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Identification of Novel Paclitaxel Sensitizers for Glioblastoma Therapy through High-Throughput Screening

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Abstract: *Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumor that originates in the brain's glial cells. Due to its rapid growth and resilience against many therapies, the prognosis for individuals with GBM remains bleak. Taxol (paclitaxel), a widely used chemotherapy treatment for various types of cancer, is also effective in killing glioblastoma cells, according to multiple studies. Here, we report through a comprehensive screening of 1,001 FDA-approved drugs, 37 drugs were identified to sensitize LN-229 glioblastoma cells to Taxol treatment. Remarkably, four of these drugs have not been previously linked to GBM treatment. Further experiments showed that three of them are even efficient in inhibiting glioblastoma cell migration. These new candidates create the potential of developing novel paclitaxel-based chemotherapy combined treatments for GBM in the future.*

Keywords: *Glioblastoma, Combining Treatment, Paclitaxel, High-Throughput Screening, Cell Death*

1. Introduction

Glial cells are several types of non-neuronal cells in the central nervous system and peripheral nervous system that provide physical and chemical support to neurons and maintain their environment. Glioblast cells are the progenitors of all glia cells; therefore, glioblastoma (GBM) has the most malignant characteristics among all gliomas. Glioblastoma accounts for 54% of all gliomas and 16% of all primary brain tumors [1]. It has an extremely poor prognosis, and patients generally succumb within 14 months of diagnosis [2].

Temozolomide (TMZ), an alkylating agent capable of penetrating the blood-brain barrier (BBB), is a chemotherapy drug commonly used to treat brain cancers such as glioblastoma multiforme and anaplastic astrocytoma. However, TMZ is not as widely used as another BBB-impenetrable chemotherapy drug, paclitaxel (Taxol), in tumors outside the brain since it is 1,400-fold less efficient than Taxol, which limits the final clinical outcome [3]. Taxol expedites the assembly of microtubules from microtubule dimers while hindering their disassembly, resulting in abnormal mechanical reorganization of the microtubules and inhibiting normal cell division [4], [5]. The effect of Taxol in glioblastoma has been supported by in vitro evidence early in the 1990s [6], [7]. However, the in vivo use of Taxol in GBM treatment is limited by its poor ability to cross the BBB [8]. Therefore, identifying a new approach to help Taxol penetrate the BBB is valuable in the treatment of brain tumors, including, but not limited to, GBM.

Several strategies have been explored to enhance paclitaxel delivery across the BBB, including nanoparticles [9], [10], payload liposomes [11], and ultrasound delivery [3]. Although these approaches improve brain delivery, they only moderately enhance therapeutic outcomes, highlighting the need for more effective combinatorial strategies [3], [9]. Taxol combined therapy is widely used to treat various cancers like lung cancer [12], [13], ovarian cancer [14], and breast cancer [15] to reach a better clinical outcome than Taxol alone. Therefore, finding new drugs in combination with Taxol could be a new approach to develop future GBM therapy.

An FDA-approved drug library is a collection of drugs that have been approved by the United States Food and Drug Administration (FDA) for use in humans. Since the safety of the drugs in the library has already been tested by previous clinical trials, finding a new function of the existing drugs can be transformed into a new therapy much faster than de novo drugs. Therefore, FDA-approved drug library screening has become a powerful tool to repurpose drugs. For example, Barrows et al. (2016) tested 774 FDA-approved compounds' activity in blocking ZIKA virus infection, and they found more than 20 candidates have this antiviral activity [16]. In another study, Stavrovskaya et al. (2004) found that 28 out

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of 1,040 FDA-approved drugs can delay the mitochondrial permeability transition (mPT), providing a class of safe, tolerable drugs for stroke and neurodegeneration, as well as new tools for understanding mitochondrial roles in neuronal cell death [17].

