Research Article BEU Fen Bilimleri Dergisi 15(3): 1314-1322 (2026) DOI: 10.17798/bitlisfen.1896158

BİTLİS EREN UNIVERSITY
FEN BİLİMLERİ DERGİSİ
ISSN: 2147-3129 / e-ISSN: 2147-3188

COMBINED EFFECTS OF OXALIPLATIN AND TETRACAINE ON PROLIFERATION AND MIGRATION IN TRIPLE-NEGATIVE BREAST CANCER

Serife YERLIKAYA [1*], Nama Bınte SHAPAN [2], Zeynep Pelin GOV [2]

[1] *Istanbul Medipol University Research Institute for Health Sciences and Technologies, Istanbul, Türkiye*
[2] *Istanbul Medipol University, International Faculty of Medicine, Istanbul, Türkiye*
**** Corresponding Author: serife.yerlikaya@medipol.edu.tr***

Article Info

Received: *February 23, 2026*
Revised: *July 8, 2026*
Accepted: *July 9, 2026*

Keywords
Metastasis,
Combinatorial Therapy,
Triple Negative Breast Cancer,
Migration,
Proliferation.

ABSTRACT

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by the absence of estrogen, progesterone, and HER2 receptors, presenting significant challenges in treatment due to a lack of targeted therapies. This study investigates the combination effects of oxaliplatin, a platinum-based chemotherapeutic agent, and tetracaine, a sodium channel modulator, on the proliferation and migration of MDA-MB-231 cells, a highly metastatic TNBC cell line. We hypothesized that the combined application of these agents would enhance anti-proliferative and anti-migratory responses through mechanisms that may involve voltage-gated sodium channel-associated pathways linked to tumor invasion. Using cell viability assays, MTT assays, and wound healing assays, we determined the optimal non-toxic concentrations of oxaliplatin and tetracaine and evaluated their individual and combined effects on cell growth and migration. Our findings reveal that the combination treatment significantly reduces cell proliferation and migration compared to either agent alone, indicating a potential therapeutic strategy for TNBC through drug repurposing and combinatorial approaches. These findings provide a rationale for mechanistic dissection of Nav1.5-dependent signaling pathways and support subsequent in vivo validation of this combinatorial strategy in translational TNBC models.

1. INTRODUCTION

Breast cancer is recognized as the most commonly diagnosed cancer among women worldwide, making it a significant public health concern [1]. This disease is characterized by its diversity and hormone sensitivity, showcasing a broad spectrum of biological behaviors and responses to treatment [2]. Approximately 65–75% of breast cancer cases are classified as hormone receptor-positive (HR+), meaning they possess estrogen and/or progesterone receptors, which make them responsive to hormonal therapies [3]. In addition to this, about 15–20% of breast cancers are characterized by the overexpression of the HER2 protein, indicating a more aggressive form of the disease [4]. The remaining 15% of cases are categorized as triple-negative breast cancer (TNBC), which does not exhibit any of the three receptors—estrogen, progesterone, or HER2—rendering conventional hormonal or targeted therapies ineffective [5]. For those with HR+ and HER2+ breast cancers, there are various targeted treatment options available. These include hormonal therapies, such as tamoxifen and aromatase inhibitors, as well as biological therapies that specifically target HER2, like trastuzumab (Herceptin) [6]. These treatments are designed to inhibit the overactive signaling pathways and biological processes that drive tumor growth and progression.

License: CC BY-NC 4.0

In contrast, triple-negative breast cancer presents a more formidable challenge due to the absence of targeted therapies. Treatment for TNBC primarily hinges on chemotherapy, which, while effective in shrinking tumors initially, often faces complications such as resistance and frequent relapses [6,7]. This lack of effective targeted treatment options plays a significant role in the aggressive nature of TNBC and contributes to its overall poor prognosis, emphasizing the pressing need for ongoing research and development of more effective therapeutic strategies in this particularly difficult-to-treat subtype of breast cancer.

In our research, we selected oxaliplatin and tetracaine as the primary experimental agents to investigate the intricate relationship between chemotherapy and the modulation of ion channels in cancer cells. Oxaliplatin is a third-generation platinum compound that exerts its cytotoxic effects through the formation of DNA crosslinks. This mechanism disrupts the integrity of the cancer cell's genetic material, making oxaliplatin a critical component in the treatment of various solid tumors, including preclinical models of triple-negative breast cancer (TNBC) [8]. However, despite its effectiveness in combating malignancies, oxaliplatin is associated with a significant drawback: dose-dependent neurotoxicity. This adverse effect manifests particularly as peripheral neuropathy, which leads to sensory disturbances such as tingling, numbness, and pain. These symptoms can severely impact a patient's quality of life, highlighting the necessity for ongoing research into mitigating these side effects while improving therapeutic outcomes [9].

