Repurposing Taxane Compounds for Glioblastoma: A Comparative In-Silico Analysis of Target Interactions

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Abstract

Glioblastoma multiforme (GBM) is the most aggressive primary brain tumour in adults, and current treatment options provide minimal survival benefits. In search of improved therapeutic candidates, this study focuses on in-silico drug repurposing FDA-approved taxanes – Paclitaxel (PTX), Docetaxel (DOC), and Cabazitaxel (CTX) against GBM-associated molecular targets. GBM-relevant genes were retrieved, and overlapping targets with each taxane were identified and analyzed through molecular interaction studies. Among the evaluated compounds, PTX exhibited the most favourable binding affinity and biological relevance, particularly with CDK4, indicating a dual mechanism involving mitotic spindle disruption and inhibition of cell-cycle progression. DOC showed strong affinity for EGFR, while PTX demonstrated broader and more functionally significant target engagement. These findings suggest that PTX, as the parent taxane compound, holds superior therapeutic promise over its derivatives for GBM treatment and merits further validation through in vitro and targeted delivery studies to enhance its brain bioavailability and clinical applicability.

Keywords: Glioblastoma, Taxane, drug repurposing, Gene Ontology, Molecular Docking

1. Introduction

Glioblastoma multiforme (GBM) represents the most malignant form of astrocytoma and remains one of the most challenging cancers to treat in neuro-oncology. Accounting for nearly 50% of all primary malignant brain tumors, it is characterized by extensive molecular and cellular heterogeneity [1]. Hallmarked by uncontrolled proliferation, diffuse infiltration, angiogenesis, and resistance to apoptosis, coupled with intrinsic genetic and epigenetic plasticity, enables tumor cells to evade conventional therapies, resulting in a median survival of less than 15 months despite maximal surgical resection, radiotherapy, and temozolomide chemotherapy [2, 3]. These challenges underscore the urgent need for innovative therapeutic strategies that can precisely target critical oncogenic pathways.

A significant challenge in GBM therapy is the blood-brain barrier (BBB), a highly selective and tightly regulated endothelial interface that preserves central nervous system homeostasis by restricting the entry of xenobiotics, including most chemotherapeutic agents [4]. While essential for neural protection, the BBB significantly impeded drug delivery, contributing to therapeutic resistance and tumor recurrence in GBM [5]. Consequently, the development of targeted therapeutic strategies capable of traversing the BBB and modulating key oncogenic pathways is critical for improving treatment efficacy and patient outcomes.

Taxanes-including paclitaxel (PTX), Docetaxel (DOC), and Cabazitaxel (CTX), are FDA-approved microtubule-stabilizing chemotherapeutics that disrupt mitotic spindle dynamics, induce cell-cycle arrest, and trigger apoptosis in rapidly dividing cells [6]. Beyond their established roles in ovarian, prostate, and breast cancers, taxanes are being explored in GBM due to their capacity to interfere with microtubule-dependent signaling pathways involved in tumor cell proliferation, migration, and invasion [7]. Notably, newer generation derivatives such as cabazitaxel demonstrate enhanced BBB permeability and reduced efflux via P-glycoprotein, providing a pharmacological advantage for central nervous system malignancies [8].

This study focuses on the molecular convergence between taxane targets and GBM-associated genes, highlighting potential therapeutic nodes and offering a rationale for repurposing these well-characterized agents in glioblastoma therapy.

2. Methods

2.1 Retrieval of Glioblastoma-Associated Genes

Glioblastoma-related genes were retrieved from the GeneCards database (https://www.genecards.org/), accessed in 2025. Protein-coding genes associated with GBM were obtained by searching for the keyword "Glioblastoma". The most relevant target genes with a relevance score ≥ 20 were selected with a primary relevance score threshold of 41, for downstream bioinformatic analysis [9].

2.2 Identification of Taxane Drug Targets

Three taxane-based anticancer agents - Paclitaxel, Docetaxel, and Carbazitaxel — were selected for this study. The putative molecular targets of each drug were retrieved from the SwissTargetPrediction database (https://www.swisstargetprediction.ch/). For each compound, the top 100 predicted protein targets were selected based on probability scores, ensuring comprehensive coverage of their potential interaction profiles [10].

2.3 Selection of Hub genes

Venn diagrams were constructed to identify overlapping genes between the GBM-associated gene set and the target genes of each FDA-approved Taxane drug (n = 100 for each). The comparisons were conducted separately for PTX, DOC, and CTX using Venny 2.0 (https://bioinfogp.cnb.csic.es/tools/venny/) [11].