In this study, an FDA-approved drug library screening was applied to explore new drugs that can sensitize glioblastoma cell LN-229 to Taxol treatment in vitro, which could potentially be developed into future glioblastoma therapies. LN-229 cell survival assay was set as a high-throughput screening system and screened 1,001 FDA-approved compounds in combination with Taxol. Four new candidate drugs that can decrease LN-229 cell survival in combination with Taxol treatment were proposed. Further experiments confirmed that they can also increase the apoptotic rate and decrease the migration rate of glioblastoma cells in vitro.

2. Methods

2.1 Reagents

Human glioblastoma cell line LN-229 (BNCC341218) was obtained from the BeNa Culture Collection (Suzhou, China). The solutions of Dimethyl sulfoxide (DMSO), Pancreatin, and Paclitaxel are obtained from Aladdin (Shanghai, China). Trypsin-EDTA was obtained from Cytiva (Shanghai, China). TUNEL Apoptosis Detection Kit and CCK-8 Cell Counting Kit were purchased from Vazyme (Nanjing, China).

2.2 Cell culture

The cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM glutamine, and 1 unit/ml penicillin. Cells were incubated at 37°C with 5% CO2 for 24 hours. Cultures were observed under the microscope to ensure that most of the cells are already attached to the flask wall. Cells were then seeded in 75-cm2 flasks and incubated at 37°C in a fully humidified atmosphere with 5% CO2. Once the cells reached 80% confluency, trypsin was added to detach the cells. After 3 minutes, the solution with 10% FBS was added to stop the reaction. The mixture is centrifuged for 5 minutes at 1,000 rpm. Discard the supernatant and add a new culture medium. Cells were seeded into a 96-well plate at a concentration of 10^4 cells per well. Cells were incubated with the inhibitors in addition to Taxol for 24 or 48 hours.

2.3 Compound library

The library used was DiscoveryProbe™ FDA-approved Drug Library (Catalog No. L1021) from APExBIO. All drugs were from approved institutions such as FDA, EMA, or pharmacopoeia, such as USP, BP. The vendor provided the compounds as pre-dissolved DMSO solutions in 96-well microplates. Each well contains 20 μl of compound at 10 mM stock concentration in DMSO solution.

2.4 High-throughput screening

LN-229 cells were plated into 96-well plates at 1,000 cells per well with 100 μl DMEM supplemented with 10% FBS and P/S. Diluted water is added at the edge wells to maintain the humidity inside the plate and prevent errors from evaporation. Cells were incubated at 37℃ and 5% CO2 overnight to allow full attachment. Different concentrations of Taxol solutions were added after incubation. Cells were then incubated at 37℃ and 5% CO2 for 1 hour. Drugs from the DiscoveryProbe™ FDA-approved Drug Library Catalog are diluted and added into each well, and the cells are incubated at 37℃ and 5% CO2 for another 24 and 48 hours.

2.5 Cell viability assay

The CCK-8 assay was performed following the kit manufacturer's protocol (Vazyme, A311-02). Briefly, after a certain time of incubation, each well of LN-229 cells is supplemented with 10 μl CCK8 solution. Cells were incubated at 37℃ and 5% CO2 for another 2 hours. After that, a Microplate reader was used to determine the OD value of each well at 450 nm. Cell viability was calculated as the percentage of control cells.

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2.6 Cell migration assay

In vitro scratch assay involves creating a gap in a cell layer, taking periodic images to track cell movement, and is suitable for studying cell interactions, mimicking wound healing, and live cell imaging during migration [18]. The cell migration assay was performed following a published protocol [18]. Briefly, LN-229 cells were plated onto a prepared 6-well dish at a density of 10^6 to create a confluent monolayer and incubated for 12 hours at 37℃. Cell monolayers were scraped to create a straight line of scratch using a P1000 pipette tip. Debris was removed, and the edges of the scratches were smoothed. By washing the cells once with 1 ml of the growth medium and then replacing with 2 ml of medium with Taxol and the indicated compound. The dish was etched lightly with a razor blade on the outer bottom of the dish to create a reference point to obtain the same field during acquisition. Images of the cells were taken after 0, 24, and 48 hours of incubation, and distances between one side of the scratch and the other were analyzed quantitatively by ImageJ.

