







Research Article | Araştırma Makalesi

ANTIPROLIFERATIVE EFFECTS OF EMPAGLIFLOZIN ON HUMAN PANCREATIC CANCER MIA PaCa-2 CELLS

EMPAGLİFLOZİNİN İNSAN PANKREAS KANSERİ Mia PaCa-2 HÜCRELERİ ÜZERİNDEKİ ANTİPROLİFERATİF ETKİLERİ

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ABSTRACT

Objective: Pancreatic cancer remains one of the most aggressive malignancies with limited therapeutic options, emphasizing the need to identify novel antiproliferative agents. Empagliflozin, a sodium–glucose co transporter-2 (SGLT2) inhibitor widely used in the treatment of type 2 diabetes, has recently gained attention due to its potential anticancer and metabolic regulatory properties. The present study aimed to investigate the antiproliferative effects of empagliflozin on the human pancreatic cancer cell line Mia PaCa-2.

Methods: Mia PaCa-2 cells were cultured under standard conditions and treated with increasing concentrations of empagliflozin (0.1–20 µM). Cell viability was assessed at 24, 48, and 72 hours using the MTT assay. Morphological alterations in treated cells were evaluated by phase-contrast microscopy. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test.

Results: Empagliflozin significantly reduced cell viability in a time- and concentration-dependent manner. At 24 hours, significant inhibition was observed at 2–20 µM. At 48 hours, significant reductions occurred at 0.5–20 µM. The strongest inhibitory effect was observed at 72 hours, where all tested concentrations significantly decreased cell viability compared with control. The highest concentration (20 µM) reduced viability to approximately 37.4%. Morphological analysis confirmed decreased cell density, cell rounding, and detachment.

Conclusion: These findings demonstrate that empagliflozin exerts a significant antiproliferative effect on Mia PaCa-2 cells in a time- and dose-dependent manner, suggesting that empagliflozin may represent a promising candidate for further investigation as a potential therapeutic agent against pancreatic cancer.

Keywords: Pancreatic cancer, empagliflozin, antiproliferative activity, MTT assay, Mia PaCa-2 cells

Öz

Amaç: Pankreas kanseri, sınırlı tedavi seçenekleriyle en agresif malignitelerden biri olmaya devam etmekte olup, yeni antiproliferatif ajanların belirlenmesi ihtiyacını vurgulamaktadır. Tip 2 diyabet tedavisinde yaygın olarak kullanılan bir sodyum-glukoz kotransporter-2 (SGLT2) inhibitörü olan Empagliflozin, potansiyel antikanser ve metabolik düzenleyici özellikleri nedeniyle son zamanlarda dikkat çekmiştir. Bu çalışma, empagliflozinin insan pankreas kanseri hücre hattı MiaPaCa-2 üzerindeki antiproliferatif etkilerini araştırmayı amaçlamıştır.

Yöntem: MiaPaCa-2 hücreleri standart koşullar altında kültüre edildi ve artan konsantrasyonlarda empagliflozin (0,1–20 µM) ile muamele edildi. Hücre canlılığı, MTT testi kullanılarak 24, 48 ve 72 saatte değerlendirildi. Muamele edilen hücrelerdeki morfolojik değişiklikler faz kontrast mikroskopi ile değerlendirildi. Veriler, tek yönlü ANOVA ve ardından Tukey'nin post hoc testi kullanılarak analiz edildi.

Bulgular: Empagliflozin, hücre canlılığını zamana ve konsantrasyona bağlı olarak önemli ölçüde azalttı. 24 saatte, 2–20 µM aralığında önemli bir inhibisyon gözlemlendi. 48 saatte, 0,5–20 µM aralığında önemli azalmalar meydana geldi. En güçlü inhibitör etki 72 saatte gözlemlendi; bu saatte test edilen tüm konsantrasyonlar, kontrol grubuna kıyasla hücre canlılığını önemli ölçüde azalttı. En yüksek konsantrasyon (20 µM), canlılığı yaklaşık %37,4 oranında azalttı. Morfolojik analiz, hücre yoğunluğunda azalma, hücre yuvarlaklaşması ve hücre ayrılması gibi durumları doğruladı.