2.4 Gene Ontology Enrichment Analysis

Functional enrichment analysis was performed using the ShinyGO tool (https://bioinformatics.sdstate.edu/go/). Two distinct analyses were conducted: first, a broad analysis of all 16 core GBM genes to identify potential cell-surface localizations, and second, a focused analysis of the 5 hub genes to delineate their specific spatial organization within cellular machinery, with a statistical threshold of an adjusted p-value <0.05 applied to select significant GO terms and KEGG pathways [12].

2.5 Molecular Docking of the target compounds with the common genes

Maestro from Schrödinger suite was used to assess the binding affinities and interaction profiles of the overlapping genes. The protein structure was processed with the Protein

Preparation Wizard, and the ligand was prepared using LigPrep. The three-dimensional crystal structures of the target proteins and drug were retrieved from the PubChem and RCSB Protein Data Bank (PDB) using PDB IDs 2ITV, 8VBS, 2W96, 3DPK, and 8EXL (https://www.rcsb.org/) [13]. Ligplot+ and PyMOL were used to visualize the 2D and 3D structures of the docked protein-ligand complexes [14].

3. Results

3.1 Identification of GBM-Associated Genes

A total of 7689 protein-coding genes associated with glioblastoma were retrieved from the GeneCards database. Filtering based on a relevance score of ≥ 20 resulted in a refined panel of 16 highly GBM-relevant genes, indicating their strong disease association and biological significance in GBM pathogenesis.

3.2 Overlapping GBM-relevant targets across Taxanes

The overlapping genes between GBM and taxane targeting genes were identified by generating a Venn diagram to identify the hub genes. The Venn diagram revealed three common overlapping target genes between each taxane drug and the GBM-associated gene set (Fig. 1A - 1C). A total of five recurrent GBM-associated targets were identified across the taxane compounds, consisting of Epidermal growth factor (EGFR) and Phosphatidylinositol-4.5-biphosphate 3kinase (PIK3CA) as the most frequently co-occurring genes, followed by erb-b2 receptor tyrosine kinase2 (ERBB2), Fibroblast growth factor receptor 1 (FGFR1), and Cyclin dependent kinase 4 (CDK4), reflecting gene-level convergence among PTX, DOC, and CTX (Table 1).

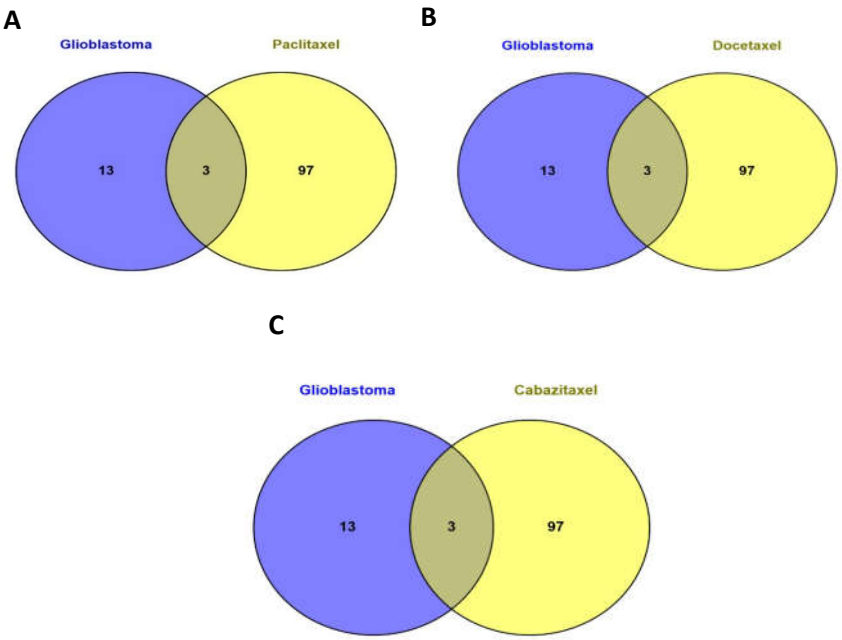

Figure 1: Venn diagrams to obtain hub genes for GBM. **(A)** Hub genes between GBM and PTX. **(B)** Hub genes between GBM and DOC. **(C)** Hub genes between GBM and CTX.