2.7 TUNEL staining assay

TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labelling) staining uses terminal deoxynucleotidyl transferase (TdT) to label the ends of double-stranded DNA breaks. Briefly, 10^5 cells were cultured on polylysine-coated slides and given apoptosis induction treatment. After incubation, cells are fixed with 4% paraformaldehyde (freshly prepared in 1 × PBS) at 4℃ for 25 min. After PBS wash twice, each sample was dripped with 100 μl of 20 μg/ml Proteinase K for 5 min at room temperature. Cells are equilibrated at room temperature for 30 min, and then incubated with 50 μl TdT buffer at 37℃ for 60 min. After washing with PBS twice, the samples were re-stained with 2 μg/ml DAPI solution for 5 min at room temperature before 3 times final washes of PBS. Images were taken under a fluorescence microscope.

3. Results

3.1 Set up of Taxol-induced glioblastoma cell death screening

Taxol-induced glioblastoma cell death, as an in vitro assay, has been used in many previous studies [19], [20]. We chose LN-229 as the cell line to perform the screen, since it expresses more tumor cell markers, has a higher ability to migrate, and can form more tumor-like colonies in vitro compared to other glioblastoma cell lines [21].

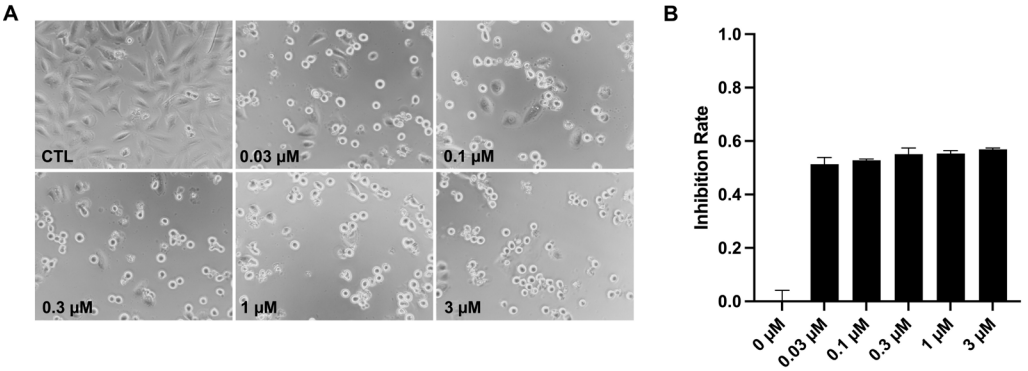

Figure 1: Determine the concentration of Taxol to perform the screen. (A)Representative bright field images of LN-229 cells after 24hrs treatment with different concentrations of Taxol. (B)Quantification of inhibition rates on LN-229 survival after 24hrs Taxol treatment.

To determine the optimal Taxol concentration for screening, Taxol's efficacy in inhibiting LN-229 cells was first tested at 3μM, 1μM, 0.3μM, 0.1μM, and 0.03μM. It is found that every concentration can significantly inhibit LN-229 cell survival by about 40% after 24 hours of Taxol treatment (Figures 1A and 1B). The cells exhibited more sensitivity to Taxol than previous study [20]. Therefore, the lowest concentration (0.03 μM) was used to carry out the screen.

3.2 Drug library screening identified candidate drugs in sensitizing glioblastoma cells to Taxol

After determining the Taxol concentration, 1,001 FDA-approved drugs were screened in combination

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with Taxol to find out each of their inhibition rate against LN-229 cell survival. Following previous literature [16], [22], compounds were applied at a final concentration of 10 μM in the large-scale screen. The screen timeline was shown in Figure 2A.

