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ORIGINAL ARTICLE

Empagliflozin Modulates Angiogenesis and Migration Through the NF-κB1 Axis in Breast Cancer Cells

Empagliflozin'in Meme Kanseri Hücrelerinde NF-κB1 Aracılı Anjiyogenez ve Hücre Göçü Üzerine Etkisi

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ABSTRACT

Aim: Triple-negative breast cancer (TNBC) and hormone receptor-positive breast cancer remain challenging to treat due to their aggressive behavior and resistance to conventional therapies. Empagliflozin (EMPA), a sodium-glucose co-transporter 2 (SGLT2) inhibitor, has recently attracted attention for its potential anticancer properties. This study aimed to evaluate the effects of EMPA on cell viability, migration, and gene expression in breast cancer cell lines, focusing on its role in modulating angiogenesis and epithelial-to-mesenchymal transition (EMT) pathways.
Methods: The effects of EMPA were assessed in MDA-MB-231 (TNBC) and MCF-7 (Luminal A) breast cancer cell lines using WST-1 cytotoxicity assays, scratch wound migration assays, and quantitative reverse transcription PCR (qRT-PCR). Gene expression analyses were conducted for NF-κB1, N-cadherin, VEGFA, and FGF1 to investigate EMPA's impact on inflammation, angiogenesis, and EMT.
Results: EMPA exhibited dose-dependent cytotoxicity, with MCF-7 cells showing greater sensitivity (IC_{50}: 521 μM) compared to MDA-MB-231 cells (IC_{50}: 1080 μM). EMPA significantly inhibited cell migration in both cell lines. In MDA-MB-231 cells, qRT-PCR revealed downregulation of NF-κB1, VEGFA, and FGF1, indicating anti-inflammatory and anti-angiogenic activity. In contrast, MCF-7 cells showed NF-κB1 upregulation along with VEGFA and FGF1 downregulation, suggesting a subtype-specific molecular response.
Conclusions: EMPA suppresses breast cancer cell proliferation, migration, and angiogenic signaling, potentially through NF-κB1 modulation. Its distinct effects on different breast cancer subtypes suggest a context-dependent therapeutic potential. These findings support further investigation into EMPA as a repurposed agent for targeted breast cancer therapy, particularly in aggressive forms such as TNBC.

Keywords: Angiogenesis, breast cancer, cell migration, empagliflozin, NF-κB1 signaling,

ÖZ

Amaç: Üçlü negatif meme kanseri (TNBC) ve hormon reseptörü pozitif meme kanseri, agresif klinik seyirleri ve standart tedavilere karşı geliştirdikleri direnç nedeniyle halen önemli birer terapötik zorluk oluşturmaktadır. Sodyum-glukoz kotransportör 2 (SGLT2) inhibitörlerinden biri olan Empagliflozin (EMPA), son dönemde antineoplastik etkileriyle dikkat çekmektedir. Bu çalışmada, EMPA'nın meme kanseri hücre hatlarında hücre canlılığı, migrasyon ve gen ekspresyonu üzerindeki etkileri değerlendirilmiş; özellikle anjiyogenez ve epitel-mezenkimal geçiş (EMT) süreçlerine yönelik potansiyel düzenleyici rolü araştırılmıştır.
Gereç ve Yöntemler: EMPA'nın biyolojik etkileri, MDA-MB-231 (TNBC) ve MCF-7 (Luminal A) hücre hatlarında WST-1 sitotoksisite analizi, yara iyileşme (scratch) migrasyon testi ve kantitatif ters transkripsiyon polimeraz zincir reaksiyonu (qRT-PCR) ile analiz edilmiştir. İnflamasyon, anjiyogenez ve EMT ile ilişkili genlerden NF-κB1, N-kaderin, VEGFA ve FGF1'in ekspresyon düzeyleri değerlendirilmiştir.
Bulgular: EMPA, her iki hücre hattında da doza bağımlı sitotoksisite göstermiştir. MCF-7 hücreleri EMPA'ya karşı daha yüksek duyarlılık sergilemiş (IC_{50}: 521 μM), bu oran MDA-MB-231 hücrelerinde daha yüksek bulunmuştur (IC_{50}: 1080 μM). EMPA tedavisi, her iki hücre hattında da hücre migrasyonunu anlamlı düzeyde inhibe etmiştir. MDA-MB-231 hücrelerinde EMPA uygulaması, NF-κB1, VEGFA ve FGF1 ekspresyonlarında azalmaya yol açarak anti-inflamatuar ve anti-anjiyogenik etkiler göstermiştir. Buna karşın, MCF-7 hücrelerinde NF-κB1 ekspresyonu artarken, VEGFA ve FGF1 düzeylerinde azalma gözlenmiştir. Bu durum, EMPA'nın alt tipe özgü moleküler yanıtları tetikleyebileceğini göstermektedir.
Sonuçlar: Bu çalışma, EMPA'nın meme kanseri hücrelerinde proliferasyon, migrasyon ve anjiyojenik sinyal yolaklarını baskılayarak antitümöral etki oluşturabileceğini ortaya koymaktadır. NF-κB1 aracılığıyla gerçekleşen bu etkiler, tümör alt tipine özgü farklı mekanizmalarla şekillenmektedir. Bulgular, EMPA'nın özellikle TNBC gibi tedaviye dirençli alt tiplerde yeniden konumlandırılabilir potansiyel bir ajan olarak değerlendirilmesini desteklemektedir.