Sonuç: Bu bulgular, empagliflozinin Mia PaCa-2 hücreleri üzerinde zamana ve doza bağlı olarak önemli bir antiproliferatif etki gösterdiğini ve empagliflozinin pankreas kanserine karşı potansiyel bir terapötik ajan olarak daha fazla araştırma için umut vadeden bir aday olabileceğini göstermektedir.

Anahtar Kelimeler: Pankreas kanseri, empagliflozin, antiproliferatif aktivite, MTT testi, Mia PaCa-2 hücreleri

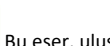
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Introduction

Pancreatic cancer is one of the most aggressive and lethal malignancies of the gastrointestinal tract, characterized by exceptionally poor prognosis and rising incidence rates globally.¹ According to the GLOBOCAN 2020 database, pancreatic cancer accounted for approximately 495,773 new cases and 466,003 deaths globally, ranking among the leading causes of cancer-related mortality despite its relatively lower incidence compared with other malignancies.² Recent clinical data, pancreatic ductal adenocarcinoma (PDAC) accounts for approximately 90% of cases, with the majority of patients (over 80%) presenting with advanced-stage disease at the time of diagnosis.³ Pancreatic cancer is also characterized by profound metabolic reprogramming and increased glucose dependency, which supports rapid tumor proliferation and survival.⁴ Current treatment options, including multi-agent chemotherapy regimens such as FOLFIRINOX or gemcitabine-based combinations, provide benefit only in selected patients and are often limited by toxicity, intrinsic resistance, or rapid disease progression.⁵ Despite significant advancements in precision surgery and neoadjuvant therapeutic regimens, the 5-year relative survival rate has only marginally improved to approximately 11-13%, underscoring a critical lack of early detection methods and effective long-term treatments.^{1,3} These persistent challenges, largely driven by profound chemoresistance and late-stage clinical presentation, highlight an urgent need for the development of novel therapeutic strategies that target the unique molecular and metabolic vulnerabilities of this aggressive disease.

Originally developed for the clinical management of type 2 diabetes mellitus, Empagliflozin (EMPA) is a selective sodium-glucose co-transporter-2 (SGLT-2) inhibitor that has recently emerged as a potential anticancer agent. Growing evidence indicates that EMPA can suppress tumor cell proliferation by interfering with glucose metabolism and modulating essential intracellular signaling networks.⁶ SGLT2 has been reported to be expressed in several tumor types, including pancreatic, prostate, lung, and breast cancers, suggesting that inhibition of this transporter may disrupt the metabolic requirements of rapidly proliferating tumor cells. SGLT2 has also been reported to be overexpressed in several cancer models, where increased glucose uptake supports tumor growth, and pharmacological inhibition of this transporter may therefore suppress tumor development and proliferation.⁷ Recent studies have demonstrated that SGLT2 inhibitors exert antitumor activity through multiple molecular mechanisms. These agents can reduce glucose uptake and intracellular ATP production,

thereby inducing metabolic stress in cancer cells and limiting their proliferative capacity.⁶ In addition, activation of AMP-activated protein kinase (AMPK) by SGLT2 inhibition has been shown to suppress the mTOR signaling pathway, leading to inhibition of cell growth, induction of apoptosis, and arrest of the cancer cell cycle.⁸ Experimental studies have further reported that empagliflozin may inhibit tumor cell migration and promote apoptosis through AMPK-dependent pathways and modulation of oncogenic signaling molecules.⁹ Considering the metabolic dependency of pancreatic cancer cells on glucose utilization and glycolytic pathways, targeting glucose transport and metabolism may represent a promising therapeutic approach in pancreatic cancer. Recent evidence also suggests that SGLT2 inhibitors may exert antitumor activity by disrupting glucose-dependent metabolic pathways in cancer cells, thereby suppressing tumor growth and proliferation.¹⁰ Direct antiproliferative effects of SGLT2 inhibitors have also been reported in liver and breast cancer models.^{11,12} However, despite the growing evidence regarding the anticancer properties of SGLT2 inhibitors, the direct antiproliferative effects of empagliflozin on pancreatic cancer cells remain insufficiently characterized.