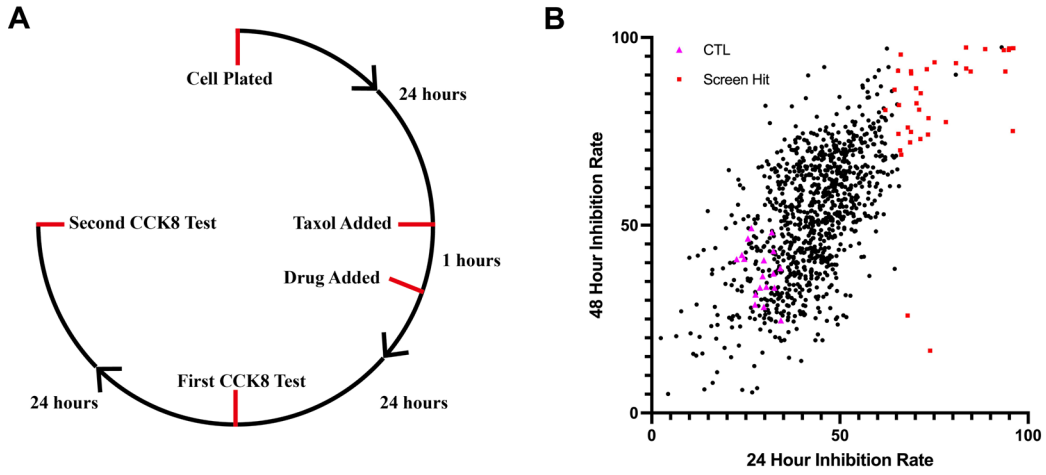

Figure 2: A screen of FDA-approved drugs identified glioblastoma suppressors. (A)Screening timeline. LN-229 cell was plated 24 hours prior Taxol treatment and 25 hours prior drug treatment. 24 and 48 hours after drugs' treatment, cells were performed with cell viability assay (CCK8 Test). (B)Results of the high throughput screen. Inhibition rate of 24 hours is exhibited against corresponding drugs' inhibition rate at 48 hours.

We set criteria for a two-fold inhibition rate compared to Taxol alone. Among 1,001 compounds, 37 of them (Figure 2B) were found to be effective against LN-229 cell survival. The initial positive rate (37/1,001) is close to previous reported FDA-approved drug screens in blocking ZIKA virus infection (20/774) [16] and in delaying the mitochondrial permeability transition (28/1,040) [17].

3.3 Literature search to determine the potential novel drugs in glioblastoma treatment

Table 1: Summary of positive drugs in the screen

Drug Name	Known mechanism	Progress Related to Glioblastoma	Reference
YM155	Inhibitor of survivin	Basic Research	West et al., 2023
Romidepsin (FK228, depsipeptide)	Inhibitor of histone deacetylase	Phase I/II trial: failed	Iwamoto et al., 2011
Staurosporine	Inhibitor of a broad spectrum of protein kinases	Basic Research	Linkous et al., 2019
Erlotinib Hydrochloride	Inhibitor of epidermal growth factor receptor (EGFR/HER-1) tyrosine kinase	Phase II trial	NCT00054496
Verteporfin	Photosensitizer for photodynamic therapy	Phase II trial	NCT04590664
LDK378	Inhibitor of anaplastic lymphoma kinase (ALK)	Phase 0/II trail	NCT02605746
Rosuvastatin Calcium	HMG-CoA reductase inhibitor and a type of statin	Basic Research	Bhat et al., 2021
GSK2126458	Inhibitor of PI3K/mTOR	Basic Research	Zhao et al., 2017
BI6727 (Volasertib)	Selective inhibitor of Plk1, Plk2, and Plk3	Basic Research	Dong et al., 2018
AZD-9291	Irreversible Inhibitor of EGFR tyrosine kinase	Basic Research	Chagoya et al., 2020
Pacritinib (SB1518)	Inhibitor of Janus kinase 2/Fms-like tyrosine kinase-3 (JAK2/FLT3)	Basic Research	Jensen et al., 2017
Vandetanib (ZD6474)	Inhibitor of VEGFR-2 and EGFR	Phase I/II trial: failed	Kreisl et al., 2012

