

Repurposing antidiabetic medications for cervical cancer therapy: a preclinical comparison of teneligliptin, rosiglitazone, and metformin

Rawaa Mohammed Obaid ¹

¹Department of Biology, College of Education for Pure Science, Tikrit University, Tikrit, Iraq

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Corresponding author

Rawaa Mohammed Obaid
rawamuhammad@tu.edu.iq

ABSTRACT

Repurposing existing medications is a valuable strategy for identifying new anticancer agents. Antidiabetic medications may exhibit promising anticancer properties. This study explored the anticancer properties of three antidiabetic medications, teneligliptin, metformin, and rosiglitazone, and compared their anticancer activity and selective toxicity against cancer cells. The MTT assay was used to evaluate the anticancer activity and cytotoxic safety of teneligliptin, metformin, and rosiglitazone using the HeLa cancer cell line, derived from human cervical cancer, and human-derived adipose tissue (NHF) cell lines. Incubation periods were 24 and 72 h, with concentrations ranging from 0.1 to 1000 µg/mL. Vincristine was included for comparison. The selectivity index was estimated to assess the selective toxicity of these medications against cancer cells. The MTT assay revealed that these antidiabetic medications exhibited anticancer effects characterized by inhibition patterns that varied according to concentration and incubation duration. Rosiglitazone and teneligliptin showed superior activity compared with metformin. There was no significant difference in growth inhibition between the antidiabetic medications and vincristine chemotherapy at most concentrations, particularly at higher concentrations after 72 h of incubation. Regarding cytotoxic safety, the three antidiabetic medications, especially teneligliptin, followed by rosiglitazone and metformin, demonstrated selectivity in targeting cancer cells, as indicated by a higher selectivity index that increased with longer incubation. In contrast, vincristine showed low selective toxicity, especially after 72 h, with a lower selectivity index. The three antidiabetic medications, particularly rosiglitazone and teneligliptin, may represent promising candidates for anticancer drug repositioning strategies against cervical cancer, mainly because of their established pharmacokinetic properties and safety profiles.

Keywords: *HeLa cell line, metformin, NHF cell line, rosiglitazone, Teneligliptin*

1 INTRODUCTION

Cervical cancer is a major global health burden, largely caused by persistent infection with high-risk human papillomavirus (HPV) types, particularly HPV-16 and HPV-18, which account for nearly 70% of cases [1, 2]. The disease develops through the gradual progression of precancerous cervical intraepithelial neoplasia into malignancy [3, 4]. Globally, it is the fourth most common cancer among women, with 604,000 new cases and 342,000 deaths reported in 2020 [5, 6]. Key risk

factors include early sexual activity, multiple partners, immunosuppression, and smoking [7, 8]. Treatment strategies depend on the stage of disease, ranging from surgical options such as conization or hysterectomy in early stages to chemoradiotherapy in advanced cases [9, 10]. Although HPV vaccination has reduced incidence rates in several countries, Pap smears and HPV testing remain critical for early detection [11–13]. Chemotherapy, especially cisplatin-based regimens, plays a central role in advanced or metastatic cervical cancer [14]. Concurrent

chemoradiation with cisplatin improves survival in locally advanced cases [15], and bevacizumab has shown benefits in recurrent disease [16]. However, platinum-based therapies are associated with nephrotoxicity, neurotoxicity, myelosuppression, and gastrointestinal complications, alongside drug resistance and poor efficacy in hypoxic tumor microenvironments [17–20]. Monoclonal antibodies (mAbs) have introduced targeted treatment opportunities but face limitations, including high production costs, limited tumor penetration, resistance mechanisms, and organ-specific toxicities such as trastuzumab-induced cardiotoxicity [21–23]. These drawbacks highlight the need for alternative therapeutic approaches.

Drug repurposing, particularly with antidiabetic medications, has emerged as a promising strategy. Rosiglitazone, a PPAR γ agonist, demonstrates anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic effects in cervical cancer [24–28]. Metformin, a widely prescribed biguanide, reduces cancer incidence, inhibits the mTOR pathway, induces apoptosis, and counteracts HPV oncogene activity [29–35]. Teneligliptin, a DPP-4 inhibitor, shows antiproliferative, pro-apoptotic, and anti-inflammatory properties through modulation of the PI3K/AKT/mTOR pathway and cytokine signaling [25, 36–39]. Beyond cervical cancer, these drugs display broad-spectrum anticancer activity in breast, ovarian, prostate, lung, colon, liver, and pancreatic cancers [24, 38, 40–44]. Despite extensive studies, comparative evaluation of their anticancer impacts in cervical cancer and their selective toxicity toward malignant cells remains limited. This study aims to address these gaps.