Conditions	Common Genes
GBM + PTX	EGFR, ERBB2, CDK4
GBM + DOC	EGFR, FGFR1, PIK3CA
GBM + CTX	EGFR, ERBB2, PIK3CA

Table 1: Hub genes obtained from Venn diagram

3.3 GO and KEGG enrichment analysis of genes

To characterize the functional roles of core GBM genes, functional enrichment analyses using GO and KEGG pathways analyses were performed. GO functional analysis includes biological process (BP), cellular component (CC), and molecular function (MF). Analysis of the 16 core GBM genes revealed their significant involvement in glioma-specific pathways through KEGG analysis, confirming their relevance to disease pathology (Fig. 2A). BP mapping demonstrated strong enrichment in cell cycle regulation and apoptotic processes, highlighting their role in controlling cellular proliferation and survival (Fig. 2B). CC analysis showed localization to neuronal structures, including synapses and postsynaptic membranes, reflecting GBM's origin in glial cells and its interaction with the neural environment (Fig. 2C). MF analysis further

confirmed kinase activities and nucleotide-binding capabilities essential for signal transduction in GBM (Fig.2D).

The focused five-gene hub (EGFR, ERBB2, PIK3CA, CDK4, FGFR1) exhibited more specialized functions across all categories. KEGG pathway analysis showed concentrated involvement in ErbB signalling and PI3K-Akt pathways (Fig. 3A), while BP mapping revealed specific enrichment in epidermal growth factor receptor signalling and positive regulation of mitotic cell cycle (Fig. 3B). CC analysis demonstrated precise localization to receptor complexes and key signalling platforms including the cyclin D2-CDK4 complex and phosphatidylinositol 3-kinase complexes (Fig. 3C). MF analysis confirmed their specialized roles in transmembrane receptor protein tyrosine kinase activity and growth factor binding, establishing this hub as a central co-ordinator of oncogenic signalling in GBM (Fig. 3D).

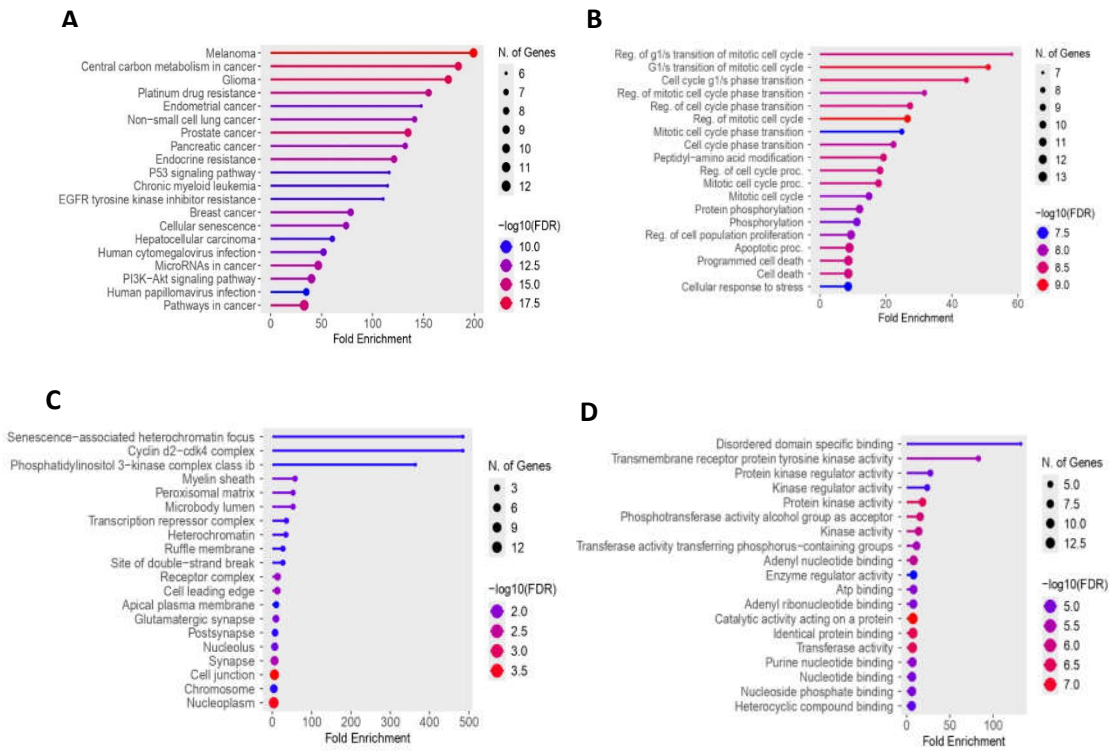

Figure 2: Functional Enrichment Analysis of 16 core GBM genes. Comprehensive functional profiling of the 16 genes identifies their broad association with oncogenic processes. **(A)** KEGG pathway enrichment analysis performed using ShinyGO shows significant enrichment in specific cancer types. **(B-D)** GO analysis reveals enrichment in **(B)** Biological

Processes, **(C)** Cellular Components, and **(D)** Molecular Functions. Dot size corresponds to the number of genes per term, and colour represents the statistical significance (-log10(FDR)).