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Lapatinib	Potent inhibitors of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER-2) tyrosine kinases	Phase I/II trial: failed	Thiessen et al., 2010
Afatinib (BIBW2992)	Inhibitor of HER2 and EGFR	phase II trial: Successed	Reardon et al., 2015
EPZ-6438	Potent and bio-available inhibitor of EZH2	Basic Research	Mishra et al., 2020
Gefitinib (ZD1839)	Potent and orally-bioavailable small-molecule inhibitor of EGFR tyrosine kinase	Phase II trial: Successed	Rich et al., 2003
Lurasidone HCl	Inhibitor of Dopamine D2, 5-HT2A, 5-HT7, 5-HT1A and noradrenaline α2C	Basic Research	Suzuki et al., 2021
Cetylpyridinium Chloride	Cationic quaternary ammonium compound used as oropharyngeal antiseptic.	Basic Research	Allen et al., 2020
Ponatinib (AP24534)	Second-generation pan inhibitor of BCR-Abl kinases	Basic Research	Zhang et al., 2014
Embelin	Naturally occurring para-benzoquinone that selectively inhibitor of 5-LOX and microsomal prostaglandin E2 synthase-1	Basic Research	Park et al., 2013
Cilengitide	Inhibitor of the FAK/Src/AKT pathway	Phase II trial: Successed	Gilbert et al., 2011
Lopinavir	Potent inhibitor of HIV protease	Phase II trial: failed	Ahuwalia et al., 2010
(S)-Crizotinib	Selectively inhibitor of MTH1 catalytic activity	Basic Research	Das et al., 2015
Enzastaurin (LY317615)	ATP-competitive, selective oral inhibitor of protein kinase Cβ	Phase II trial: Failed	Odia et al., 2015
Neratinib (HKI-272)	Potent and irreversible inhibitor of HER2/EGFR	Phase II trial: Failed	Ryan et al., 2022
Nelfinavir	Potent inhibitor of HIV-1 protease	Phase I trial: Failed	Alonso-Basanta et al., 2013
Nilotinib (AMN-107)	Selective inhibitor ofBcr-Abl kinase	Basic Research	Frolov et al., 2016
Mesoridazine Besylate	Phenothiazine dopamine receptor anatagonist	Basic Research	Johannessen et al., 2019
ABT-199	Potent and selective inhibitor of Bcl-2	Basic Research	Pareja et al., 2014
(+)-Ketoconazole	Potent inhibitors of CYP3A and CYP2C9 enzyme subtypes	Basic Research	Agnihotri et al., 2019
Fingolimod (FTY720)	S1P receptors agonist.	Basic Research	Kolodziej et al., 2020
Tepotinib (EMD-1214063)	Potent and selective inhibitors of c-Met	None	None
Zosuquidar 3HCL (LY335979)	Inhibitor of P-glycoprotein	None	None
Cetrimonium Bromide (CTAB)	Quaternary ammonium surfactant	None	None
Domiphen Bromide	Chemical antiseptic and a quaternary ammonium compound	None	None
Taladegib (LY2940680)	Smo antagonist	None	None
Floxuridine	Anti-metabolite and pyrimidine analog	None	None

Literature search was applied to check whether these positive compounds have been previously studied in glioblastoma treatment. 30 compounds were found to have already been reported to be

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effective in inhibiting glioblastoma cell survival in vitro or in vivo, and some have even been clinically tested (Table 1).

The fact that the majority (31/37) of our positive compounds have been reported shows our screen is successful. The screen efficiently identified effective compounds in the library. Some of the reported compounds have already failed in clinical trials, showing the difficulty in tackling this deadly disease. The unreported 6 compounds (Table 1) were then subjected to further confirmation.

3.4 Follow-up confirmation of the positive compounds

Within the high-throughput screening, compounds were used at a final concentration of 10μM. For further confirmation, 1μM, 3μM, 10μM, and 30μM of compounds were used in combination with Taxol. In both the 24-hour and the 48-hour group, at 1 μM, all six drugs exhibited comparative inhibition rates to the control group (Taxol Only. The inhibition rates became slightly increased at 3μM, and further significantly increased at 10μM and 30μM for Tepotinib, Zosuquidar 3HCL, Cetrimonium Bromide, and Domiphen Bromide, while the effect of Taladegib and Floxuridine was not significant (Figures 3A and 3B).