2 MATERIALS AND METHODS

2.1 Medications

Teneligliptin, metformin, rosiglitazone, and vinblastine were sourced as raw materials from the Samarra Pharmaceutical Factory, Iraq. They were serially diluted in MEM medium to obtain concentrations ranging from 0.1 to 1000 $\mu\text{g/ml}$.

2.2 Cytotoxicity assay

Cytotoxicity was assessed in the HeLa cell line to evaluate the anticancer effectiveness of Teneligliptin, metformin, rosiglitazone, and vinblastine. The cytotoxic effects of these Medications were also analyzed on the NHF cell line, which represents normal, healthy cells. The viability of both cancerous and healthy cells was measured over a range of concentrations from 0.1 to 1000

$\mu\text{g/ml}$.

The following cell lines were used:

1. HeLa cell line, derived from human cervical cancer cells [45, 46].
2. NHF cell line, derived from normal human adipose tissue [47].

2.3 Cell culture conditions

The cell lines were cultured in MEM medium (US Biological, USA), supplemented with 10% (v/v) fetal bovine serum (FBS) (Capricorn-Scientific, Germany). To reduce bacterial contamination, the medium contained 100 IU/mL penicillin and 100 $\mu\text{g/mL}$ streptomycin (Capricorn-Scientific, Germany). Cells were maintained in a humidified incubator at 37°C, and all experiments were conducted when the cellular population was in the exponential growth phase [40].

2.4 MTT assay

The MTT colorimetric assay evaluates cell viability by examining the impacts of antidiabetic and chemotherapy agents. In this approach, viable cells transform the yellow MTT tetrazolium salt into purple formazan crystals, aided by mitochondrial dehydrogenase enzymes. The procedure consists of culturing cells in 96-well plates and applying various concentrations of test compounds. After an appropriate incubation time, the MTT reagent is introduced to each well for additional incubation. Only metabolically active living cells can convert MTT into the insoluble purple formazan product. After the crystals dissolve, the solution's absorbance is measured spectrophotometrically at a specified wavelength, enabling a quantitative evaluation of cell viability.

The viable cell count directly impacts formazan production. A decrease in formazan levels following treatment with the test chemical indicates cytotoxicity, which influences absorbance. The dose-response curve is essential for identifying the half-maximal inhibitory concentration (IC₅₀) [41].

Cells were seeded into 96-well microplates at a density of 10,000 cells per well and incubated at 37°C for 24 hours to achieve confluence. During the two incubation periods of 24 and 72 hours, the cytotoxicity of the tested compounds was evaluated using the MTT assay, with concentrations spanning from 0.1 to 1000 $\mu\text{g/ml}$ and six replicates for each concentration. A total of 20 untreated wells acted as negative controls.

After 24 and 72 hours of treatment, each well received 28 μ L of MTT solution (2 mg/mL) and was incubated for 3 hours. Following this, formazan crystals were dissolved with 100 μ L of DMSO over a 15-minute incubation

period. The absorbance at 570 nm was recorded using a microplate reader. Cytotoxicity percentages were calculated using the following formula [42].

$$\text{Growth inhibition \%} = \frac{\text{optical density of control wells} - \text{optical density of treated wells}}{\text{optical density of control wells}} * 100\%$$

2.5 Selective toxicity index

The selective toxicity index evaluated the effectiveness of antidiabetic and chemotherapy agents against cancer cells during 24- and 72-hour incubation periods. After determining the IC₅₀ levels for the tested agents, the selective cytotoxicity index was calculated using a mathematical equation based on cell growth curves for each HeLa and NHF cell line [43].

$$\text{Selective toxicity Index (SI)} = \frac{\text{IC}_{50} \text{ of normal cell lines}}{\text{IC}_{50} \text{ of cancer cell lines}}$$

An SI score above 1.0 suggests that a drug is more effective at targeting cancer cells than normal cells. The IC₅₀ level estimation was conducted using GraphPad Prism 9.5.0.

2.6 Ethical approval

This study utilized only in vitro cell line models, without involving human participants or laboratory animals. Nevertheless, all methods adhered to the ethical guidelines established by the institution for laboratory research.