Therefore, the present study aimed to investigate the antiproliferative effects of empagliflozin on the human pancreatic cancer cell line Mia PaCa-2. The impact of EMPA on cell viability was evaluated at different concentrations and exposure times using the MTT assay, to determine whether empagliflozin can inhibit pancreatic cancer cell proliferation in a time- and dose-dependent manner.

Methods

Cell Culture

The human pancreatic cancer cell line Mia PaCa-2 (ATCC, Germany) was used in this study. Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) (Lonza, Germany) supplemented with 10% fetal bovine serum (Lonza, Germany) and 1% penicillin-streptomycin solution (Capricorn, Germany). Cultures were maintained at 37 °C in a humidified incubator with 5% CO₂.

Empagliflozin (MedChem, USA) was obtained from a commercial supplier and dissolved in Dimethyl sulfoxide (Sigma, Germany) to prepare stock solutions. The stock was further diluted in culture medium to achieve working concentrations, keeping the final DMSO concentration below 0.1% in all treatments.

Antiproliferative Activity

Cells were seeded into 96-well plates at a density of 5×10^4 cells/mL (180 μ L per well) and allowed to adhere overnight. Empagliflozin Control wells received the

corresponding volume of DMSO without the test compound.

Cell viability was assessed at 24, 48, and 72 hours using the MTT assay. Briefly, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma, USA) was added to each well and incubated for 2 hours at 37 °C. The resulting formazan crystals were dissolved in DMSO, and absorbance was measured at 540 nm using a microplate reader (Thermo, Germany). Cell viability was expressed as a percentage of the untreated control.

All experiments were performed in triplicate, and results were expressed as mean \pm standard deviation (SD).

Statistical Analysis

Data were analyzed using GraphPad Prism. Differences among groups were assessed using one-way analysis of variance (One-way ANOVA) followed by Tukey's post hoc test. A p value <0.05 was considered statistically significant. IC_{50} values were calculated from nonlinear regression analysis of the dose-response curves generated from the MTT assay data.

Results

Time- and concentration-dependent antiproliferative effect of empagliflozin on Mia PaCa-2 cells

The antiproliferative effect of empagliflozin on Mia PaCa-2 was assessed at 24, 48, and 72 hours using the MTT assay. Cell viability decreased in a concentration- and time-dependent manner across all tested concentrations. Representative phase-contrast images of Mia PaCa-2 cells treated with increasing concentrations of empagliflozin are shown in Figure 1. The images illustrate a clear reduction in cell density and morphological changes, particularly at higher concentrations, confirming the cytotoxic effect of the compound.

At 24 hours, treatment with 20, 10, 5, and 2 μ M empagliflozin significantly reduced cell viability compared to control (100%), with survival rates of 71.5%, 77.9%, 82.4%, and 87.7%, respectively. Tukey's multiple comparisons test indicated significant differences for 20 μ M ($p<0.0001$), 10 μ M ($p = 0.0009$), 5 μ M ($p=0.0054$), and 2 μ M ($p=0.0285$), while lower concentrations (0.5 and 0.1 μ M) were not statistically significant (89.9% and 92.3%, $p>0.05$) (Figure 2a). After 48 hours, cell viability further decreased in a dose-dependent manner, with 57.7%, 64.1%, 68.8%, 75.0%, and 79.9% survival for 20, 10, 5, 2, and 0.5 μ M, respectively. The 0.1 μ M group showed a slight non-significant reduction (82.0%, $p=0.0546$). Significant differences compared to control were observed for 20 μ M ($p<0.0001$), 10 μ M ($p=0.0002$), 5 μ M ($p=0.0014$), 2 μ M ($p=0.0073$), and 0.5 μ M ($p=0.0297$) (Figure 2b). At 72 hours, empagliflozin exhibited the strongest

inhibitory effect, reducing viability to 37.4%, 46.2%, 51.4%, 54.3%, 62.3%, and 71.2% at 20, 10, 5, 2, 0.5, and 0.1 μ M, respectively. All concentrations showed statistically significant reductions compared to control ($p<0.0001$). Higher doses significantly suppressed cell proliferation compared to lower concentrations (e.g., 20 μ M vs 0.1 μ M, $p<0.0001$) (Figure 2c).