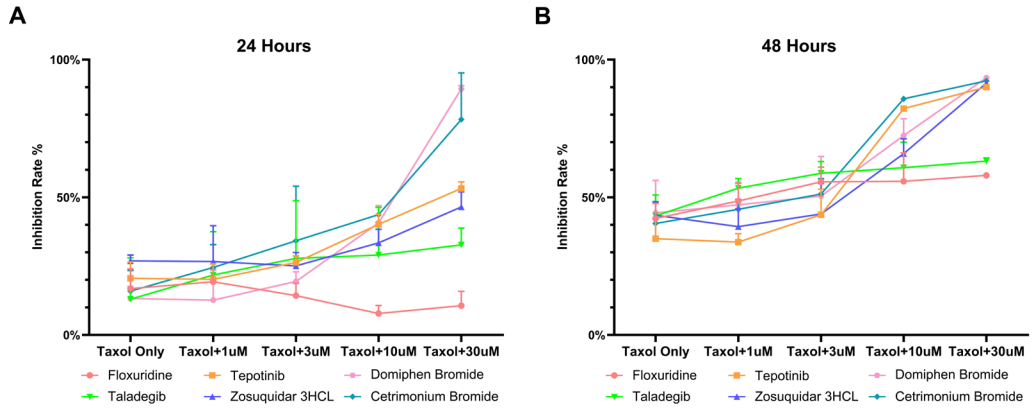

Figure 3 A screen of FDA-approved drugs identified glioblastoma suppressors. (A)Inhibition rates of LN-229 cells for 24 hours as a function of drug concentration in combination use of Taxol. (B)Inhibition rates of LN-229 cells for 48 hours as a function of drug concentration in combination use of Taxol.

3.5 Follow-up validation of drug-induced apoptosis

It is widely reported in many cancer cells that Taxol inhibits cell viability by apoptosis [4], [23], [24]. For further confirmation of their efficacy, the 4 candidate drugs Tepotinib, Zosuquidar 3HCL, Cetrimonium Bromide, and Domiphen Bromide were then subjected to TUNEL assay to test their activity in promoting glioblastoma cell apoptosis when applied together with Taxol. The results showed that all these 4 candidates significantly increased Taxol-induced LN-229 apoptosis (Figures 4A and 4C). This result mechanistically confirmed the efficiency of Tepotinib, Zosuquidar 3HCL, Cetrimonium Bromide, and Domiphen Bromide in inhibiting glioblastoma cells' survival in vitro.

3.6 Validating the effect of combined treatment in regulating glioblastoma cell migration

Glioblastoma cells can spread to nearby brain tissue and along with the white matter tract. It can also spread to the opposite side of the brain through the corpus callosum or ventricular system [25]. In rare cases, it even metastasizes to peripheral tissues like lymph nodes, lung, bone, or liver [26]. This limits the range of therapeutic alternatives and increases the probability of secondary tumors formation. Since LN-229 has the ability to migrate in vitro [21], we tested whether the four positive drugs can limit this ability using the in vitro scratch assay.

As expected, Taxol significantly reduced the migration rate of in vitro cultured LN-229 cells after 24 or 48 hours (Figures 4B and 4D). For the co-treatment groups, it was found that Tepotinib and Domiphen Bromide further limited the migration rate at 24 hours, while Cetrimonium Bromide and Domiphen Bromide decreased the migration rate at 48 hours (Figures 4B and 4D).