Anahtar Kelimeler: Anjiyogenez, empagliflozin, hücre göçü meme kanseri, NF-κB1 sinyal yolu,

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INTRODUCTION

Breast cancer is the most common invasive cancer among women globally, accounting for approximately 12% of all new cancer cases annually (1). Despite advancements in early detection and treatment, triple-negative breast cancer (TNBC) and hormone receptor-positive subtypes remain challenging due to their aggressive nature and resistance to conventional therapies (2). These challenges highlight the need for novel therapeutic strategies targeting key molecular pathways involved in cancer progression.

Empagliflozin (EMPA), a sodium-glucose co-transporter-2 (SGLT2) inhibitor primarily used for the management of type 2 diabetes mellitus, has recently attracted attention for its potential anti-cancer properties. Studies suggest that EMPA may exert anti-proliferative and anti-inflammatory effects in cancer cells by modulating glucose metabolism and key signaling pathways (3). However, the specific effects of EMPA on breast cancer cell motility, viability, and angiogenesis-related factors remain under investigation.

Cancer cell migration and angiogenesis are critical processes in tumor progression and metastasis. Epithelial-to-mesenchymal transition (EMT), characterized by the downregulation of epithelial markers and upregulation of mesenchymal markers such as N-cadherin, enhances cell motility (4). Pro-angiogenic factors like vascular endothelial growth factor A (VEGFA) and fibroblast growth factors (FGFs) contribute to tumor vascularization, supporting growth and dissemination (5). The transcription factor NF-κB1, implicated in inflammation and cancer progression, is also linked to these processes (6). Targeting these pathways may offer therapeutic benefits in aggressive breast cancer subtypes.

This study aims to evaluate the effects of EMPA on breast cancer cell viability, migration, and the expression of key genes associated with angiogenesis and EMT in MDA-MB-231 and MCF-7 cell lines. Utilizing cytotoxicity assays, scratch assays, and quantitative real-time polymerase chain reaction (qRT-PCR), this research seeks to elucidate EMPA's potential role as an anti-cancer agent and its underlying mechanisms of action.

MATERIALS and METHODS

Cell Culture and Maintenance

The MDA-MB-231 and MCF-7 breast cancer cell lines, representing triple-negative breast cancer (TNBC) and hormone receptor-positive Luminal A subtype, respectively, were obtained from the American Type Culture Collection (ATCC) and supplied by ***. Both cell lines were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Sigma-Aldrich, USA) supplemented with high glucose, 10% fetal bovine serum (FBS; Gibco, Thermo Fisher Scientific, USA), penicillin (100 U/mL), and streptomycin (100 µg/mL) (Gibco, Thermo Fisher Scientific, USA). Cells were maintained in a humidified incubator at 37ºC with 5% CO_2 (Thermo Fisher Scientific, USA). Since commercially available cell lines were used, ethical approval was not required. A stock solution of Empagliflozin (Selleckchem, No. S8022, USA) was prepared in dimethyl sulfoxide (DMSO; Sigma-Aldrich, USA) at a concentration of 50 mM.