2.7 Statistical analysis

Cytotoxicity results are presented as mean $\pm$ standard deviation (SD). Intergroup variability was assessed using one-way analysis of variance (ANOVA), followed by post-hoc pairwise comparisons using the least significant difference (LSD) test. For direct group comparisons, paired t-tests were used. All analyses were performed using SPSS version 20, with statistical significance set at $p < 0.05$ [48].

To enhance data interpretation, a letter-coding system was used in the tables. Groups denoted by the same letter represent statistically similar

means, whereas different letters indicate significant differences ($p < 0.05$) between groups. Capital letters were used to compare means within each column, and lowercase letters were used to compare means across each row. This visual method enables rapid comparison across multiple groups, minimizes the need for repetitive statistical annotations, and maintains rigor while improving readability.

3 RESULTS

3.1 Teneligliptin cytotoxicity

The cytotoxic effect of teneligliptin on the viability of cervical cancer cell lines demonstrated its ability to reduce cell viability, particularly after longer incubation periods. The decrease in the IC value supports this effect, indicating that growth inhibition occurred in a time-dependent manner. Furthermore, higher teneligliptin concentrations produced a stronger inhibitory response, suggesting a concentration-dependent mechanism of action. Regarding the effect of teneligliptin on the NHF cell line, the results showed a lower inhibitory effect compared with its effect on cancer cell growth. However, growth inhibition was concentration-dependent, with no apparent effect of incubation time on growth inhibition, Table 1.

3.2 Metformin cytotoxicity

The cytotoxic impact of Metformin on the viability of cervical cancer cell lines demonstrates its capacity to reduce cellular viability, particularly at higher concentrations and longer incubation periods. This suggests that growth inhibition occurs in a

Table 1 Impact of Teneligliptin on the survival of HeLa and NHF cells at 24 and 72 hours

Concentration ($\mu\text{g/mL}$)	Cellular growth suppression (mean $\pm$ SD)					
	HeLa cell line			NHF cell line		
	24 h	72 h	P value	24 h	72 h	P value
0.1	C 3.00 $\pm$ 2.000	C 28.00 $\pm$ 3.000	0.0001*	C 0.00 $\pm$ 0.000	B 0.00 $\pm$ 0.000	N.S.
1	C 8.00 $\pm$ 1.000	C 34.00 $\pm$ 4.000	0.0001*	C 0.00 $\pm$ 0.000	B 1.00 $\pm$ 1.000	0.158
10	B 21.00 $\pm$ 1.000	B 44.00 $\pm$ 4.000	0.0001*	BC 2.00 $\pm$ 1.000	AB 4.00 $\pm$ 2.000	0.196
100	A 35.00 $\pm$ 5.000	AB 51.00 $\pm$ 1.000	0.006*	B 5.00 $\pm$ 1.000	A 9.00 $\pm$ 4.000	0.168
1000	A 40.00 $\pm$ 1.000	A 55.00 $\pm$ 2.000	0.0001*	A 9.00 $\pm$ 2.000	A 11.00 $\pm$ 1.000	0.196
LSD value	9.2	9.48	0-	3.98	7.64	-
IC ₅₀	> 1000 $\mu\text{g/mL}$	85.7 $\mu\text{g/mL}$	-	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	-

Note. *Significant at $P < 0.05$.

manner dependent on both concentration and duration. Regarding its effect on the NHF cell line, the results indicated a less inhibitory impact compared to its effect on cancer cell growth. However, growth inhibition exhibited a concentration- and time-dependent characteristic pattern, Table 2.

Table 2 Impact of Metformin on the survival of HeLa and NHF cells at 24 and 72 hours

Concentration ($\mu\text{g/mL}$)	Cellular growth suppression (mean $\pm$ SD)					
	HeLa cell line			NHF cell line		
	24 h	72 h	P value	24 h	72 h	P value
0.1	C 1.00 $\pm$ 1.000	D 3.00 $\pm$ 1.000	0.070	C 1.00 $\pm$ 1.000	C 2.00 $\pm$ 2.000	0.482
1	C 3.00 $\pm$ 2.000	C 11.00 $\pm$ 1.000	0.003*	BC 4.00 $\pm$ 1.000	BC 6.00 $\pm$ 4.000	0.448
10	C 7.00 $\pm$ 2.000	BC 26.00 $\pm$ 2.000	0.0001*	ABC 7.00 $\pm$ 2.000	ABC 11.00 $\pm$ 1.000	0.036*
100	B 23.00 $\pm$ 3.000	B 30.00 $\pm$ 2.000	0.028*	AB 10.00 $\pm$ 3.000	AB 14.00 $\pm$ 4.000	0.238
1000	A 35.00 $\pm$ 2.000	A 47.00 $\pm$ 2.000	0.002*	A 13.00 $\pm$ 3.000	A 21.00 $\pm$ 1.000	0.012*
LSD value	7.64	6.08	-	7.98	10.04	-
IC ₅₀	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	-	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	-

Note. *Significant at $P < 0.05$.