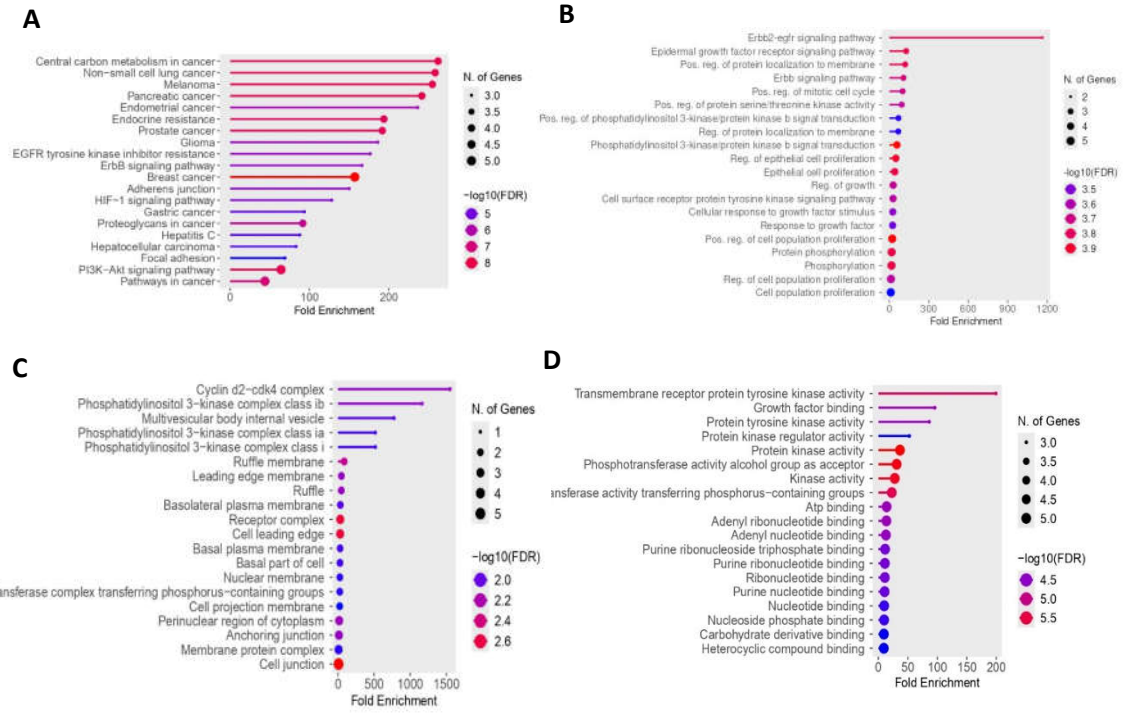

Figure 3. Focused Enrichment Profile of Hub Genes

Functionally annotation of the 5 hub genes delineates their role in specific, spatially-organized oncogenic complexes. **(A)** KEGG pathway enrichment analysis, performed using ShinyGO, highlights their central involvement in the ErbB signalling pathway, PI3K-Akt signalling, Glioma, and pathways related to therapy resistance. **(B-D)** GO analyses demonstrate significant enrichment in **(B)** Biological Processes, **(C)** Cellular components, and **(D)** Molecular Functions. Dot size corresponds to the number of genes per term, and colour represents the statistical significance (-log10(FDR)).

3.4 Molecular Docking of Taxanes with Overlapping GBM targets.

A structure-based molecular docking was carried out using Schrodinger Glide to evaluate the binding Profiles of PTX, DOC, and CTX against GBM-associated genes, focusing on their binding capacity at the active sites (Fig. 4A – 4R)

Paclitaxel consistently demonstrated stronger binding affinities compared to DOC and CTX across the evaluated targets. Table 2 displays the docking score for each hub gene against each compound. Notably, CDK4 exhibited the most favorable docking score for PTX (-5.273).