Cytotoxicity Analysis

To assess the cytotoxic effects of EMPA, MCF-7 and MDA-MB-231 cells were seeded

into 96-well plates at a density of 10^4 cells per well. Cells were treated with EMPA at concentrations of 100, 200, 400, 600, 800, and 1200 µM. Cytotoxicity was evaluated using the WST-1 assay 24 hours post-treatment. Following incubation with 10 µL of WST-1 reagent for 2 hours, absorbance was measured at 450 nm using a microplate reader. The half-maximal inhibitory concentration (IC_{50}) values were determined through regression analysis.

Gene Expression Analysis

Total RNA was isolated from both EMPA-treated and control groups of MDA-MB-231 and MCF-7 cell lines using the RNeasy Mini Kit (QIAGEN, USA), following the standardized protocol established in previous studies (7). The purity and concentration were subsequently assessed with the Nanodrop system (Thermo Scientific, USA). Subsequently, cDNA synthesis was performed using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, USA). For real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis, NF-κB1, N-cadherin, VEGFA, FGF1, and β-actin primers (QIAGEN) were used (Table 1), and reactions were conducted with SYBR™ Green PCR Master Mix (Thermo Fisher Scientific) as per the manufacturer's guidelines (8). The Roche Light Cycler 480 System (Roche, USA) was used for the PCR reactions, with β-actin serving as the reference gene. All experiments were performed in three biological replicates, each with three technical replicates, to ensure reproducibility and accuracy. Relative mRNA expression levels were normalized to β-actin and calculated using the $2^{-}\Delta\Delta CT$ method.

Migration Assay

Cell migration was assessed using a scratch assay following established protocols. Briefly, MDA-MB-231 and MCF-7 cells were seeded into 6-well plates at a density of 0.3×10^6 cells per well and cultured until reaching confluency. A uniform scratch was created across the cell monolayer using a sterile 200 µL pipette tip. Detached cells and debris were removed by washing with phosphate-buffered saline (PBS), and fresh culture medium containing EMPA at its IC_{50} concentration was added. Images of the scratched area were captured at 0, 24, and 48 hours using a light microscope. Wound closure percentages were quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA) to assess migration rates (9). Representative phase-contrast images illustrate wound closure at the specified time points in both untreated control and EMPA-treated (IC_{50}) groups for each cell line. Quantitative analysis of wound closure (%) at 24 and 48 hours, relative to 0 hours, is depicted in bar graphs.

Table 1. Primer sequences used in qRT-PCR analysis. All primers were obtained from QIAGEN and validated for specificity. Amplicon sizes are indicated in base pairs (bp).

Genes	**Forward Primer** (5′→3′)	**Reverse Primer** (5′→3′)
NF-κB1	5′-CTGGAAACCCGTGGTATCAGA-3′	5′-CATCCAGCTGTCCTGTCCATT-3′
VEGFA	5′-GGCCTCCGAAACCCATGAAC-3′	5′-GCTGCGCTGATAGACATCCA-3′
FGF1	5′-CTTTTATACGGCTCACAGACACC-3′	5′-CTCCCATTTCTTCATGGAGCCAA-3′
N-Cadherin	5′-TGCCCGGTTTCATTTAGGGG-3′	5′-TGTTCCAGGCTTTGATCCCTCA-3′
β-*actin*	5′-CCTGCTGGGGAATCGGGAATT-3′	5′-ATTAGCTGAGGCGCTGGCAT-3′

Statistical Analysis

The statistical analysis of data and associated graphical representations was performed using GraphPad Prism 9.1.0 (La Jolla, CA, USA). All experiments were conducted in three independent biological replicates, each performed in technical triplicate. The levels of qRT-PCR gene expression were analyzed by one-way analysis of variance (ANOVA). Relative quantification of the target genes in qRT-PCR analysis was normalized to β-actin and calculated using the $2^{-}\Delta\Delta CT$ method (10,11). Differences with $p<0.05$ were considered statistically significant.

RESULTS

Cytotoxicity analysis

The cytotoxic effects of EMPA on the viability of MDA-MB-231 and MCF-7 cells are shown in Figure 1. In MDA-MB-231 cells (Figure 1. A), EMPA exhibited a dose-dependent reduction in cell viability. Significant decreases in viability were observed at concentrations of 400 µM and higher ($p<0.05$). At the highest concentration (1200 µM), cell viability was reduced to approximately 20% compared to the untreated control group. The calculated IC_{50} value for MDA-MB-231 cells was 1080 µM. Similarly, in MCF-7 cells (Figure 1.B), EMPA treatment caused a significant decline in cell viability starting at 200 µM ($p<0.05$), with viability decreasing to approximately 15% at the highest dose of 1200 µM. The IC_{50} value for MCF-7 cells was determined to be 521 µM, indicating greater sensitivity to EMPA compared to MDA-MB-231 cells.