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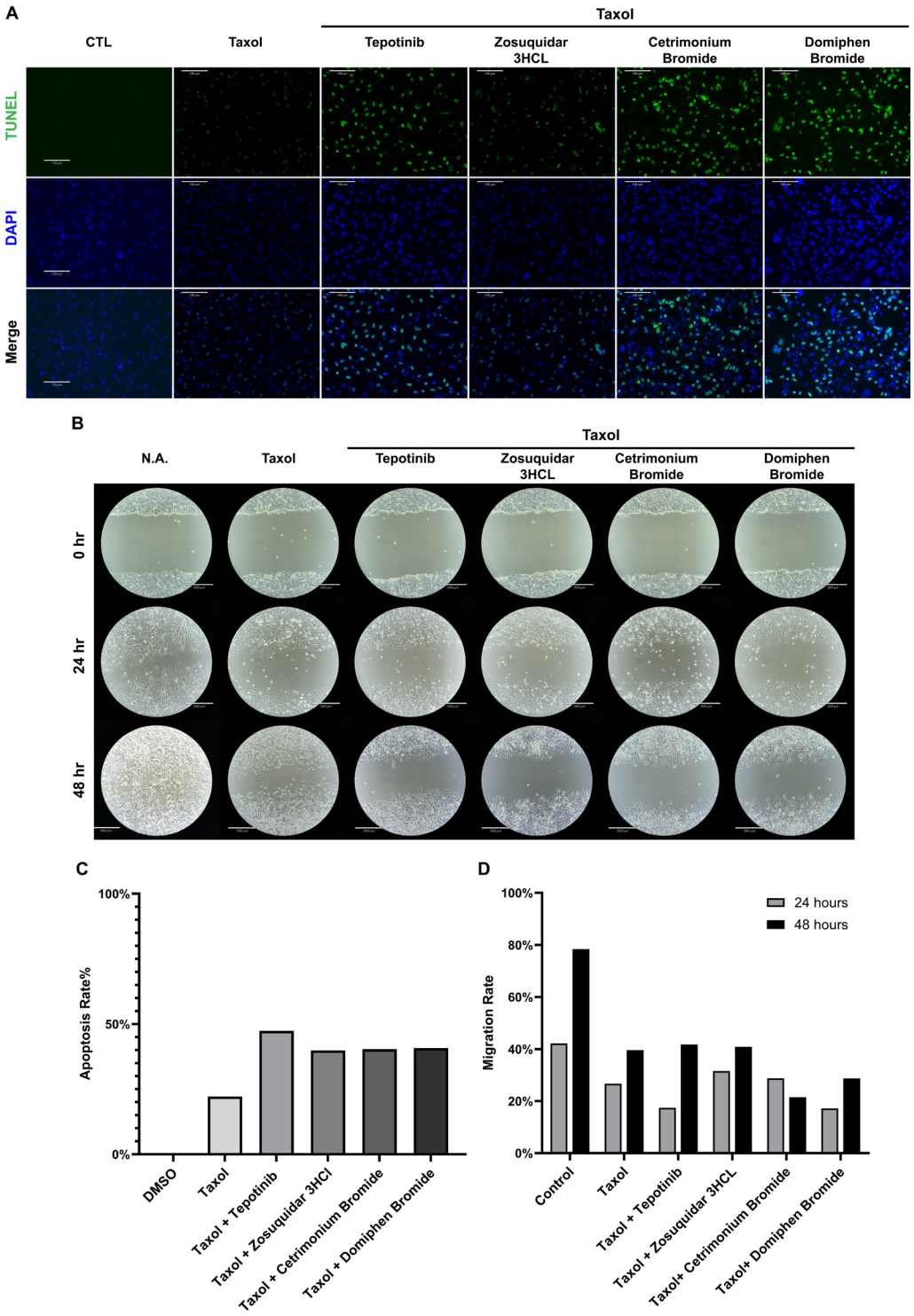

Figure 4 Effect of 4 selected candidate drugs in apoptosis and migration in combination with Taxol. (A)Representative images of TUNEL assay, TUNEL stained for ongoing apoptosis. (B)Representative bright field images of LN-229 cell migration assay. (C)Quantitative analysis of TUNEL assay, through cell counting. (D)Quantitative analysis of LN-229 cells migration.