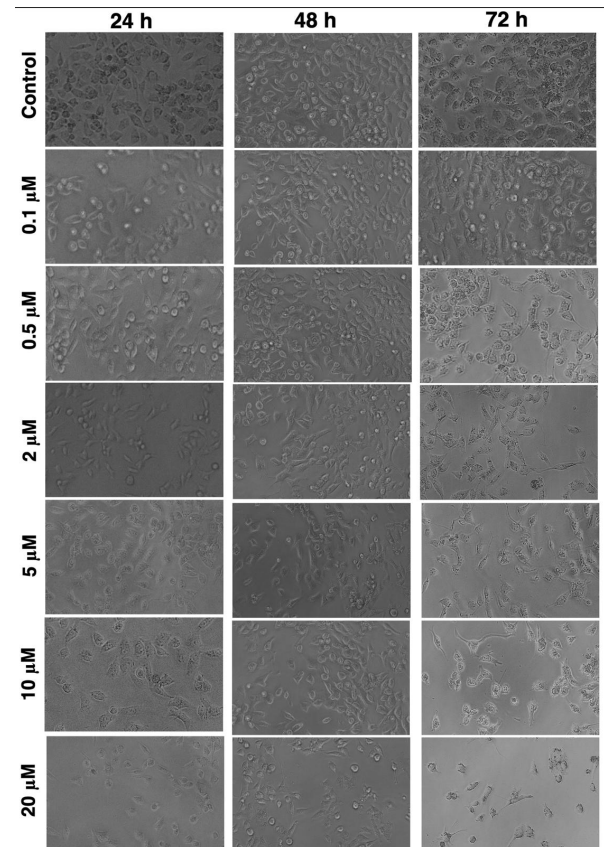


Figure 1. Time- and concentration-dependent morphological changes of Mia PaCa-2 cells upon empagliflozin treatment. Phase-contrast images show cells treated with empagliflozin at concentrations 0.1, 0.5, 2, 5, 10, and 20 μ M for 24 h, 48 h, and 72 h. Progressive reduction in cell density, cell rounding, and detachment are observed with increasing concentration and time (Scale bar, 100 μ m).

To further characterize the antiproliferative potency of empagliflozin, dose-response curves were generated, and the half-maximal inhibitory concentration (IC_{50}) was calculated. As shown in (Figure 3), empagliflozin produced a clear concentration-dependent decrease in cell viability at all evaluated time points. However, at 24 and 48 hours, cell viability remained above the 50% threshold across the tested concentration range (0.1–20 μ M), preventing reliable IC_{50} determination at these time points. In contrast, after 72 hours of treatment, cell viability fell below 50% at higher concentrations, enabling calculation of the IC_{50} value. The estimated IC_{50} for empagliflozin in Mia PaCa-2 cells at 72 hours was approximately 6.03 μ M, indicating that prolonged exposure markedly enhances its antiproliferative

activity. These findings further support the time-dependent cytotoxic effect of empagliflozin, with maximal inhibition observed after extended treatment durations. These results are consistent with growing evidence suggesting that SGLT2 inhibitors may possess antitumor properties beyond their established antidiabetic effects.