3.3 Rosiglitazone cytotoxicity

The cytotoxic effect of Rosiglitazone on cervical cancer cell lines illustrates its capacity to reduce cellular viability, particularly at higher concentrations of Rosiglitazone and longer incubation periods. A decrease in the IC₅₀ value emphasizes the importance of time. While it affected the NHF cell line, its inhibitory effect was less pronounced compared to its impact on cervical cancer growth, displaying a growth inhibition pattern that depends on concentration and time, Table 3.

Table 3 Impact of Rosiglitazone on the survival of HeLa and NHF cells at 24 and 72 hours

Concentration ($\mu\text{g/mL}$)	Cellular growth suppression (mean $\pm$ SD)					
	HeLa cell line			NHF cell line		
	24 h	72 h	P value	24 h	72 h	P value
0.1	D 5.00 $\pm$ 1.000	D 7.00 $\pm$ 2.000	0.196	B 0.00 $\pm$ 0.000	C 1.00 $\pm$ 1.000	0.158
1	CD 9.00 $\pm$ 5.000	D 14.00 $\pm$ 4.000	0.248	B 1.00 $\pm$ 1.000	C 3.00 $\pm$ 2.000	0.196
10	BC 17.00 $\pm$ 2.000	C 32.00 $\pm$ 2.000	0.001*	B 3.00 $\pm$ 1.000	BC 7.00 $\pm$ 2.000	0.036*
100	AB 23.00 $\pm$ 2.000	B 47.00 $\pm$ 2.000	0.0001*	A 7.00 $\pm$ 1.000	AB 11.00 $\pm$ 1.000	0.008*
1000	A 31.00 $\pm$ 1.000	A 61.00 $\pm$ 1.000	0.0001*	A 10.00 $\pm$ 1.000	A 14.00 $\pm$ 2.000	0.036*
LSD value	9.68	8.76	-	3.26	6.08	-
IC ₅₀	> 1000 $\mu\text{g/mL}$	214.2 $\mu\text{g/mL}$	-	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	-

Note. *Significant at $P < 0.05$.

3.4 Vincristine cytotoxicity

Vincristine was chosen as a positive control for comparison purposes. Its cytotoxicity showed that it could effectively inhibit the growth of both HeLa and NHF cell lines, with the effect depending on the concentration and exposure time. The IC₅₀ value was lower at 72 hours compared to 24 hours of incubation, demonstrating a time-dependent inhibitory effect on each cell line, Table 4.

Table 4 Impact of Vincristine on the survival of HeLa and NHF cells at 24 and 72 hours

Concentration ($\mu\text{g/mL}$)	Cellular growth suppression (mean $\pm$ SD)					
	HeLa cell line			NHF cell line		
	24 h	72 h	P value	24 h	72 h	P value
0.1	C 10.00 $\pm$ 1.000	C 21.00 $\pm$ 2.000	0.001*	D 3.00 $\pm$ 2.000	D 11.00 $\pm$ 1.000	0.003*
1	B 19.00 $\pm$ 4.000	B 37.00 $\pm$ 2.000	0.002*	C 12.00 $\pm$ 2.000	C 23.00 $\pm$ 3.000	0.006*
10	B 20.00 $\pm$ 2.000	AB 42.00 $\pm$ 2.000	0.0001*	B 20.00 $\pm$ 1.000	C 30.00 $\pm$ 3.000	0.005*
100	AB 25.00 $\pm$ 2.000	AB 44.00 $\pm$ 4.000	0.002*	A 43.00 $\pm$ 3.000	B 51.00 $\pm$ 1.000	0.012*
1000	A 38.00 $\pm$ 1.000	A 50.00 $\pm$ 3.000	0.003*	A 49.00 $\pm$ 1.000	A 62.00 $\pm$ 2.000	0.001*
LSD value	8.3	9.9	-	7.1	7.98	-
IC ₅₀	> 1000 $\mu\text{g/mL}$	949.4 $\mu\text{g/mL}$	-	> 1000 $\mu\text{g/mL}$	95.2 $\mu\text{g/mL}$	-

Note. *Significant at $P < 0.05$.