Against EGFR, a key driver of GBM aggrievances, DOC displayed the best binding affinity (-7.862), while PIK3CA exhibited a high docking score for CTX (-3.173).

Compound	Genes	Molecular Docking – XP Gscore (kcal/mol)
Paclitaxel (PTX)	EGFR	-2.118
	ERBB2	0.872
	CDK4	-5.273
Docetaxel (DOC)	EGFR	-7.862
	FGFR1	-1.274
	PIK3CA	-3.574
Cabazitaxel (CTX)	EGFR	-0.953
	ERBB2	-2.658
	PIK3CA	-3.173

Table 2: Docking scores for hub genes with Paclitaxel, Docetaxel, and Cabazitaxel

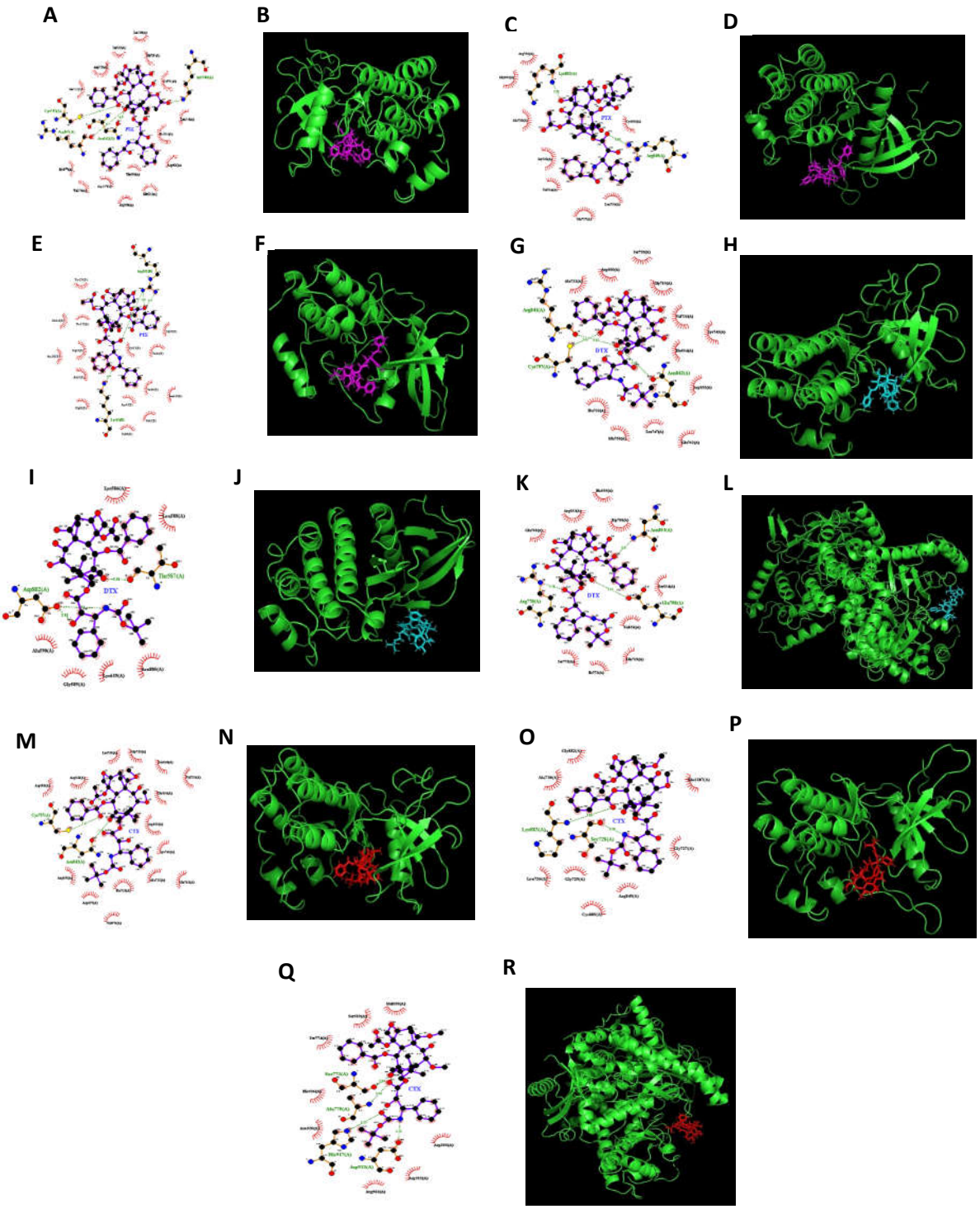

Figure 4. Molecular Docking of hub genes with their respective drug compound. **A, C, E, G, I, K, M, O, and Q** are 2D structures. **B, D, F, H, J, L, N, P and R** are 3D structures.