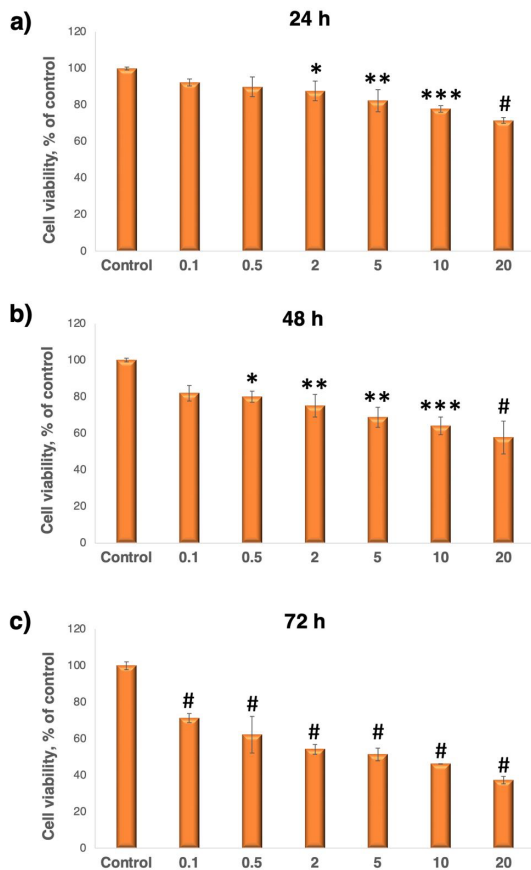


Figure 2. Time- and concentration-dependent antiproliferative effect of empagliflozin on Mia PaCa-2 cells assessed by MTT assay. Cell viability is shown for 24 h (a), 48 h (b), and 72 h (c) after treatment with 0.1–20 µM empagliflozin. Data represent mean ± SD of three independent experiments. Significant differences versus control are indicated as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and # $p < 0.0001$.

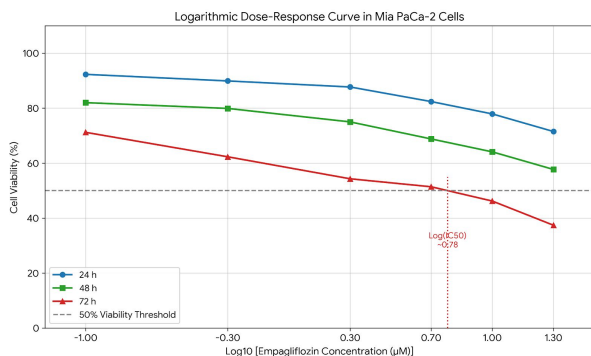


Figure 3. Logarithmic dose-response curve and IC₅₀ determination of empagliflozin-induced cytotoxicity in Mia

PaCa-2 pancreatic cancer cells. Cells were treated with increasing concentrations of empagliflozin (0.1, 0.5, 2, 5, 10, and 20 µM) for 24, 48, and 72 hours, and cell viability was evaluated using the MTT assay. The X-axis represents the log₁₀-transformed concentrations of empagliflozin, and the Y-axis displays the percentage of cell viability relative to the untreated control group (set to 100%). The gray dashed horizontal line indicates the 50% cell viability threshold. The red dotted vertical line denotes the calculated half-maximal inhibitory concentration (IC₅₀) for the 72-hour treatment period, which was determined to be approximately 6.03 µM (Log IC₅₀ ≈ 0.78). Data are presented as the mean ± SD of three independent experiments.

These results demonstrate a clear time- and concentration-dependent antiproliferative effect of empagliflozin on Mia PaCa-2 cells, with higher concentrations and longer exposure resulting in greater cytotoxicity. Even the lowest concentration (0.1 µM) significantly inhibited proliferation at 72 hours, highlighting the compound's potent effect over time.

Discussion

The present study demonstrates that empagliflozin exerts a significant antiproliferative effect on Mia PaCa-2 pancreatic cancer cells in a time and concentration-dependent manner. Cell viability progressively decreased following treatment with increasing concentrations of empagliflozin, with the strongest inhibitory effect observed after 72 hours of exposure. Morphological observations further confirmed these findings, revealing reduced cell density, cell rounding, and detachment in treated cultures. Together, these results indicate that empagliflozin interferes with the proliferative capacity of pancreatic cancer cells and may exert cytotoxic effects under prolonged exposure conditions.

Recent studies have increasingly suggested that sodium-glucose co transporter-2 (SGLT2) inhibitors possess anticancer properties beyond their well-established antidiabetic effects. SGLT2 expression has been identified in several tumor types, including pancreatic, prostate, lung, and breast cancers, indicating that these transporters may contribute to tumor cell metabolic adaptation and survival. Inhibition of SGLT2 activity has therefore emerged as a promising strategy to disrupt glucose uptake and energy metabolism in rapidly proliferating cancer cells. Empagliflozin and other SGLT2 inhibitors have been shown to reduce tumor cell proliferation, migration, and survival by interfering with glucose transport and intracellular energy production pathways.^{6,13} The antiproliferative effects observed in the present study are consistent with these reports and further support the hypothesis that SGLT2 inhibition may represent a promising metabolic-targeted strategy in cancer therapy.