Voltage-gated sodium channels (VGSCs), and in particular the Nav1.5 subtype, play a significant role in the pathology of metastatic breast cancer. These channels are often found to be overexpressed in metastatic breast cancer cells, contributing critically to the processes of invasion and migration that are essential for cancer spread [10]. Among the various pharmacological agents tested for their effects on VGSCs, tetracaine—a long-acting local anesthetic—has been selected due to its well-documented inhibitory effects on these channels. Tetracaine is known to effectively suppress sodium currents, thereby influencing key cellular signaling pathways that govern cell proliferation and motility [11]. The accumulation of abnormal sodium levels within cancer cells has been linked to various physiological changes, including alterations in intracellular pH levels, increased cellular mobility, and, consequently, enhanced metastatic capabilities. This phenomenon is particularly evident in triple-negative breast cancer (TNBC) cells, where research utilizing patch-clamp electrophysiology techniques has demonstrated markedly elevated sodium current activity when compared with non-cancerous cells. Such findings highlight a significant association between VGSC activity and the metastatic behavior of cancer cells, further supporting the potential of targeting these channels as a therapeutic strategy [12].

Recent evidence suggests that both oxaliplatin and tetracaine may influence voltage-gated sodium channel (VGSC)-related pathways. Electrophysiological studies have shown that oxaliplatin can modulate sodium channel activity through calcium-dependent mechanisms associated with its oxalate metabolite [13], while tetracaine has been reported to suppress migration and invasiveness in several cancer models through VGSC inhibition [14]. Collectively, these findings provide a strong rationale for evaluating the combined effects of oxaliplatin and tetracaine in highly metastatic TNBC cells characterized by elevated VGSC activity.

This study sought to explore the effects of two pharmacological agents—oxaliplatin and tetracaine—on the viability and motility of MDA-MB-231 cells, which represent a highly metastatic cell line characteristic of triple-negative breast cancer (TNBC). These particular cells are noted for their high expression of the Nav1.5 sodium channel, a protein that plays a significant role in cellular processes related to metastasis. We hypothesized that oxaliplatin, a well-known chemotherapeutic drug, and tetracaine, a local anesthetic with potential cellular effects, would demonstrate complementary actions when administered either separately or in combination. Specifically, we anticipated that the combination could elicit more pronounced anti-proliferative and anti-migratory effects, potentially involving Nav1.5-related signaling pathways. The significance of this research lies in its potential to harness established treatments in innovative ways. Both oxaliplatin and tetracaine are well-documented and widely used in clinical settings, underscoring the feasibility of drug repurposing and combinatorial strategies in the fight against TNBC. This study not only highlights the promise of such approaches for enhancing treatment efficacy but also sets the stage for more in-depth mechanistic investigations and subsequent in vivo studies to validate our findings.

2. MATERIALS AND METHODS

2.1. Cell Culture Maintenance

Triple-negative and highly metastatic MDA-MB-231 breast cancer cells were cultured under controlled conditions in Dulbecco's Modified Eagle's Medium (DMEM). This culture medium was enriched with 10% fetal bovine serum (FBS) to provide essential growth factors and nutrients essential for cell proliferation. Additionally, the medium contained 0.01 mg/ml of human insulin to help support cellular metabolism and growth, and 1% non-essential amino acids to ensure that the cells had access to all the required building blocks for protein synthesis. To prevent contamination and support cell health, 0.1% penicillin/streptomycin was added to the medium, providing antibacterial protection. The cells were incubated at a constant temperature of 37°C within a humidified incubator that maintained an atmosphere of 5% carbon dioxide (CO2). This specific environment is vital for mimicking physiological conditions, ensuring optimal cell growth and viability. Routine sub-culturing was performed when the cell cultures reached a confluency of 70-80%, indicating that the cells had multiplied adequately. During this process, 0.25% trypsin-EDTA was employed to detach the cells from the culture dish surface, allowing for easy passage. Following detachment, the cells were gently resuspended in fresh growth medium, counted, and subsequently seeded onto new cell culture petri dishes or flasks to maintain their growth for future experiments. This careful approach ensures the health and longevity of the MDA-MB-231 cell line for ongoing research applications [15].

