, UK), anti-PTEN (1:1000, ab267787, Abcam, Cambridge, UK), anti-caspase-3 (1:1000, ab32351, Abcam, Cambridge, UK) and anti-GAPDH (1:1000, ab8245, Abcam, Cambridge, UK) antibodies overnight at 4 °C after being blocked for one hour at room temperature with 5% nonfat milk. Subsequently, the membrane was incubated for an hour at room temperature with the matching secondary antibody (Santa Cruz Biotechnology, Inc.). ECL reagent (P0018S, Beyotime, Nanjing, China) was used to improve protein signaling for 10 mins, which was subsequently analyzed utilizing a Western Blot Imaging and Quantification System (v1.8.0, Bio-Rad Laboratories, Inc., Hercules, CA, USA). The National Institutes of Health's ImageJ program (v1.8.0) was used for quantification.

### 2.7 Statistical analysis

Three sets of the experiment were conducted, and the mean ± standard deviation was reported for each set of data. Statistical analyses were performed using GraphPad Prism statistical software (version 6, GraphPad Software, Inc., San Diego, CA, USA). Separated One-way analysis of variance was utilized to examine comparisons between multiple groups, and the Student's *t* test was employed to examine differences between two groups. For each test, $p < 0.05$ was considered statistically significant.

## 3. Results

### 3.1 Apigenin inhibits the proliferation of endometrial cancer cells

Based on previous research, this study selected 20 $\mu$M apigenin as our mid-dose concentration [13]. Fig. 1a, shows the chemical structure of apigenin. Ishikawa and HEC-1A were incubated with different concentrations of apigenin (0, 10, 20, 40 $\mu$M) for 24 h, 48 h and 72 h, and the OD value was measured using the CCK8 kit. Studies have observed proliferation in the endometrial cancer cells over time. Compared with the group without apigenin, the use of apigenin can inhibited endometrial cancer cells (Fig. 1b). The results of the EDU staining experiment were also similar to the CCK results. Compared with the non-apigenin group, apigenin inhibited the proliferation of endometrial cancer cells in a dose-dependent manner (Fig. 1c).

### 3.2 Apigenin promotes apoptosis of endometrial cancer cells

This study utilized flow cytometric technique to examine apoptosis and gain insight into the precise mechanism by which apigenin induces cell death in endometrial cancer cells. Upon investigation, it was observed that the percentage of cells undergoing apoptosis significantly increased in a manner directly proportional to the dosage when endometrial cancer cells were incubated with apigenin (Fig. 2a). Simultaneously, studies have discovered proteins linked to apoptosis. The levels of pro-apoptotic proteins (BAX, Cleaved-Caspase-3) were greatly increased in a dose-dependent manner when endometrial cancer cells were subjected to apigenin, as observed through Western blot analysis. Conversely, the expression of BCL-2 was significantly reduced (Fig. 2b). The findings suggest that apigenin triggers programmed cell death in endometrial cancer cell lines in a dose-dependent manner.

### 3.3 Apigenin inhibits aerobic glycolysis in endometrial cancer cells

Further investigation explored the involvement of apigenin in the process of aerobic glycolysis in endometrial cancer cells. The study's results showed that apigenin can decrease ATP levels, glucose intake, lactate release, and migratory capacity in endometrial cancer cell lines in dose-dependent manner (Fig. 3). These results indicate that apigenin inhibits aberrant glycolysis in endometrial cancer cell lines in a dose-dependent manner.