The metabolic dependency of pancreatic cancer cells on glucose utilization may partially explain the inhibitory effects observed in this study. Pancreatic ductal adenocarcinoma is characterized by profound metabolic reprogramming and increased glucose consumption to sustain rapid cell growth. Therefore, pharmacological interventions that interfere with glucose transport and energy metabolism may significantly impair tumor cell survival. SGLT2 inhibitors have been reported to reduce intracellular glucose uptake and ATP production, thereby inducing metabolic stress in cancer cells and limiting their proliferative potential.⁸ In addition, activation of AMP-activated protein kinase (AMPK) and subsequent inhibition of the mTOR signaling pathway have been proposed as key mechanisms contributing to growth suppression and apoptosis following SGLT2 inhibition. Activation of AMPK has also been reported to suppress tumor development by promoting a catabolic cellular state and limiting anabolic processes required for cancer cell growth and proliferation.¹⁴ These signaling pathways are closely associated with cell cycle regulation and tumor cell metabolism, suggesting that empagliflozin may exert its antiproliferative effects through metabolic and signaling alterations.

Importantly, SGLT2 expression has also been demonstrated in pancreatic cancer tissues. A landmark study by Scafoglio et al. showed that pancreatic tumors can actively utilize SGLT2 for glucose uptake, suggesting that SGLT2 inhibitors may directly interfere with tumor metabolism.¹⁴ This finding provides strong biological support for targeting glucose transporters as a therapeutic strategy in pancreatic cancer.

Although studies specifically evaluating empagliflozin in pancreatic cancer cell lines remain limited, increasing evidence suggests that SGLT2 inhibitors exhibit antiproliferative activity in pancreatic cancer models. Preclinical studies have demonstrated that SGLT2 inhibition can suppress tumor growth by reducing glucose uptake and altering cancer cell energy metabolism, leading to metabolic stress and inhibition of cancer cell proliferation.¹⁰ Consistent with these findings, our results showed that empagliflozin significantly decreased the viability of Mia PaCa-2 cells in a time- and concentration-dependent manner. Experimental studies using SGLT2 inhibitors such as dapagliflozin and canagliflozin in pancreatic cancer cell lines including PANC-1 and AsPC-1 have demonstrated reduced cell viability and induction of apoptosis.¹⁶ Consistent with these findings, our results showed that empagliflozin significantly decreased the viability of Mia PaCa-2 cells in a time- and concentration-dependent manner. In particular, the antiproliferative effect became more pronounced with longer exposure times, with the strongest inhibition observed after 72 hours of treatment. These findings support the hypothesis that

SGLT2 inhibition may impair pancreatic cancer cell proliferation through metabolic targeting.

Similar antiproliferative effects of SGLT2 inhibition have also been reported in other pancreatic cancer models. For example, canagliflozin (CANA), another SGLT2 inhibitor, has been shown to suppress the proliferation of pancreatic cancer cell lines such as Capan-1 and PANC-1. In that study, treatment with CANA for 48 hours resulted in dose-dependent reductions in cell viability, with peak inhibition rates of approximately 54.3% and 57.6% in Capan-1 and PANC-1 cells, respectively.¹⁷ These findings are comparable to the results observed in the present study, where empagliflozin significantly reduced the viability of Mia PaCa-2 cells in a time- and concentration-dependent manner, with the strongest inhibitory effect observed after 72 hours of treatment. Although different pancreatic cancer cell lines were used, the comparable inhibition patterns suggest that SGLT2 inhibitors may exert consistent antiproliferative effects across various pancreatic cancer models.