2.2. Cell Viability Assay

To accurately determine the non-toxic doses of oxaliplatin and tetracaine, a comprehensive cell viability assay was conducted using the CellTiter-Glo method, which is widely recognized for its sensitivity and reliability. The experimental procedure began with the seeding of MDA-MB-231 cells, a human breast cancer cell line, into appropriate culture plates. MDA-MB-231 cells were seeded at 5×10^3 cells/well in black 96-well plates. These cells were allowed to adhere overnight under optimal conditions to ensure proper attachment and growth. Following the adhesion period, the cells were treated with a range of concentrations of oxaliplatin and tetracaine (10 µM oxaliplatin, 50 µM tetracaine, 75 µM tetracaine and combinations of oxaliplatin and tetracaine). The concentrations were selected based on established therapeutic references for both oxaliplatin and tetracaine [16,17], ensuring that the study was grounded in relevant clinical data. After the treatment period, the cells were meticulously harvested to assess cell viability. This assessment was performed according to the CellTiter-Glo protocol, which involves the addition of a luminescent reagent that quantifies the ATP present in viable cells. The CellTiter-Glo® Luminescent Cell Viability Assay measures viable cells by quantifying ATP, a marker of metabolism. When cells lyse, ATP reacts with the reagent to produce a luminescent signal related to cell count. The protocol involves one reagent addition and takes 10 minutes for results. The resulting luminescence was measured using a plate reader, providing a precise evaluation of cell viability across the different treatment groups. Cell Viability Assay. Absorbance of each sample was recorded by using the microplate spectrophotometer (CLARIOstar microplate reader). The data obtained from the cell viability tests and luminescence readings were subsequently analyzed using appropriate statistical methods to ascertain the significance of the results [15,18]. This rigorous approach allowed for a clear understanding of the non-toxic dosage levels of both oxaliplatin and tetracaine, contributing valuable insights into their safe application in therapeutic contexts.

2.3. Cell Proliferation Assay (MTT)

The MTT assay was utilized to assess cell proliferation in response to treatment with non-toxic concentrations of oxaliplatin and tetracaine. MDA-MB-231 cells were plated at a density of 3×10^3 cells per well in black 96-well plates. These cells were allowed to adhere overnight under optimal conditions to facilitate proper attachment and growth. After the adhesion period, the cells underwent treatment with various concentrations of oxaliplatin and tetracaine (10 µM oxaliplatin, 50 µM tetracaine, 75 µM tetracaine, and combinations of oxaliplatin and tetracaine). Following the treatment, the cells were incubated with MTT solution, which is taken up by metabolically active cells and subsequently converted into formazan crystals. These crystals were solubilized, and the resulting absorbance was measured using a microplate reader at an appropriate wavelength, typically around 570 nm. The absorbance values obtained were recorded and analyzed to determine the percentage of cell survival in

relation to the control group. For this analysis, GraphPad Prism software was employed to facilitate the statistical evaluation and interpretation of the data, ensuring accurate results to reflect the effects of the treatments on cell viability [19].

2.4. Lateral Motility (Wound Healing Assay)

MDA-MB-231 breast cancer cells were cultured in a complete growth medium, composed of DMEM supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin, in sterile tissue culture plates. The cells were incubated at 37°C in a humidified atmosphere with 5% CO2 until they reached approximately 80-90% confluency, which is optimal for the experimental procedure. To assess the cell migration ability, standardized wounds were generated in the cell monolayer using a sterile 200 µL pipette tip. This process involved making straight, uniform scratches across the surface of the cultured cells, ensuring each scratch was of similar width to maintain consistency across all samples. Following the wounding, the wells were gently washed with sterile phosphate-buffered saline (PBS) to remove any detached cells and debris that might interfere with the migration assessment.

The cells were then treated with specific doses of oxaliplatin and tetracaine, which were carefully prepared and diluted in the growth medium to achieve the desired concentrations. Treatment was applied, and the cells were subsequently incubated for a defined period, allowing time for the effects of the drugs on cell migration and morphology to manifest. Cellular responses, including the degree of wound closure and changes in cell morphology, were documented by capturing high-resolution images under an inverted microscope. Digital photographs of the scratched areas were taken at predefined time points to allow for quantitative analysis of migration and provide a visual reference for any morphological changes observed in the treated and control groups [19].

2.5. Statistical Analysis

Data are presented as mean ± SD (standard deviation). All statistical analyses were performed using GraphPad Prism 10. Depending on the normality of data distribution, two-group comparisons were conducted using either the Student's t-test or the Mann–Whitney test. Comparisons among three biological replicates (performed in triplicate) were analyzed using one-way ANOVA. The specific statistical tests applied are indicated in the corresponding figure legends. A p value < 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSIONS

Triple Negative Breast Cancer (TNBC) constitutes approximately 15-20% of all breast cancer diagnoses, presenting a challenging and aggressive form of the disease. This subtype is particularly concerning as it tends to manifest more frequently in younger women, who may face the dual burden of a life-threatening illness at a pivotal time in their lives [20]. Alarmingly, TNBC carries a significantly increased mortality rate, with statistics indicating that up to 40% of patients may succumb to the disease within the first five years following diagnosis, particularly in advanced stages. The term "triple negative paradox" captures the intriguing yet troubling nature of TNBC's response to treatment. Patients often experience an unexpectedly favorable initial response to neoadjuvant chemotherapy, which is used to shrink tumors before surgery [21]. However, this initial positivity is misleading, as long-term outcomes for these patients tend to be considerably poorer compared to those with other breast cancer subtypes. This paradox highlights the aggressive characteristics of TNBC, which often develops resistance to chemotherapy—a cornerstone of its treatment regimen. Given the complexities and challenges posed by TNBC, there is a pressing need for innovative and effective treatment strategies that can improve patient outcomes and address the unique biology of this formidable cancer type.