Gene expression analysis

qRT-PCR analysis demonstrated that EMPA significantly modulates the expression of genes associated with inflammation, EMT, and angiogenesis in both breast cancer cell lines (Figure 2).

In MDA-MB-231 cells (Figure 2A), NF-κB1 expression was significantly downregulated (0.4-fold, $p<0.001$), while N-cadherin expression was increased (1.2-fold), although this change did not reach statistical significance. Both VEGFA (0.3-fold, $*p<0.0001$) and FGF1 (0.5-fold, $p<0.001$) were significantly downregulated, indicating a potential anti-angiogenic effect of EMPA in this triple-negative breast cancer model.

In MCF-7 cells (Figure 2B), NF-κB1 expression was significantly upregulated (1.5-fold, $p<0.01*$), while N-cadherin (0.5-fold, $p<0.01*$) and FGF1 (0.14-fold, $*p<0.0001$) were significantly downregulated. VEGFA expression also showed a reduction (0.7-fold), but this decrease did not reach statistical significance.

Migration analysis

The effect of EMPA on cancer cell migration was assessed using a scratch assay in MDA-MB-231 and MCF-7 cell lines (Figure 3). At 24 and 48 hours, control cells demonstrated significant wound closure, indicating a high level of cell migration. In contrast, EMPA-treated cells exhibited a notable reduction in migration, as evidenced by a significantly larger wound area remaining open at both time points. Quantitative analysis showed that in MDA-MB-231 cells, wound closure was approximately 38% at 24 hours and 75% at 48 hours in the control group,

whereas EMPA-treated cells exhibited significantly lower closure rates of 11% and 25%, respectively. Similarly, in MCF-7 cells, the control group displayed 4.5% wound closure at 24 hours and 29% at 48 hours, while EMPA-treated cells showed minimal closure of 1.8% and 5%, respectively. These reductions were statistically significant ($p<0.05$).

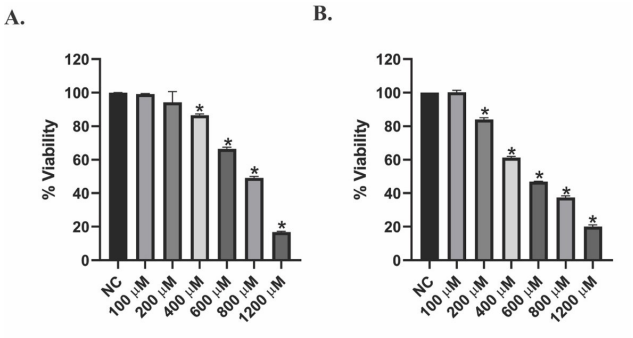

Figure 1. WST-1 cytotoxicity analysis of Empagliflozin (EMPA) on breast cancer cell lines. (A) MDA-MB-231 and (B) MCF-7 cells were treated with increasing concentrations of EMPA (100, 200, 400, 600, 800, and 1200 µM) for 24 hours. Cell viability was assessed using the WST-1 assay. Data are presented as mean±standard deviation (SD) from three independent experiments. Statistical significance was determined using one-way ANOVA; *p<0.05 compared to the negative control (NC).

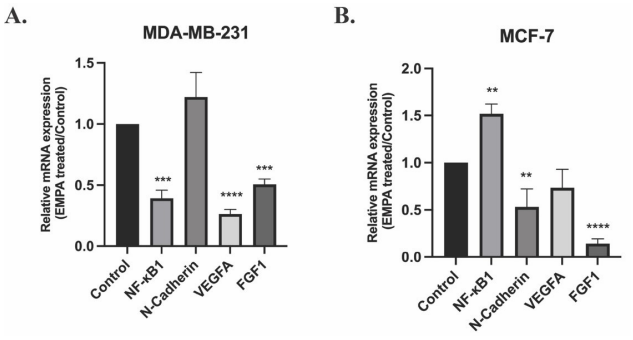

Figure 2. Relative mRNA expression levels of NF-κB1, N-cadherin, VEGFA, and FGF1 after EMPA treatment in breast cancer cells. (A) MDA-MB-231 and (B) MCF-7 cells were treated with empagliflozin at their respective IC_{50} doses for 24 hours. Gene expression was measured by qRT-PCR and normalized to β-actin. Results are expressed as fold change relative to control. Data are shown as mean±SD from three biological replicates, each performed in technical triplicate. Statistical significance was determined using unpaired t-tests comparing treated groups to the controls for each gene. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