3.5 Comparison of cytotoxicity between antidiabetic medications and chemotherapy

A comparison was conducted between the antidiabetic medications and vincristine to evaluate their anticancer effects relative to those of vincristine. After 24 h of incubation, the results revealed that teneligliptin exhibited the strongest anticancer effect among the tested antidiabetic medications, followed by metformin and rosiglitazone. No significant difference in growth inhibition was observed between vincristine and the three antidiabetic medications at most concentrations, especially at higher concentrations. Furthermore, after 72 h of incubation, particularly at higher concentrations, the results showed that rosiglitazone exhibited a significant anticancer effect

among the tested antidiabetic medications compared with the growth inhibition caused by vincristine. This was followed by teneligliptin and metformin, which showed no significant difference compared with vincristine, Tables 5 and 6.

Table 5 Comparison of the growth inhibition of Teneligliptin, Metformin, Rosiglitazone, and Vincristine on the HeLa cancer cell line after a 24-hour incubation period

Concentration ($\mu\text{g/mL}$)	Cellular growth suppression (mean $\pm$ SD)				
	Teneligliptin	Metformin	Rosiglitazone	Vincristine	LSD value
0.1	C 3.00 $\pm$ 2.000 b	C 1.00 $\pm$ 1.000 b	D 5.00 $\pm$ 1.000 b	C 10.00 $\pm$ 1.000 a	4.98
1	C 8.00 $\pm$ 1.000 ab	C 3.00 $\pm$ 2.000 b	CD 9.00 $\pm$ 5.000 ab	B 19.00 $\pm$ 4.000 a	12.78
10	B 21.00 $\pm$ 1.000 a	C 7.00 $\pm$ 2.000 b	BC 17.00 $\pm$ 2.000 a	B 20.00 $\pm$ 2.000 a	6.78
100	A 35.00 $\pm$ 5.000 a	B 23.00 $\pm$ 3.000 b	AB 23.00 $\pm$ 2.000 b	AB 25.00 $\pm$ 2.000 a	11.95
1000	A 40.00 $\pm$ 1.000 a	A 35.00 $\pm$ 2.000 b	A 31.00 $\pm$ 1.000 b	A 38.00 $\pm$ 1.000 ab	4.98
LSD value	9.2	7.64	9.68	8.3	—
IC ₅₀	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	—

Note. *Significant at $P < 0.05$.

Table 6 Comparison of the growth inhibition of Teneligliptin, Metformin, Rosiglitazone, and Vincristine on the HeLa cancer cell line after a 72-hour incubation period

Concentration ($\mu\text{g/mL}$)	Cellular growth suppression (mean $\pm$ SD)				
	Teneligliptin	Metformin	Rosiglitazone	Vincristine	LSD value
0.1	C 28.00 $\pm$ 3.000 a	D 3.00 $\pm$ 1.000 b	D 7.00 $\pm$ 2.000 b	C 21.00 $\pm$ 2.000 a	7.98
1	C 34.00 $\pm$ 4.000 a	C 11.00 $\pm$ 1.000 b	D 14.00 $\pm$ 4.000 b	B 37.00 $\pm$ 2.000 a	11.46
10	B 44.00 $\pm$ 4.000 a	BC 26.00 $\pm$ 2.000 b	C 32.00 $\pm$ 2.000 b	AB 42.00 $\pm$ 2.000 a	7.54
100	AB 51.00 $\pm$ 1.000 a	B 30.00 $\pm$ 2.000 b	B 47.00 $\pm$ 2.000 a	AB 44.00 $\pm$ 4.000 a	9.42
1000	A 55.00 $\pm$ 2.000 ab	A 47.00 $\pm$ 2.000 c	A 61.00 $\pm$ 1.000 a	A 50.00 $\pm$ 3.000 bc	7.98
LSD value	9.48	6.08	8.76	9.9	—
IC ₅₀	85.7 $\mu\text{g/mL}$	> 1000 $\mu\text{g/mL}$	214.2 $\mu\text{g/mL}$	949.4 $\mu\text{g/mL}$	—

Note. *Significant at $P < 0.05$.