In this study, we investigated whether modulation of VGSC activity using non-cytotoxic concentrations of oxaliplatin and the VGSC blocker tetracaine could alter proliferation and migration in highly metastatic MDA-MB-231 breast cancer cells, while comparing responses to control. We decided to repurpose tetracaine and oxaliplatin—both of which are already FDA-approved—as part of a combination therapy, hoping to observe a combination non-toxic effect on the modulation of voltage-gated sodium channels (VGSC). Recent research has highlighted the advantages of combination therapies. For instance, a combinatorial treatment for glioblastoma using temozolomide (TMZ)

alongside 5-ethynyl-2′-deoxyuridine (EdU) demonstrated significantly improved antitumor efficacy compared to either drug used alone. This was observed not only in vitro with GBM cell lines but also in three different orthotopic GBM xenograft models and with passage-zero GBM patient tumor tissues grown in an organotypic brain slice culture-based platform [20]. In another study involving mice bearing leukemic cells, the intraperitoneal administration of cisplatin combined with procaine on days 1 and 5 achieved cure rates of 33% and 50%, respectively. In contrast, the cure rates with cisplatin alone were only 17% and 9% [21,22].

One of the primary strengths of this study lies in the intentional selection of non-cytotoxic drug concentrations. To ensure accuracy, we conducted CellTiter-Glo assays, which demonstrated that the concentrations of oxaliplatin (10 µM) and tetracaine (50–75 µM), as well as their combinations, did not lead to a significant decrease in cell viability at the 48-hour mark, as illustrated in Figure 1. This meticulous approach enabled us to evaluate functional changes in both cell proliferation and migration without the interference of acute cell death, which is often a confounding factor in such studies. Consequently, the phenotypic changes that we observed can be attributed to genuine alterations in cellular behavior, rather than being a result of nonspecific toxicity associated with high drug concentrations. This methodological choice enhances the reliability of our findings and supports a clearer understanding of the drugs' effects on cellular dynamics.

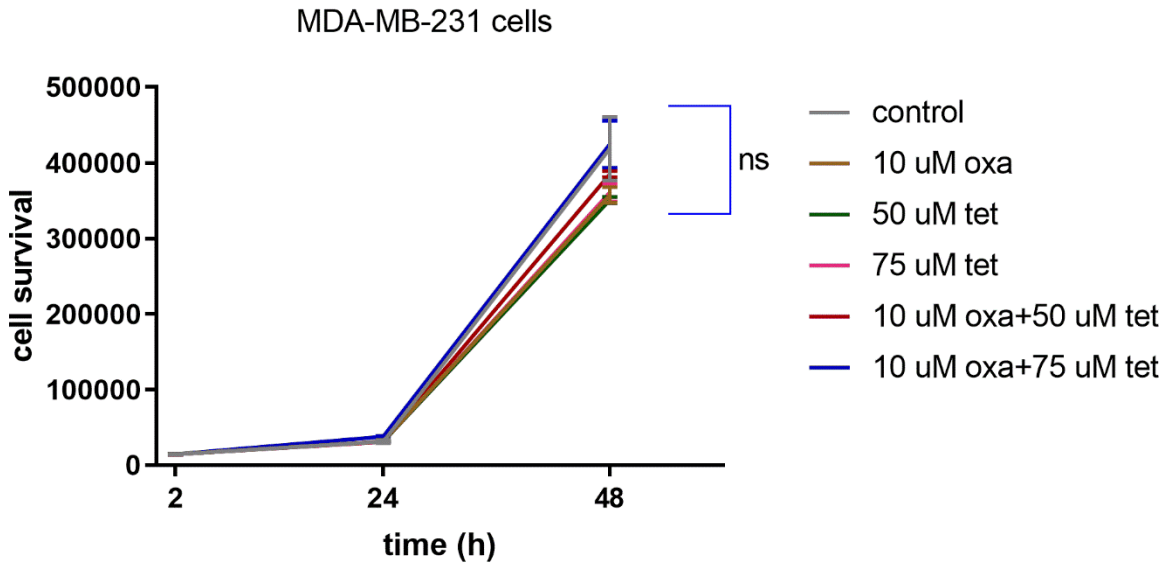
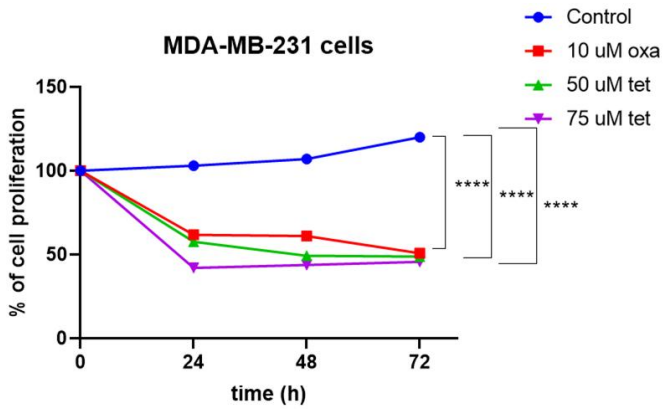