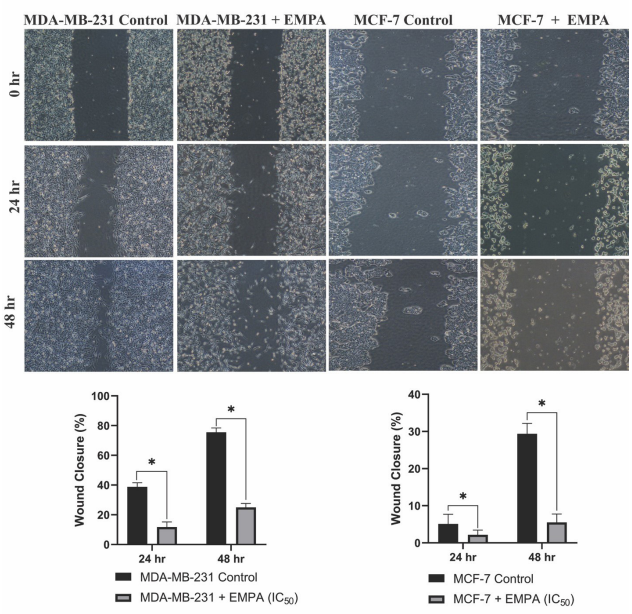

Figure 3. Scratch assay analysis of the effect of Empagliflozin (EMPA) on the migration of MDA-MB-231 and MCF-7 breast cancer cells. Representative phase-contrast images show wound closure at 0, 24, and 48 hours in untreated control and EMPA-treated (IC_{50}) groups for both cell lines. The left panel corresponds to MDA-MB-231 cells, and the right panel corresponds to MCF-7 cells. The bar graphs below depict the quantitative analysis of wound closure (%) at 24 and 48 hours compared to 0 hr. Data are presented as mean±standard deviation (SD) from three independent experiments. *p<0.05 compared to the control group.

DISCUSSION

This study investigated the effects of EMPA, an SGLT2 inhibitor, on the viability, migration, and gene expression profiles of MDA-MB-231 and MCF-7 breast cancer cell lines. Our findings demonstrate that EMPA exerts dose-dependent cytotoxic effects on these breast cancer cells, consistent with previous studies highlighting the antiproliferative properties of SGLT2 inhibitors (3). EMPA has been shown to inhibit proliferation and migration in various cancer cell types, including cervical cancer, potentially through mechanisms involving AMPK activation and suppression of the Sonic Hedgehog signaling pathway (12). Moreover, EMPA has exhibited synergistic effects when combined with

traditional cancer therapies. Notably, co-administration of EMPA with tamoxifen has resulted in enhanced cytotoxicity in breast cancer cells (13). Similarly, the combination of EMPA and doxorubicin significantly inhibited the survival of triple-negative breast cancer cells by interfering with the mTOR pathway and inhibiting calmodulin (14).

Our gene expression analysis revealed that EMPA modulates pathways critical to cancer progression, with effects varying between breast cancer subtypes. In MDA-MB-231 cells, EMPA downregulated NF-κB1 and pro-angiogenic factors VEGFA and FGF1 while upregulating N-cadherin. Conversely, in MCF-7 cells, EMPA treatment resulted in the upregulation of NF-κB1 and the downregulation of N-cadherin, VEGFA, and FGF1. These differential responses suggest that EMPA may exert subtype-specific modulation of inflammatory and angiogenic pathways. The downregulation of NF-κB1 in MDA-MB-231 cells aligns with previous findings that EMPA can inhibit the Akt pathway, leading to reduced cell proliferation and survival (15). This inhibition of NF-κB1, a key transcription factor in inflammation and cancer progression, may contribute to decreased tumor aggressiveness. In contrast, the upregulation of NF-κB1 in MCF-7 cells upon EMPA treatment suggests a complex, subtype-dependent response that warrants further investigation.