3.6 Selective toxicity index study

The SI score outcomes were as follows: after 24 hours, the SI score for Teneligliptin, Metformin, and Rosiglitazone was 1 for each drug. After 72 hours, the scores increased to 1.6, 1, and 4.6, respectively. Except for Metformin, these outcomes suggest that increasing the incubation time enhances the targeting ability of antidiabetic medications toward cancer cells. In comparison, the SI scores for vincristine were 1 and 0.10 after 24 and 72 hours of incubation, respectively, showing a decline in its selective toxicity as the incubation period progressed.

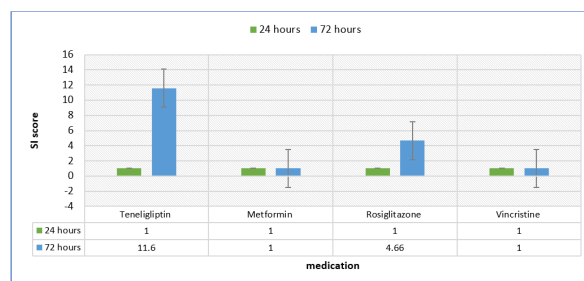


Fig. 1 Comparison of Teneligliptin, Metformin, Rosiglitazone, and Vincristine SI at 24 and 72 hours (An SI greater than 1.0 indicates that a drug is more effective against tumor cells compared to its toxicity towards normal cells)

3.7 Morphological observations of the study cell line:

Figure 2 shows the cellular morphological modification of cervical cancer after 72 hours of exposure to 1000 $\mu\text{g/mL}$ of Teneligliptin, Metformin, Rosiglitazone, and Vincristine.

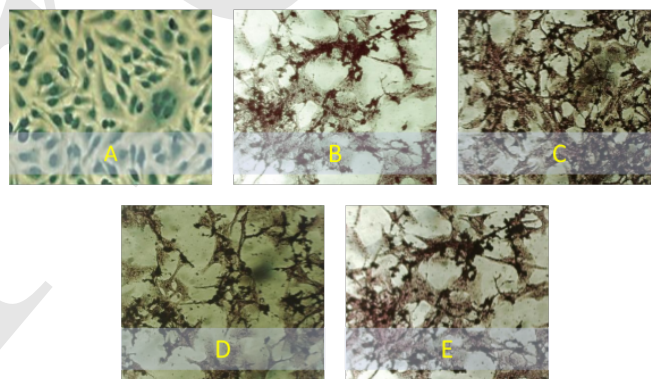


Fig. 2 Morphological characteristics of the HeLa cell line (400x)(A) Untreated HeLa cancer cell line. (B) HeLa cells treated with 1000 $\mu\text{g/mL}$ Rosiglitazone for 72 hours. (C) HeLa cells treated with 1000 $\mu\text{g/mL}$ Metformin for 72 hours. (D) HeLa cells treated with 1000 $\mu\text{g/mL}$ Teneligliptin for 72 hours. (E) HeLa cells treated with 1000 $\mu\text{g/mL}$ Vincristine for 72 hours

4 DISCUSSION

Repurposing non-cancer medications, especially antidiabetic drugs, offers a promising approach for developing alternative cancer treatments. This study presents a direct preclinical comparison of the cytotoxic effectiveness and selective toxicity of three such drugs, teneligliptin, metformin, and rosiglitazone,

against cervical cancer cells, an area with limited comparative data.

The key findings showed that all three drugs inhibited the growth of HeLa cells, with rosiglitazone and teneligliptin being more effective than metformin. Notably, the inhibition rate varied according to concentration and incubation duration, and the level of growth inhibition was similar to that of the standard chemotherapy drug vincristine at most concentrations. Particularly, the selectivity index (SI) analysis revealed that rosiglitazone and teneligliptin showed favorable selectivity toward cancer cells, in contrast to the low selective toxicity of vincristine, especially after longer incubation periods.

The distinct molecular mechanisms of these drugs may explain the observed differences in efficacy. The pronounced cytotoxicity of rosiglitazone, particularly after 72 h, corresponds with its role as a potent synthetic PPAR γ agonist. Previous evidence indicates that activation of PPAR γ induces G₁/S cell-cycle arrest in cervical cancer cells by downregulating cyclin D1 and upregulating p21 and p27 [24]. Furthermore, rosiglitazone exhibits pro-apoptotic activity through activation of caspase-3 and caspase-9 and inhibition of Bcl-2, which may have contributed to the considerable cell death observed at higher concentrations over time. Its antiangiogenic activity through VEGF reduction and modulation of the tumor microenvironment by reducing pro-inflammatory cytokines may also contribute to its potent and sustained effect, which ultimately exceeded that of vincristine at the highest concentration [25–28].