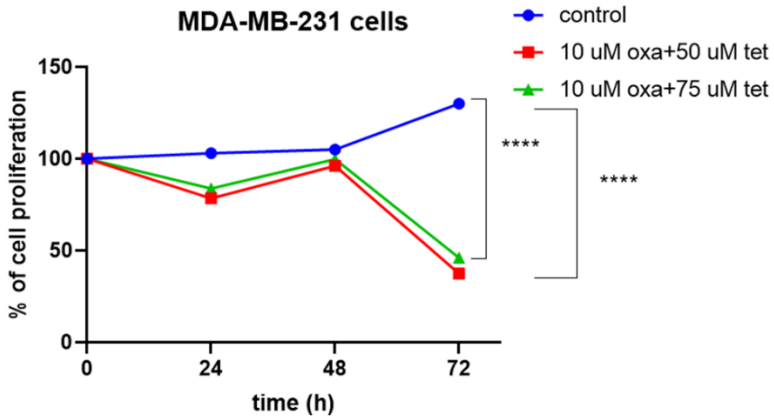
Figure 1. Effect of oxaliplatin and tetracaine on the viability of MDA-MB-231 cells. Cell viability was assessed using the CellTiter-Glo assay following treatment with 10 µM oxaliplatin (Oxa), 50 µM tetracaine (Tet), or their combination. The number of viable cells was calculated relative to the DMSO-treated control group. None of the tested treatment conditions produced a statistically significant change in cell viability compared with the DMSO control ($p > 0.05$). Data are presented as mean ± SD from independent experiments.

Proliferation assays demonstrated a clear response to treatment that was specific to each cellline. As shown in Figures 2 and Figure 3, MDA-MB-231 cells exhibited a significant reduction in proliferation across all treatment groups, with tetracaine demonstrating the strongest effect. The absence of a significant difference between the 50 µM and 75 µM tetracaine concentrations suggests a possible saturation of voltage-gated sodium channel (VGSC) inhibition, indicating that maximal functional blockade may occur at lower concentrations. These findings align with previous reports indicating that triple-negative breast cancer (TNBC) cells depend on VGSC activity to sustain their proliferative signaling.



Tukey's multiple comparisons test	95.00% CI of diff.	Significant?	Summary	Adjusted P Value
control vs. 10 uM oxa	0.2693 to 0.5580	Yes	****	<0.0001
control vs. 50 uM tet	0.5439 to 0.8326	Yes	****	<0.0001
control vs. 75 uM tet	0.6402 to 0.9289	Yes	****	<0.0001
10 uM oxa vs. 50 uM tet	0.1302 to 0.4189	Yes	***	0.0001
10 uM oxa vs. 75 uM tet	0.2266 to 0.5153	Yes	****	<0.0001
50 uM tet vs. 75 uM tet	-0.04800 to 0.2407	No	ns	0.2795

*Figure 2. Effect of oxaliplatin and tetracaine on the proliferation of MDA-MB-231 cells. Cell proliferation was evaluated by the MTT assay after 72 h of treatment with 10 µM oxaliplatin (Oxa), 50 µM tetracaine (Tet), and 75 µM tetracaine (Tet). Cell viability/proliferation rates were normalized to the DMSO-treated control group. Treatment with 10 µM Oxa, 50 µM Tet, and 75 µM Tet resulted in a statistically significant reduction in cell proliferation compared with the DMSO control after 72 h. Data represent mean values from three independent experiments performed in triplicate. Statistical significance was determined by one-way ANOVA followed by Tukey's multiple comparison test. **** $p < 0.0001$.*