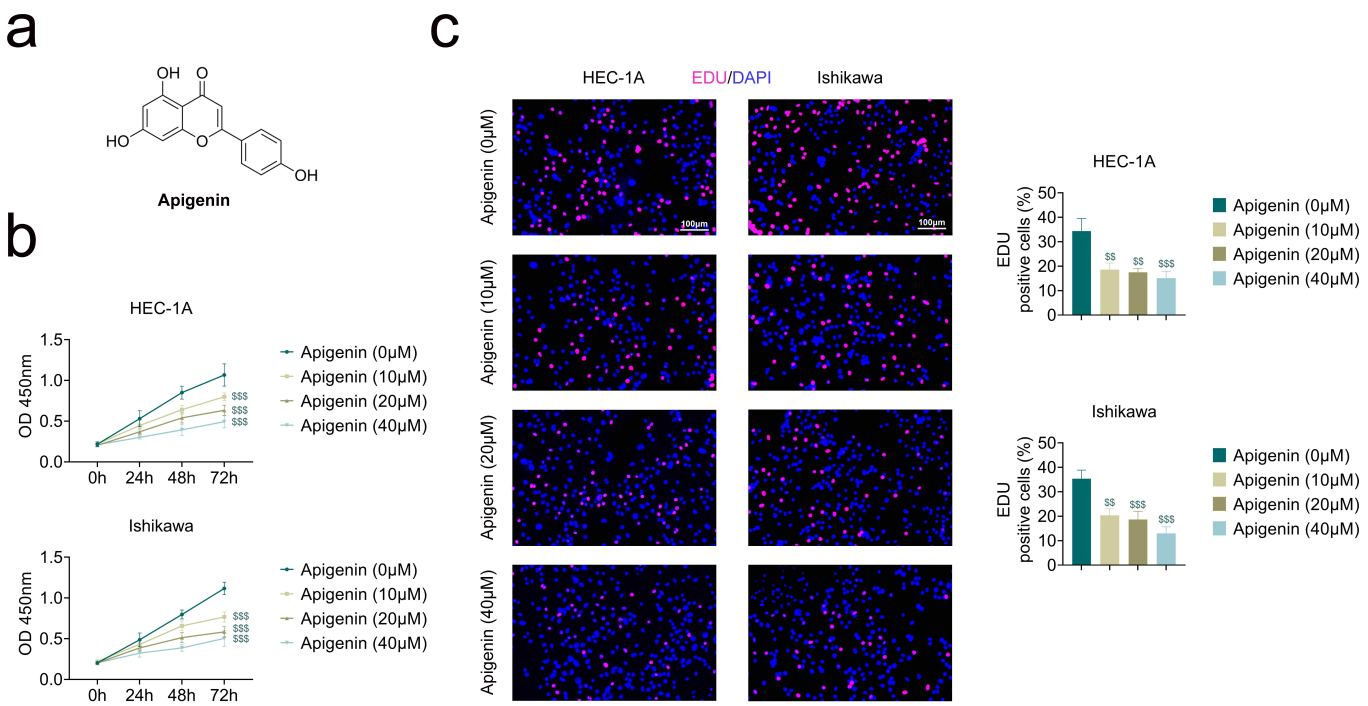


**FIGURE 1. Apigenin inhibits the proliferation of endometrial cancer cells.** (a) The chemical structure of apigenin. (b) CCK8 detects the OD value at 450 nm after 24 h, 48 h and 72 h administration. (c) EDU staining to detect proliferation of endometrial cancer cells. Values are presented as mean ± SD. $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ versus Apigenin (0 $\mu$M) group. n = 3. CCK8: Cell Counting Kit-8; OD: optical density; EDU: 5-ethynyl-2-deoxyuridine; HEC-1A: human endometrial adenocarcinoma cells.