Similarly, teneligliptin exhibited time-dependent cytotoxicity and an increase in selectivity, with the SI increasing from 1.0 to 1.6, suggesting a progressive effect. As a DPP-4 inhibitor, its anticancer effects are increasingly associated with inhibition of the PI3K/AKT/mTOR pathway, which is often dysregulated in cervical cancer [25]. The observed enhancement in efficacy and selectivity after 72 h may be attributed to the cumulative effects of G₁/S phase arrest, mediated by cyclin D1 downregula-

tion and p21 upregulation, as well as promotion of apoptosis through caspase-3 activation and PARP cleavage [38]. Importantly, teneligliptin may also modulate the tumor microenvironment by reducing key pro-inflammatory cytokines, such as IL-6 and TNF- α [45].

Although metformin exhibited a clear concentration- and time-dependent cytotoxic effect, its overall potency was lower than that of rosiglitazone and teneligliptin in this model. This difference may be attributed to its primary mechanism of action, which involves AMPK activation and mTOR inhibition [30], and may function with different kinetics or require a different metabolic environment. Nevertheless, metformin has a confirmed role in inducing cell-cycle arrest in the G₀/G₁ phase and promoting apoptosis [31, 32]. These mechanisms support its observed anticancer activity, which is further strengthened by its reported ability to target HPV oncoproteins E6/E7 and restore p53 function [33, 35]. Furthermore, its antimetastatic effects are mediated by inhibition of epithelial-mesenchymal transition (EMT) [34, 35, 38].

The main finding of this study is the favorable cytotoxic selectivity of the evaluated antidiabetic agents, as indicated by their SI scores, in contrast to vincristine. Specifically, the SI of vincristine decreased markedly from 1.0 to 0.10 after 72 h, supporting its well-established non-selective cytotoxicity and pronounced toxicity toward normal cells. Conversely, the three antidiabetic drugs either maintained or increased their SI values. Notably, the SI of rosiglitazone increased to 4.6, and that of teneligliptin increased to 1.6, indicating higher toxicity toward cancer cells than normal cells. This enhanced selective toxicity represents an important advantage for drug repurposing, as it suggests a wider therapeutic window and the potential for reduced adverse effects compared with conventional chemotherapy.

This study has certain limitations, particularly the absence of laboratory validation using molecular assays to confirm activation or inhibition of the proposed pathways, including PPAR γ ,

PI3K/AKT/mTOR, and AMPK signaling. These investigations were beyond the scope of this preliminary comparative cytotoxicity screening, primarily because of financial constraints.

5 CONCLUSION

This study explored the potential repurposing of three antidiabetic medications, teneligliptin, metformin, and rosiglitazone, for cervical cancer treatment. All three agents demonstrated time- and concentration-dependent inhibitory effects on cancer cell growth, with possible mechanisms involving both cell-cycle-specific and non-specific pathways. Comparative analysis with vincristine revealed that the antidiabetic drugs achieved similar inhibition across most concentrations. Notably, rosiglitazone exhibited superior anticancer activity at higher concentrations after 72 h, highlighting its therapeutic potential in this context.

From a cytotoxic safety perspective, teneligliptin and rosiglitazone showed higher selectivity toward malignant cells compared with vincristine, suggesting a more favorable toxicity profile. This selective targeting is important for improving treatment outcomes while minimizing adverse effects, which remains a major challenge in conventional chemotherapy. Collectively, these findings highlight the potential of repurposed antidiabetic medications, especially rosiglitazone and teneligliptin, as promising candidates for further investigation as adjunctive or alternative approaches to existing therapies. Future clinical and preclinical studies should prioritize validating their efficacy, refining dosage strategies, and assessing long-term safety. Such efforts are essential to translate these preclinical findings into clinically applicable strategies and expand therapeutic options for patients with cervical cancer.

Author contributions

Rawaa Mohammed Obaid designed the study; conducted experiments, analyzed the data and wrote the manuscript.

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N/A

DECLARATIONS

Conflict of interest

The authors declare no competing interests

Consent to publish

N/A

Ethical approval

N/A

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