Tukey's multiple comparisons test	95.00% CI of diff.	Significant?	Summary	Adjusted P Value
control vs. 10 uM oxa+50 uM tet	0.6818 to 0.9522	Yes	****	<0.0001
control vs. 10 uM oxa+75 uM tet	0.5397 to 0.8102	Yes	****	<0.0001
10 uM oxa+50 uM tet vs. 10 uM oxa+75 uM tet	-0.2773 to -0.006841	Yes	*	0.0388

*Figure 3. Effect of combination treatment on the proliferation of MDA-MB-231 cells. Cell proliferation was evaluated by the MTT assay after 72 h of treatment with 10 µM oxaliplatin (Oxa) plus 50 µM tetracaine (Tet), and 10 µM oxaliplatin plus 75 µM tetracaine (Tet). Cell viability/proliferation rates were normalized to the DMSO-treated control group. Treatment with combination resulted in a statistically significant reduction in cell proliferation compared with the DMSO control after 72 h. Data represent mean values from three independent experiments performed in triplicate. Statistical significance was determined by one-way ANOVA followed by Tukey's multiple comparison test. **** $p < 0.0001$.*

Wound-healing assays were conducted to investigate the impact of voltage-gated sodium channels (VGSCs) on the migratory ability of MDA-MB-231 cells, a highly motile breast cancer cell line. The results revealed that control cells exhibited a remarkable capacity to close wounds within a 24-hour period, underscoring their naturally high motility (see Figure 4). Interestingly, treatment with oxaliplatin alone did not produce a significant reduction in cell migration. This suggests that administering DNA-damaging chemotherapy at non-cytotoxic doses is inadequate for inhibiting cellular motility. In striking contrast, treatment with tetracaine—a local anesthetic known to block VGSCs—demonstrated a clear, dose-dependent reduction in wound closure. Notably, at a concentration of 75 µM tetracaine, the cells displayed the most significant decrease in their migratory capacity, as illustrated in Figure 4. Furthermore, the combination of oxaliplatin and tetracaine resulted in an even greater diminishment of migration compared to the effects of oxaliplatin alone. This combined treatment closely mirrored the anti-migratory effects observed with tetracaine solely. These findings strongly indicate that the blockade of VGSCs plays a pivotal role in mediating the anti-migratory response observed in this study.

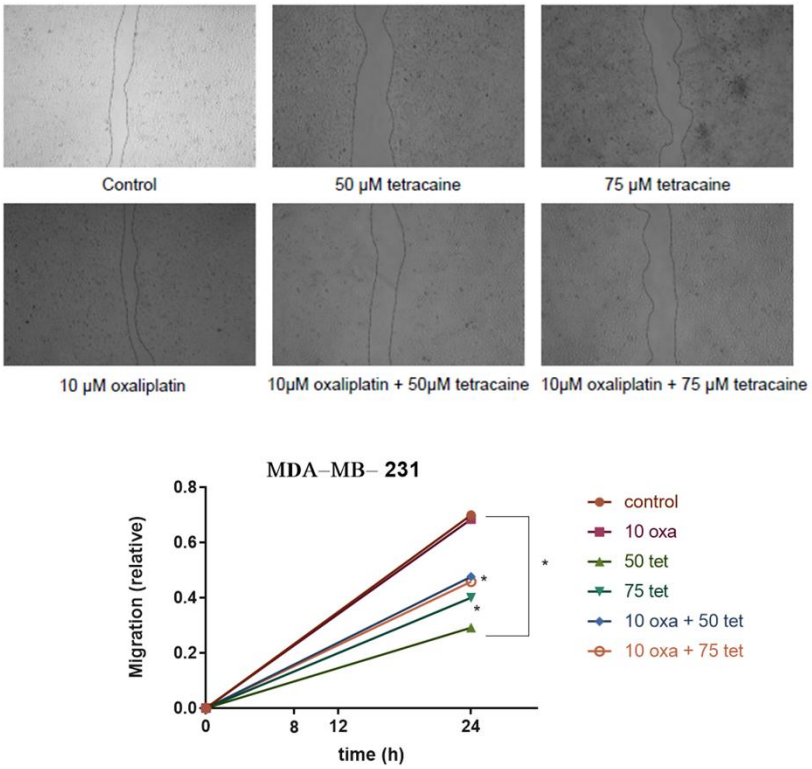


Figure 4. Effect of oxaliplatin, tetracaine, and their combination on the migration of MDA-MB-231 cells. Cell migration was evaluated using a wound healing assay, and cell morphology was examined under a microscope at 0 and 24 h time points. To exclude the contribution of cell proliferation to wound closure, cells were treated with Mitomycin C prior to drug exposure. Quantitative analysis of wound closure demonstrated that treatment with 50 µM and 75 µM tetracaine (Tet), as well as tetracaine in combination with oxaliplatin (Oxa), significantly reduced cell migration compared with the untreated control group ($p < 0.05$). Data are presented as mean ± SD from independent experiments performed in replicates.