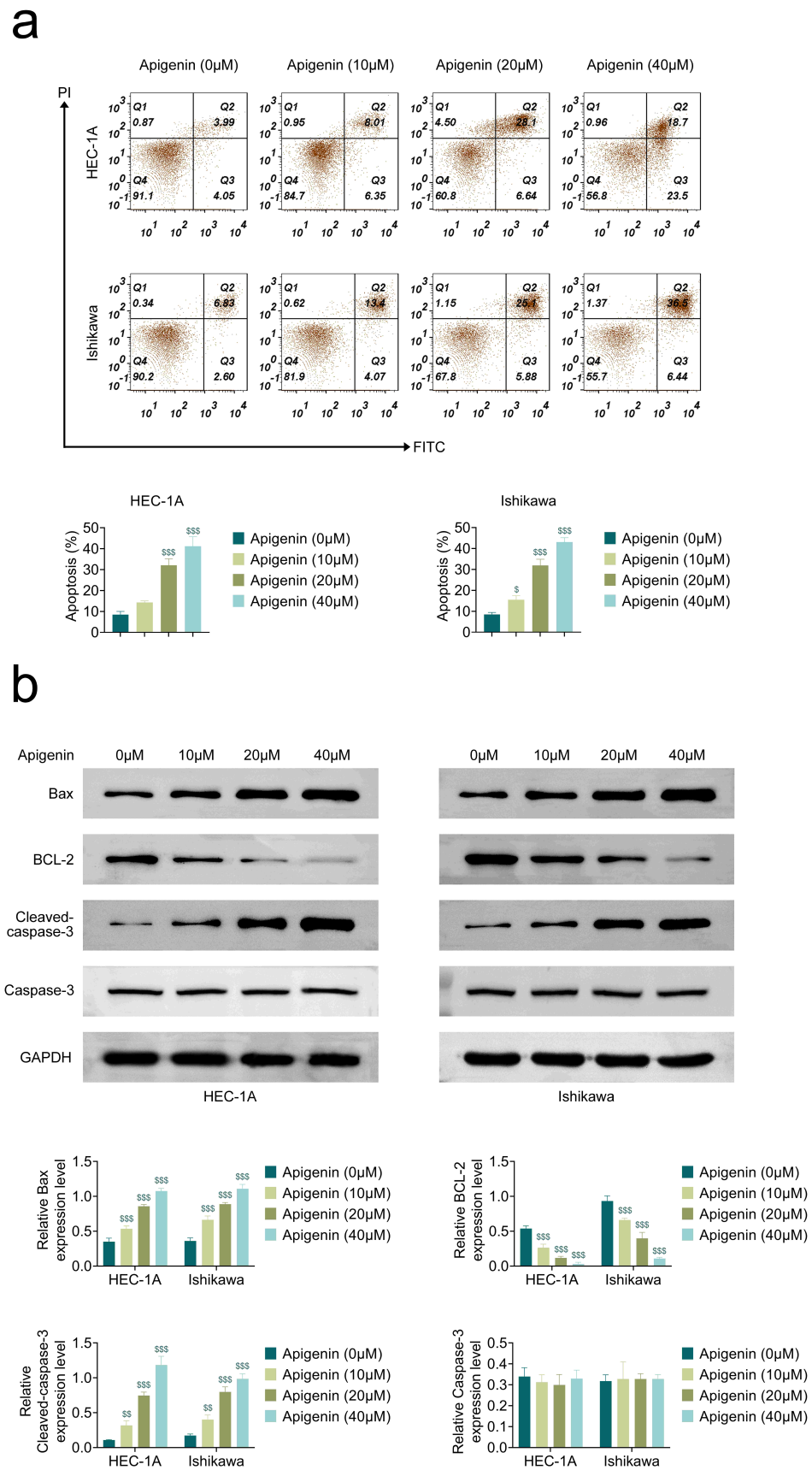


**FIGURE 2. Apigenin promotes apoptosis of endometrial cancer cells.** (a) Flow cytometry to detect the apoptosis rate of endometrial cancer cells after administration. (b) Protein expression of BAX, BCL-2, Caspase-3 and Cleaved Caspase-3 in endometrial cancer cells after administration. Values are presented as mean ± SD. $^{\$}p < 0.05$, $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ versus Apigenin (0 $\mu$M) group. n = 3. BAX: Bcl2-Associated X; BCL-2: B-cell lymphoma 2; HEC-1A: human endometrial adenocarcinoma cells.