4. Discussion

GBM is the most lethal form of primary brain cancer in adults, driven by uncontrolled proliferation, invasive behavior, and rapid therapeutic resistance [15]. Conventional

multimodal treatment yields only marginal improvements in survival, highlighting the need for new or repurposed therapies that target key molecular vulnerabilities in GBM [16].

Taxanes primarily act by stabilizing microtubules and inhibiting mitotic spindle formation, thereby arresting cells in mitosis and promoting apoptosis [17]. Paclitaxel represents the original molecular scaffold, unlike second-generation analogues (DOC, CTX), which are heavily modified to improve pharmacokinetics and efflux resistance. This enables PTX to preserve binding flexibility and target engagement in novel contexts [18, 19].

GO analysis further depicts these findings within the broader molecular functions of GBM. The enrichment of the five genes (EGFR, ERBB2, PIK3CA, CDK4, FGFR1) in specific cellular components – including receptor complexes, cyclin D2-CDK4 complexes, and phosphatidylinositol 3-kinase complexes demonstrates their spatial organization into functional signalling units that drive GBM progression [20, 21]. Similarly, the collective involvement in biological processes such as ERBB2-EGFR-CDK signalling and positive regulation of mitotic cell cycle highlights the interconnected pathways through which these molecules coordinate oncogenic signals [22, 23].

CDK4 - a key regulator of the G1 to S phase cell-cycle transition frequently amplified in GBM, exhibited the most favorable docking score for PTX, suggesting a potential inhibitory role of paclitaxel in disrupting cell-cycle progression in GBM cells [24]. DOC displayed the best binding affinity against EGFR - a key driver of GBM, but PTX still showed appreciable interaction potential. Conversely, PTX demonstrated a positive score for ERBB2, indicating weak interaction relative to CTX.

PTX has a highly stable and strong binding interaction with tubulin, through extensive molecular dynamics simulations [25]. Our docking results conclusively demonstrate that PTX lacks direct binding affinity for these kinases, validating its established microtubule-targeting mechanism while explaining its indirect efficacy through synthetic lethality in hyper-proliferative cells. Most significantly, the abundant plasma membrane localization of these targets, particularly in structures like ruffle membranes and receptor complexes, identifies them as ideal candidates for engineered exosome delivery systems [26]. This approach could overcome the critical delivery challenges that limit PTX efficacy in GBM treatment, potentially enhancing its therapeutic index through target delivery to tumor cells [27].

While the blood-brain barrier remains a key obstacle for taxane delivery in GBM cells, advanced formulation strategies can significantly improve taxane brain penetration [28].

Emerging nanotechnologies, particularly extracellular vehicles (EVs), offer promising solutions [29, 30]. These naturally occurring nanoparticles can be engineered for enhanced brain penetration and tumor-specific targeting [31]. Our findings provide a rational basis for loading PTX into EVs functionalized to target the identified hub proteins, potentially overcoming current limitations in drug delivery. By leveraging PTX's dual mechanism of action (microtubule/mitotic spindle disruption and CDK-4-mediated cell cycle arrest) and directing it specifically to GBM cells through targeted EVs, we may achieve more effective tumor control while minimizing systemic exposure. This approach represents a convergent strategy that addresses both the molecular vulnerabilities of GBM and the pharmacological challenges of brain tumor drug delivery.

5. Conclusion

Paclitaxel's anti-tumour activity in GBM contexts operates through indirect mechanisms rather than direct kinase inhibition, as confirmed by molecular docking studies. The comprehensive cellular component analysis identified numerous cell-surface targets within the GBM signaling network, providing a strong rationale for developing targeted delivery systems. BBB penetration also remains a limitation. We propose that small extracellular vesicles engineered against these specific membrane components represent a promising strategy to achieve tumour-specific delivery of paclitaxel, potentially overcoming the fundamental limitation of current chemotherapy for Glioblastoma and paving the way for more effective therapeutic interventions against this lethal disease. Collectively, these findings establish paclitaxel as a promising candidate for GBM therapy and justify further experimental validation.

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