While the combination treatment did not reveal distinct synergistic effects on cellular migration beyond what was achieved with tetracaine alone, the findings indicate that oxaliplatin does not inhibit the functionality of voltage-gated sodium channels (VGSCs). Instead, it may provide an additive effect by engaging complementary molecular pathways. This insight holds significant relevance in the realm of chemotherapy resistance, where targeting non-genomic mechanisms—such as alterations in membrane excitability and fluctuations in ion movement—could potentially boost the effectiveness of treatment while minimizing harmful side effects. These results highlight the potential of VGSCs as valuable therapeutic targets and reinforce the concept of integrating strategies that focus on ion channels with traditional chemotherapy approaches. This integrated method could effectively mitigate tumor growth

and reduce the metastatic potential in cases of triple-negative breast cancer (TNBC), a particularly aggressive form of the disease. Certain limitations should be acknowledged. This study focused on only one TNBC cell line, and further research using multiple models is necessary to confirm the generalizability of these findings. Despite these limitations, the consistent suppression of proliferation and migration in MDA-MB-231 cells provides strong functional evidence supporting the role of VGSCs in the aggressiveness of TNBC.

Although the observed anti-proliferative and anti-migratory effects are consistent with previous reports implicating Nav1.5/VGSC activity in TNBC progression, direct assessment of Nav1.5 expression or channel activity was beyond the scope of the present study. Therefore, the proposed mechanism remains speculative and should be confirmed by future studies employing electrophysiological and molecular approaches.

4. CONCLUSIONS

In conclusion, our research highlights the promising combination between tetracaine and oxaliplatin in the context of highly metastatic triple-negative breast cancer (TNBC) cells. This combination treatment supports further investigation of VGSC-targeted approaches as a transformative strategy in the fight against this aggressive cancer subtype. By carefully targeting complementary mechanisms of action—including the intricate signaling pathways associated with sodium channels and those involved in DNA damage response—we have identified distinct sensitivities in various cell lines. Notably, these differences manifest primarily in their responses related to cell proliferation and migration.

As we look to the future, further investigations into the underlying mechanisms and the therapeutic potential of these combination strategies are essential. Such research will provide valuable insights into their clinical applicability for TNBC treatment. Importantly, these targeted, combination-based therapies may emerge as crucial alternatives for patients battling aggressive and treatment-resistant forms of breast cancer, offering hope for improved outcomes in a challenging therapeutic landscape.

Conflict Of Interest

There is no conflict of interest

Statement of Research and Publication Ethics

The authors confirm that this study adheres to research and publication ethics.

Artificial Intelligence (AI) Contribution Statement

The authors used artificial intelligence (AI)-assisted technology solely for language editing and improvement of grammar and readability. The authors reviewed and edited the output as necessary and take full responsibility for the content of the manuscript.

Contributions of The Authors

Serife Yerlikaya conceived and designed the study, performed the experiments, analyzed and interpreted the data, conducted the literature review, and wrote and revised the manuscript. Naıma Bınte Shapan and Zeynep Pelin Gov performed the experiments and conducted the literature review. All authors has read and approved the final version of the manuscript.

Acknowledgement

We sincerely thank Istanbul Medipol University for their support of the BAP 2024/51 project.

REFERENCES

[1] A. Ahmad, Breast Cancer Metastasis and Drug Resistance, 2nd ed., vol. 1152. Cham, Switzerland: Springer International Publishing, 2019. https://doi.org/10.1007/978-3-030-20301-6

[2] M. S. Donepudi, K. Kondapalli, S. J. Amos, and P. Venkateshan, “Breast cancer statistics and markers,” J. Cancer Res. Ther., vol. 10, pp. 506–511, 2014. https://doi.org/10.4103/0973-1482.137927

[3] X. Dai, L. Xiang, and Z. Bai, “Cancer hallmarks, biomarkers and breast cancer molecular subtypes,” J. Cancer, vol. 7, pp. 1281–1294, 2016. https://doi.org/10.7150/jca.13141

[4] R. M. Sareyeldin et al., "Gene expression and miRNAs profiling: Function and regulation in human epidermal growth factor receptor 2 (HER2)-positive breast cancer," Cancers, vol. 11, p. 646, 2019. https://doi.org/10.3390/cancers11050646

[5] H. Yao et al., "Triple-negative breast cancer: Is there a treatment on the horizon?" Oncotarget, vol. 8, pp. 1913–1924, 2017. https://doi.org/10.18632/oncotarget.12284