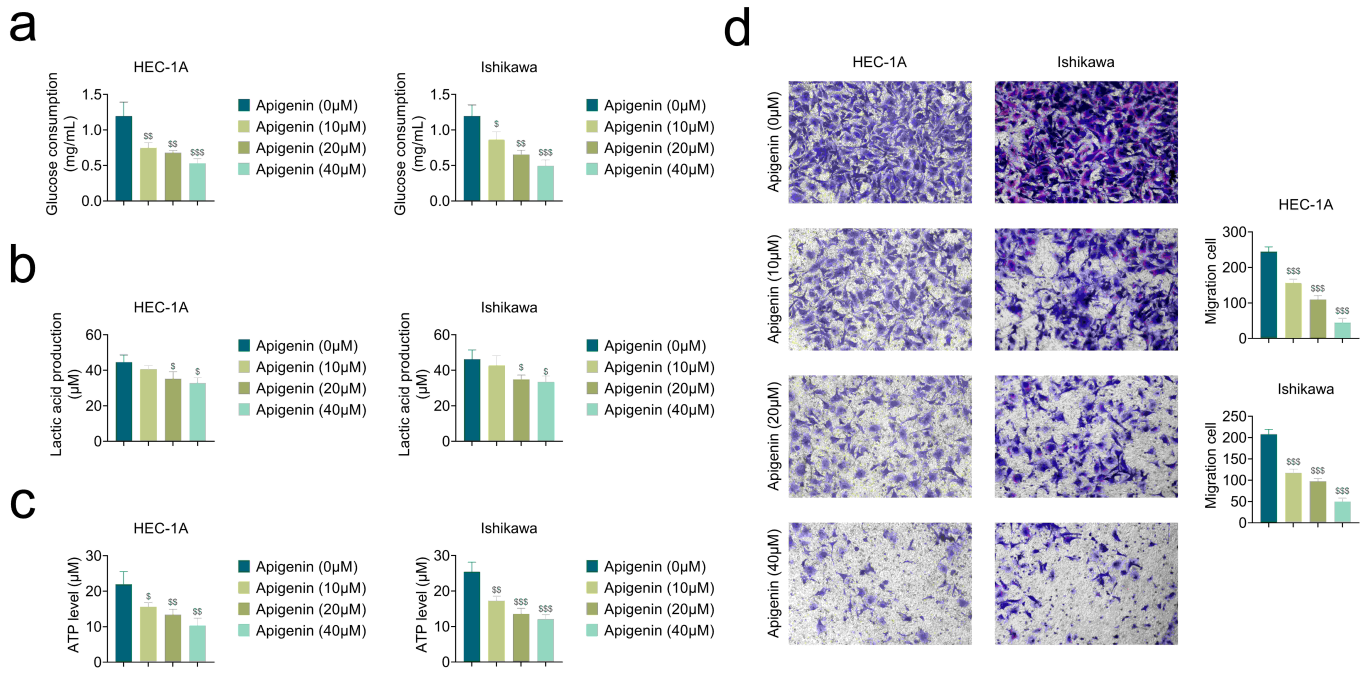


**FIGURE 3. Apigenin inhibits aerobic glycolysis in endometrial cancer cells.** (a) Glucose consumption levels of endometrial cancer cells after drug administration. (b) Lactate production levels in endometrial cancer cells after drug administration. (c) Testing ATP levels in endometrial cancer cells after drug administration. (d) Migration ability assay. Values are presented as mean ± SD. $^{\$}p < 0.05$, $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ versus Apigenin (0 $\mu$M) group. n = 3. HEC-1A: human endometrial adenocarcinoma cells; ATP: Adenosine triphosphate.

### 3.4 Apigenin inhibits the PI3K/Akt pathway

In order to gain a deeper understanding of the mechanism by which apigenin induces apoptosis, this study examined various signaling pathways that may be involved. According to our findings, apigenin can, in a dose-dependent way, increase PTEN expression and inhibit PI3K, Akt and mTOR protein phosphorylation (Fig. 4). The outcomes demonstrated that apigenin efficiently and dose-dependently blocked the PI3K/Akt pathway. This implies that apigenin's actions on the PI3K/Akt pathway may be responsible for some of its anticancer capabilities.

## 4. Discussion

In recent years, researchers have increasingly focused on natural drugs due to their potent biological activity and low cytotoxicity. Apigenin has long been used in traditional medicine and has been proven to have many physiological and pharmacological effects. Despite the potent anticancer effects of apigenin on other types of tumors, its specific role and mechanism of action in endometrial cancer remain unclear [14]. First, research has confirmed that apigenin, through blocking the PI3K/Akt signaling pathway, decreases cellular aerobic glycolysis, promotes apoptosis, and suppresses cell proliferation in a dose-dependent manner. These findings indicate that apigenin may be a potential therapeutic option for the treatment of endometrial cancer.