The observed upregulation of N-cadherin in MDA-MB-231 cells is noteworthy, as N-cadherin is associated with EMT and enhanced metastatic potential. Research has demonstrated that N-cadherin promotes metastasis through differential regulation of ERK and AKT pathways, facilitating EMT and invasion (16). Therefore, EMPA-induced N-cadherin expression in MDA-MB-231 cells might indicate a shift towards a more invasive phenotype, highlighting the need for careful consideration of EMPA's effects in different breast cancer subtypes.

Our study also revealed that EMPA treatment led to the downregulation of pro-angiogenic factors VEGFA and FGF1 in both MDA-MB-231 and MCF-7 breast cancer cell lines, suggesting a potential anti-angiogenic effect. This finding is particularly noteworthy, as previous research has primarily focused on the pro-angiogenic effects of EMPA in non-cancerous contexts. For instance, studies have demonstrated that EMPA suppresses inflammation and EMT in diabetic kidney disease, indicating its potential to modulate key pathways involved in disease progression (17,18). Our results indicate that in breast cancer cells, EMPA may exert an inhibitory effect on angiogenesis, potentially impeding tumor vascularization and growth. This highlights its anti-angiogenic effect in cancerous tissues. To our knowledge, this study is among the first to report EMPA's anti-angiogenic properties in a breast cancer setting, providing new insights into its potential therapeutic role in inhibiting tumor progression and metastasis.

Scratch assay results demonstrated that EMPA significantly inhibits cell migration in both MDA-MB-231 and MCF-7 breast cancer cell lines. This finding aligns with previous studies indicating that SGLT2 inhibitors can reduce the metastatic potential of breast cancer cells (12). Research has shown that SGLT2 inhibitors attenuate breast cancer cell proliferation and migration by inducing cell cycle arrest and apoptosis through the

activation of the AMPK/mTOR pathway (19). The observed inhibition of cell migration, coupled with changes in gene expression, suggests that EMPA may interfere with EMT processes, thereby reducing the invasiveness of breast cancer cells. EMT is a critical mechanism by which epithelial cells acquire mesenchymal characteristics, enhancing migratory capacity and invasiveness (20). By modulating pathways associated with EMT, EMPA could potentially impair the metastatic progression of breast cancer.

These findings contribute to a growing body of evidence supporting the potential anticancer effects of SGLT2 inhibitors, particularly in targeting mechanisms underlying cancer cell migration and metastasis. Our study demonstrated that EMPA treatment led to the downregulation of pro-angiogenic factors VEGFA and FGF1 in both breast cancer cell lines, suggesting a potential anti-angiogenic effect. Additionally, scratch assays revealed that EMPA significantly inhibits cell migration in these cell lines. These findings align with previous research indicating that EMPA can suppress cell migration and proliferation by modulating the NF-κB1 pathway. For instance, a study reported that EMPA reverses oxidized LDL-induced suppression of RECK, a regulator of extracellular matrix integrity, through the NF-κB1/miR-30b pathway, thereby inhibiting smooth muscle cell migration and proliferation (21). Given that NF-κB1 is a key transcription factor involved in inflammation and cancer progression, its downregulation by EMPA may contribute to reduced angiogenesis and migration in breast cancer cells. Therefore, our results suggest that EMPA inhibits angiogenesis and migration, potentially through modulation of the NF-κB1 pathway.

CONCLUSION

In conclusion, our study provides evidence that empagliflozin exerts anticancer effects in breast cancer cells by modulating key signaling pathways associated with cell survival, migration, and angiogenesis. EMPA displayed dose-dependent cytotoxicity, with MCF-7 cells exhibiting greater sensitivity than MDA-MB-231 cells. Our findings indicate that EMPA inhibits migration and angiogenesis, potentially through modulation of the NF-κB1 pathway. The differential regulation of NF-κB1 and N-cadherin between breast cancer subtypes suggests a complex, context-dependent effect that requires further investigation. Given its established safety profile in diabetic patients, EMPA presents a potential therapeutic avenue for breast cancer treatment. Future studies should focus on validating these findings in in vivo models and clinical settings to determine the feasibility of EMPA as an adjuvant cancer therapy.

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