[6] L. A. Hoeferlin, C. E. Chalfant, and M. A. Park, "Challenges in the treatment of triple negative and HER2-overexpressing breast cancer," J. Surg. Sci., vol. 1, no. 1, pp. 3–7, 2013. Available: https://pubmed.ncbi.nlm.nih.gov/24818173/

[7] V. Masoud and G. Pages, "Targeted therapies in breast cancer: New challenges to fight against resistance," World J. Clin. Oncol., vol. 8, pp. 120–134, 2017. https://doi.org/10.5306/wjco.v8.i2.120

[8] S. Dasari and P. B. Tchounwou, "Cisplatin in cancer therapy: Molecular mechanisms of action," Eur. J. Pharmacol., vol. 740, pp. 364–378, 2014. https://doi.org/10.1016/j.ejphar.2014.07.025

[9] A. Grothey et al., "Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7," J. Clin. Oncol., vol. 29, no. 4, pp. 421–427, 2011. https://doi.org/10.1200/JCO.2010.31.5911

[10] W. J. Brackenbury, "Voltage-gated sodium channels and metastatic disease," Channels, vol. 6, no. 5, pp. 352–361, 2012. https://doi.org/10.4161/chan.21910

[11] H. Kaanoglu et al., "Combinatorial treatment of glioblastoma with temozolomide (TMZ) plus 5-ethynyl-2′-deoxyuridine (EdU)," Proc. Natl. Acad. Sci. U.S.A., vol. 123, no. 1, Art. no. e2532187123, 2026. https://doi.org/10.1073/pnas.2532187123

[12] M. Ribeiro et al., "Human breast cancer cells demonstrate electrical excitability," Front. Neurosci., vol. 14, p. 404, 2020. https://doi.org/10.3389/fnins.2020.00404

[13] F. Grolleau, L. Gamelin, M. Boisdron-Celle, B. Lapied, M. Pelhate, and E. Gamelin, "A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels," J. Neurophysiol., vol. 85, no. 5, pp. 2293–2297, 2001. https://doi.org/10.1152/jn.2001.85.5.2293

[14] E. Selçuk et al., "Neuroblastoma: Anti-invasive effects of tetracaine in vitro," Basic Clin. Pharmacol. Toxicol., vol. 138, no. 3, Art. no. e70190, 2026. https://doi.org/10.1111/bcpt.70190

[15] A. Yerlikaya et al., "A novel combination treatment for breast cancer cells involving BAPTA-AM and proteasome inhibitor bortezomib," Oncol. Lett., vol. 12, no. 1, pp. 323–330, 2016. https://doi.org/10.3892/ol.2016.4597

[16] D. Keleş, M. Sipahi, Ş. İnanç-Sürer, M. B. Djamgoz, and G. Oktay, "Tetracaine downregulates matrix metalloproteinase activity and inhibits invasiveness of strongly metastatic MDA-MB-231 human breast cancer cells," Chem.-Biol. Interact., vol. 385, p. 110730, 2023. https://doi.org/10.1016/j.cbi.2023.110730

[17] S. Al-Bahlani, B. Al-Dhahli, K. Al-Adawi, A. Al-Nabhani, and M. Al-Kindi, "Platinum-based drugs differentially affect the ultrastructure of breast cancer cell types," BioMed Res. Int., vol. 2017, Art. no. 3178794, 2017. https://doi.org/10.1155/2017/3178794

[18] H. B. Kucuk et al., "Novel β hydroxy ketones: Synthesis, spectroscopic characterization, molecular docking, and anticancer activity studies," J. Mol. Struct., vol. 1250, p. 131772, 2022. https://doi.org/10.1016/j.molstruc.2021.131772 0022-2860

[19] S. Yerlikaya et al., "Investigation of chemical profile, biological properties of Lotus corniculatus L. extracts and their apoptotic-autophagic effects on breast cancer cells," J. Pharm. Biomed. Anal., vol. 174, pp. 286–299, 2019. https://doi.org/10.1016/j.jpba.2019.05.068

[20] N. Bilani et al., "Breast cancer in the United States: A cross-sectional overview," J. Cancer Epidemiol., vol. 2020, Art. no. 6387378, 2020. https://doi.org/10.1155/2020/6387378

[21] L. A. Carey et al., "The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes," Clin. Cancer Res., vol. 13, no. 8, pp. 2329–2334, 2007. https://doi.org/10.1158/1078-0432.CCR-06-1109

[22] M. Viale et al., "Combination of cisplatin-procaine complex DPR with anticancer drugs increases cytotoxicity against ovarian cancer cell lines," Anti-Cancer Drugs, vol. 9, no. 5, pp. 457–463, 1998. https://doi.org/10.1016/S0959-8049(96)00354-1