Apoptosis, a complex biological process, occurs in both normal and pathological conditions. The evasion of apoptosis by tumor cells is the driving force behind the proliferation and metastasis of malignancies. Currently, apoptosis activation is considered one of the most crucial techniques for cancer treatment [15]. The BCL-2 family regulates the expression of pro-apoptotic (BAX) and anti-apoptotic (BCL-2) members, which is critical in mitochondria-mediated apoptosis. Caspases 3 and 4 are activated when BAX and BCL-2 are expressed more frequently, which results in cell death [16]. Our findings, which are in line with earlier research, demonstrated that apigenin caused dose-dependent apoptosis, which was followed by an increase in BAX and Cleaved-Caspase-3 expression and a decrease in BCL-2 expression. These findings imply that apigenin regulates the mitochondrial apoptotic pathway, leading to the induction of apoptosis in endometrial cancer cells.

Tumor cells exhibit a higher rate of ATP production via glycolysis compared to oxidative phosphorylation, even when oxygen levels are adequate. Tumor cells undergo aerobic glycolysis, resulting in increased acidity and lactate accumulation in the extracellular compartment of the tumor. This metabolic process significantly enhances the tumor's resistance to chemotherapy, growth, and metastasis [17, 18]. Formerly recognized as a metabolic byproduct of anaerobic glycolysis, lactate is now recognized as a crucial element for the movement, infiltration, proliferation, and ability of tumor cells to avoid the immune system [19]. The results indicate that apigenin effectively suppresses aerobic glycolysis in endometrial cancer by significantly decreasing cellular glucose intake, lactate generation, and ATP levels. The proposed mechanism by which apigenin inhibits the growth of endometrial cancer involves aerobic glycolysis.