4. Discussion

4.1 The potential mechanisms of the candidate drugs

Most identified drugs have already exhibited significant inhibition efficacy against tumors. For example, YM155 has been demonstrated to inhibit breast cancer, aggressive non-Hodgkin lymphoma,

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anaplastic thyroid cancer, and to sensitize ovarian cancer cells to cisplatin [27], [28], [29], [30]. Corresponding to the observation that it also exhibited significant inhibition efficacy against glioblastoma. Moreover, Romidepsin has already shown its efficacy in curing lung cancer, metastatic castration-resistant prostate cancer (CRPC), and Non-small Cell Lung Cancer (NSCLC) [31], [32], [33]. All evidence demonstrated the credibility of the FDA-approved drug library screening.

Tepotinib is a MET tyrosine kinase inhibitor intended to treat a variety of MET-overexpressing solid tumors [34]. The mesenchymal-epithelial transition factor (MET) proto-oncogene encodes the MET receptor tyrosine kinase. Binding of hepatocyte growth factor (HGF) to MET activates the receptor, causing tyrosine residues to auto-phosphorylate. This activation then initiates downstream signaling in the RAS/MAPK, PI3K-Akt, and STAT pathways [35]. As MET overexpression, amplification, and mutations have been widely reported in glioblastoma patients [36], Tepotinib functioning through inhibiting MET could be especially promising in MET-altered GBM patients, just as Tepotinib functions in MET-altered lung cancer patients [37] and breast cancer patients [35].

Zosuquidar 3HCl is a novel and potent modulator of P-glycoprotein (P-gp) [38]. P-gp is widely expressed in the brain, liver, small intestine, and tumor cells and acts as an efflux pump responsible for multidrug resistance in tumor cells. Overexpression of P-gp in tumors results in multidrug resistance (MDR) to structurally unrelated oncolytics [39]. Recent study indicates that P-gp expression in glioblastoma endothelial cells is associated with glioblastoma MDR [40], suggesting Zosuquidar 3HCl is a highly promising candidate drug in treating glioblastoma patients through modulating P-gp.

Cetrimonium Bromide (CTAB) is a quaternary ammonium salt with antiseptic and surface-active properties. Although not widely reported, CTAB has been implicated in promoting head and neck cancer treatment [41]. Another study in breast cancer showed that CTAB can enhance chemosensitivity through activation of AMPK signaling cascades [42]. As AMPK is highly expressed in glioblastoma [43], CTAB could potentially be effective in glioblastoma treatment through the mechanism of AMPK.

Similar to CTAB, Domiphen Bromide is a chemical antiseptic and a quaternary ammonium compound. No literature links Domiphen Bromide to cancer; therefore, this screening may be the first to establish this linkage.

4.2 The possible methods of brain delivery of the candidate drugs

The key obstacle in brain tumor treatment is to deliver drugs across the blood-brain barrier. Our candidate drugs can increase Taxol's anti-tumor effect. Therefore, for potential future therapeutic usage, ideally, they should be delivered together with Taxol. For Tepotinib, evidence has shown that Tepotinib can cross the BBB [44], so there should not be a concern about Tepotinib's delivery. For Zosuquidar 3HCl, interestingly, literature was found reporting that Zosuquidar 3HCl can increase BBB permeability and facilitate Taxol delivery into the brain [45].

The current Taxol delivery methods include nanoparticles [9], [10], payload liposomes [11], and ultrasound [3]. The optimal size for a nanoparticle is approximately 100 nm [46], which possiblely be enough to include Cetrimonium Bromide or Domiphen Bromide. Liposome size varies, usually extends from 50 nm to 150 nm [47], also possiblely be enough for Cetrimonium Bromide or Domiphen Bromide. Focused ultrasound (FUS) is a non-invasive technique that can temporarily open the blood-brain barrier (BBB) in targeted brain regions. This allows drugs (Taxol, Cetrimonium Bromide or Domiphen Bromide) to be delivered in the circulation to move into the brain.

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