Ren et al. demonstrated that pharmacological inhibition of SGLT2 significantly suppressed the proliferation of pancreatic cancer cells in PANC-1 and BxPC-3 cell lines, with increasing concentrations producing stronger inhibitory effects. The study also showed that the growth-inhibitory activity of SGLT2 inhibition became more pronounced with prolonged treatment.¹⁸ Consistent with these findings, our results demonstrated that empagliflozin significantly reduced the viability of Mia PaCa-2 cells in a concentration- and time-dependent manner. In our experiments, the antiproliferative effect became progressively stronger from 24 to 72 hours, with the most pronounced inhibition observed after 72 hours of treatment. These findings suggest that SGLT2 inhibition may exert consistent growth-suppressive effects across different pancreatic cancer cell lines.

Similar findings have been reported in other studies using SGLT2 inhibitors in pancreatic cancer models. In MIA-PaCa-2 cells, canagliflozin was reported to exert a measurable antiproliferative effect after 48 h of treatment, particularly at 100 µg/mL.¹⁹ In line with this observation, our study showed that empagliflozin also suppressed MIA-PaCa-2 cell viability in a time- and concentration-dependent manner. While significant inhibition in our model became evident from 2–20 µM at 24 h and from 0.5–20 µM at 48 h, the most pronounced effect was observed at 72 h, when 20 µM empagliflozin reduced cell viability to about 37.4% of control. These findings showed that different SGLT2 inhibitors may exert comparable antiproliferative effects in MIA-PaCa-2 cells, although the magnitude and timing of response may vary depending on the compound and concentration used.

Importantly, our results indicate that the cytotoxic effect of empagliflozin becomes more pronounced with

longer exposure times, as IC₅₀ could only be determined at 72 hours but not at earlier time points. This observation suggests that empagliflozin may exert its antitumor activity through gradual metabolic stress and signaling modulation rather than rapid cytotoxicity. Similar time-dependent antiproliferative effects have been reported for other metabolic inhibitors targeting cancer cell energy homeostasis.²⁰ Collectively, these findings highlight the potential of empagliflozin as a repurposed metabolic drug with anticancer activity, although further mechanistic and in vivo studies are required to clarify its therapeutic relevance in pancreatic cancer.

Although the present study demonstrates a clear antiproliferative effect of empagliflozin on Mia PaCa-2 pancreatic cancer cells in vitro, several limitations of the study should be acknowledged. First, the experiments were performed using a single pancreatic cancer cell line, which may not fully represent the biological heterogeneity of pancreatic tumors. Second, the study did not include a non-tumoral pancreatic epithelial cell line as a control, which limits the evaluation of the selectivity of the observed antiproliferative effects toward cancer cells. In addition, the cellular response was primarily assessed using the MTT assay together with morphological observations, and therefore further validation using complementary assays evaluating apoptosis, cell cycle distribution, and molecular signaling pathways would provide a more comprehensive understanding of the underlying mechanisms.

In addition, to better assess the translational relevance of our findings, additional studies in more physiologically relevant models are needed. Planned experiments include in vivo xenograft models using MIA PaCa-2 tumors in immunodeficient mice, which will allow evaluation of tumor growth inhibition, histopathological changes and potential molecular mechanisms under physiological conditions. Such in vivo validation will be essential to clarify the therapeutic potential of empagliflozin as a repurposed metabolic drug for pancreatic cancer treatment.

Taken together, our findings provide preliminary in vitro evidence suggesting that empagliflozin may exert antiproliferative effects in pancreatic cancer cells.

In conclusion, the present study demonstrates that empagliflozin exerts a significant time- and concentration-dependent antiproliferative effect on Mia PaCa-2 pancreatic cancer cells. Prolonged exposure markedly reduced cell viability, with an IC₅₀ value of approximately 6.03 μM at 72 hours, indicating enhanced cytotoxic activity over time. These findings suggest that empagliflozin may interfere with pancreatic cancer cell proliferation through mechanisms related to metabolic regulation. Although further mechanistic and in vivo studies are required, our results highlight the potential of empagliflozin as a

promising candidate for drug repurposing in pancreatic cancer therapy.

Author Contributions

CY, NK, SY, FBA; conceptualization, CY, NK, FBA; methodology, data curation, NK, SY; software, CY, NK, ND, SY; investigation, CY, NK, ND, FBA; resources, CY, NK; writing—original draft preparation, SH, FBA; writing—review and editing, SY; supervision, CY; project administration. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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