Numerous signaling pathways and oncogenes, such as

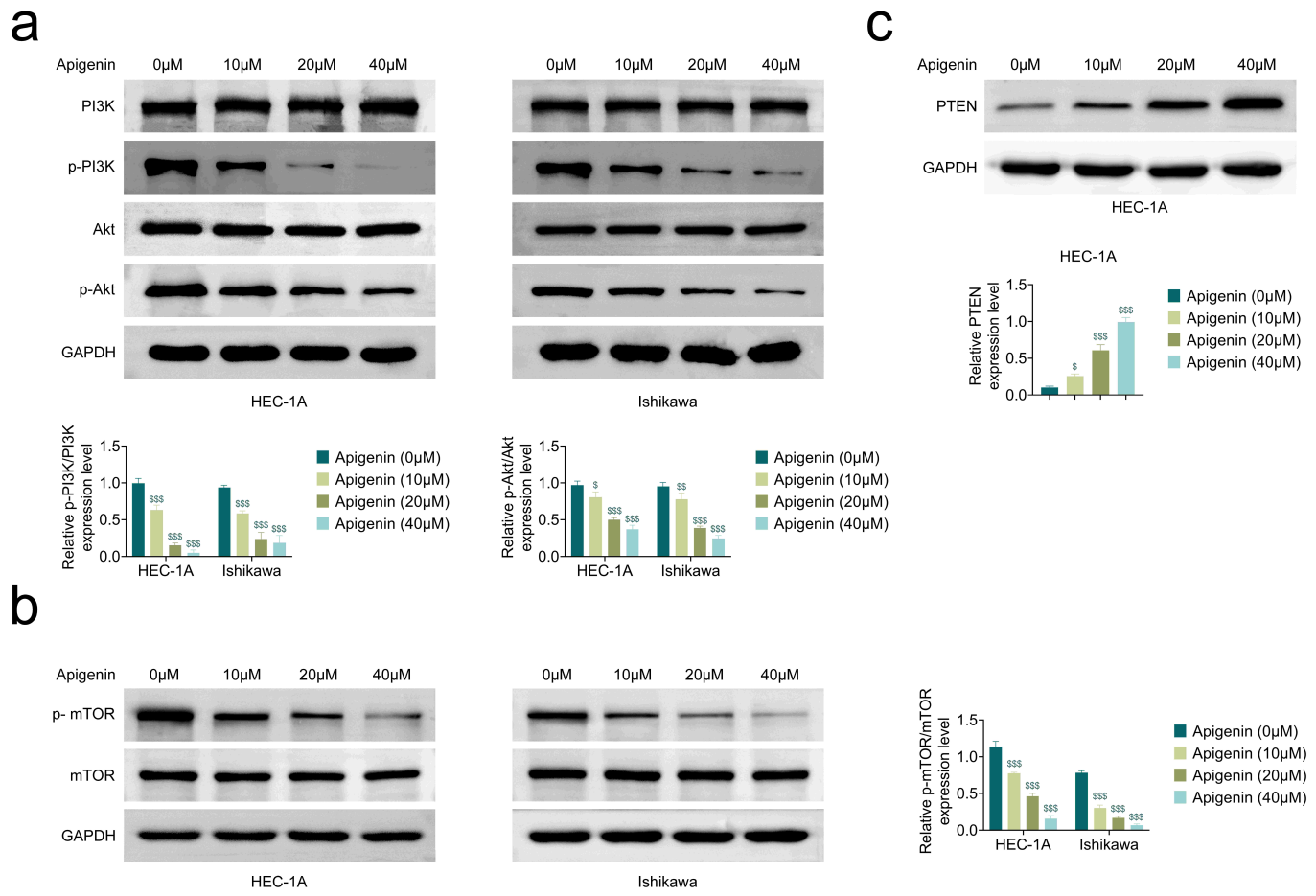


**FIGURE 4. Apigenin inhibits the PI3K/Akt pathway.** (a) Protein expression of PI3K, p-PI3K, Akt, p-Akt in endometrial cancer cells. (b) Protein expression of mTOR, p-mTOR in endometrial cancer cells. (c) Protein expression of PTEN in HEC-1A cells. Values are presented as mean ± SD. $^{\$}p < 0.05$, $^{\$\$}p < 0.05$, $^{\$\$\$}p < 0.001$ versus Apigenin (0 $\mu$M) group. n = 3. PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; mTOR: rapamycin; PTEN: Phosphatase and tensin homolog; HEC-1A: human endometrial adenocarcinoma cells.

PI3K/Akt and vascular endothelial growth factor, are activated during aerobic glycolysis, which aids in the advancement of cancer [20]. PI3K/Akt signaling has a crucial role in regulating glucose metabolism and increasing glycolytic flux, even in normoxic oxidative tumor cells [21]. Furthermore, the increase in hexokinase-II (HK-II) expression, facilitated by PI3K/Akt signaling, promotes aerobic glycolysis and enhances both pro-proliferative and anti-apoptotic effects [22]. According to our research, one significant mechanism of apigenin's cytotoxicity against endometrial cancer cells is its responsive suppression of the PI3K/Akt pathway.

More emphasis is placed on the necessity of *in vivo* investigations using animal studies. Regardless of how good the results are, data from *in vitro* studies cannot be considered a reliable indicator of a drug candidate's efficacy. Therefore, the lack of *in vivo* data emphasizes the limitations of this study, and further research using animal models is necessary to validate apigenin's *in vitro* effects. The development of three-dimensional (3D) cultures that mimic *in vivo* tissue organization prior to animal experiments is critical to study the role of cell adhesion and polarity genes in epithelial cancer pathogenesis.

## 5. Conclusions

In conclusion, apigenin induces cell death by blocking the PI3K/Akt signaling pathway and inhibits the growth and aerobic glycolysis of endometrial cancer cells. It may therefore be employed as a novel therapeutic agent for the treatment of endometrial cancer.

## AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

## AUTHOR CONTRIBUTIONS

LX and YCL—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. LX, LP, TTC, LMZ and ML—supervised the data collection. LX, LP, TTC LMZ and ML—analyzed the data. LX, LP and TTC—interpreted the data. All authors have read and approved the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.


## ACKNOWLEDGMENT

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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